Implementation of ICH E9(R1) Estimands Framework using Data Standards

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Revision History

Version	Date	Summary
1.0	2025-05-06	Initial Version

1. Overview: Purpose of This Document

This white paper provides recommendations and examples to illustrate the implementation of the estimands framework introduced by the ICH E9(R1) Addendum on Estimands and Sensitivity Analysis in Clinical Trials to the Guideline on Statistical Principles for Clinical Trials [ICH E9(R1), 2019] using data standards (as part of the clinical data flow).

The Addendum introduced the E9(R1) framework with the objective to align the planning, design, conduct, analysis and interpretation of clinical trials and flags to the reader that: *"Avoiding or over-simplifying the process of discussing and constructing an estimand risks misalignment between trial objectives, trial design, data collection and method of analysis."* The Addendum provides extensive recommendations, together with the training materials, on the rethinking of treatment effects and clinical questions formulation, as well as on the strategies suggested to handle the intercurrent events. Furthermore, the scientific community of triallists, especially statisticians, from the pharma industry and regulatory agencies have been extremely active in recent years in understanding the meaning of estimands, how to formulate clinical questions and build estimand constructs, what estimands exist, how the estimands framework could be used to account for the possible impact of the COVID-19 pandemic on trials run during this time, estimation methods, etc. As of today, there is no published work/research on the E9(R1) implementation at the data collection level, coupled with analysis (estimation) in data standards.

This paper provides recommendations to facilitate E9(R1) implementation within the data flow, promoting alignment across the industry. These consist of best practices for using existing standards, extensions to the standards where applicable, and are illustrated by examples. The recommendations contained in this paper should not be interpreted as 'required' or endorsed by any regulatory agency.

This document and appendix use the terminology and wording as described in the Addendum text and glossary, and as illustrated in the ICH E9(R1) training materials. The reader will benefit from getting acquainted with the E9(R1) Addendum and with the training materials developed by the EIWG [E9(R1) Training Material, 2021], as well as with the considerable amount of published research on the estimands framework.

2. Scope

The scope of this document is as follows:

- Impact assessment of the estimands framework and recommendations in the following areas:
  - Data Collection (CDASH)
  - Data Tabulation (SDTM)
  - Data Analysis (ADaM)
  - Data Reviewer's Guides (cSDRG and ADRG)

Out of scope for this document are:

- Implementation or description of estimands in a protocol, statistical analysis plan, study design model, analysis results and displays. More details on this can be found in Principles and Recommendations for Incorporating Estimands into Clinical Study Protocol Templates [Lynggaard et al., 2022].
- Implementation of imputation and/or sensitivity analysis in ADaM. More details can be found in the CDISC ADaM Implementation Guide and ICH E9(R1) Addendum.
- Standards development: gaps in existing standards and, where applicable, proposals for addressing these gaps will be shared with the appropriate CDISC or PHUSE teams.
- How to appropriately implement the E9(R1) estimands framework in an individual clinical study.
- Harmonising and fully explaining the nuances of similar terms and definitions from a variety of sources/references, such as those in the Glossary (see section 3.2).

3. Definitions

3.1 Acronyms and Abbreviations

Term	Definition
ADaM	Analysis Data Model
ADaMIG	Analysis Data Model Implementation Guide
ADRG	Analysis Data Reviewer's Guide
BDS	Basic Data Structure
CDASH	Clinical Data Acquisition Standards Harmonization
CDISC	Clinical Data Interchange Standards Consortium
CRF	Case Report Form
cSDRG	Clinical Study Data Reviewer's Guide
CT	Controlled Terminology
EIWG	Estimands Implementation Working Group
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IG	Implementation Guide
OCCDS	Occurrence Data Structure
OCCDSIG	Occurrence Data Structure Implementation Guide
SAP	Statistical Analysis Plan
SDTM	Study Data Tabulation Model
SDTMIG	Study Data Tabulation Model Implementation Guide

3.2 Glossary

Term	Definition*
Subject/Participant **Source: E9, E9(R1), CDISC**	In this paper we refer to individuals (healthy volunteers or suffering from a condition) participating in a clinical trial (randomised/non-randomised) as 'participants' where possible. However, 'subject' is synonymously used in E9, E9(R1) and CDISC, and therefore will be referenced as such when quoting or using conventions from these sources.
Analysis set **Source: E9**	The set of subjects whose data are to be included in the main analyses (from the set of enrolled/randomised subjects) should be defined in the statistical section of the protocol. In addition, documentation for all subjects for whom trial procedures (e.g. run-in period) were initiated may be useful.
Full analysis set (FAS) **Source: E9**	The intention-to-treat (ITT) principle implies that the primary analysis should include all randomised subjects. Compliance with this principle would necessitate complete follow-up of all randomised subjects for study outcomes. In practice, this ideal may be difficult to achieve, for reasons to be described. In this document, the term 'full analysis set' describes the analysis set which is as complete as possible and as close as possible to the intention-to-treat ideal of including all enrolled and randomised subjects, along with as many original/actual collected values as possible.
Population (attribute of the estimand) **Source: E9(R1)**	The population of patients targeted by the clinical question. This attribute might 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 the context) of a specific intercurrent event.
Participant set **New term introduced**	The term 'participant set' is meant to describe which individuals from the trial population are contributing to an analysis corresponding to an estimand (included in an analysis, without (yet) specifying which of their specific measurements are included for estimation), which is different from the term 'participant analysis dataset'.
Participant analysis dataset **New term introduced**	The term 'participant analysis dataset' aims to complement the terms introduced by E9 and E9(R1) and used by CDISC, not to replace any of the other well-established terms, and to optimise E9(R1) implementation in CDISC. The term 'participant analysis dataset' is meant to simply describe which precise individuals (participating in a clinical trial) and which of their specific measurements (original/collected or derived/imputed) comprise the analysis dataset that will be used by the estimator (analytical tool) for the estimation of a precise treatment effect.
Dataset **Source: CDISC**	A collection of structured data in a single file [CDISC, ODM, and SDS] compared to an analysis dataset or a tabulation dataset.
Analysis dataset **Source: CDISC**	An organised collection of data or information with a common theme arranged in rows and columns and represented as a single file, comparable to a database table.
ADaM **Source: CDISC**	ADaM defines dataset and metadata standards that support: • Efficient generation, replication and review of clinical trial statistical analyses • Traceability among analysis results, analysis data, and data represented in the **Study Data Tabulation Model (SDTM).**
Endpoint/Variable **Source: E9(R1)**	The **variable** (or endpoint) to be obtained for each patient that is required to address the clinical question. The specification of the variable might include whether the patient experiences an intercurrent event. For awareness and the benefit of the reader, we draw attention to the ICH E9(R1) guideline also using the following terms: "observations", "measurements (of the variable)", "(...) value of the outcome variable", in context referring to an observation, measurement or value of the **variable** (or endpoint).
Estimand **Source: E9(R1)**	A precise description of the treatment effect reflecting the clinical question posed by a given clinical trial objective. It summarises at a population level what the outcomes would be in the same participants under different treatment conditions being compared.
Estimate **Source: E9(R1)**	A numerical value computed by an estimator.
Estimator **Source: E9(R1)**	A method of analysis to compute an estimate of the estimand using clinical trial data.
Intercurrent events **Source: E9(R1)**	Events occurring after treatment initiation that affect either the interpretation or the existence of the measurement associated with the clinical question of interest. Intercurrent events should be addressed when describing the clinical question of interest to precisely define the treatment effect that is to be estimated.
Missing data **Source: E9(R1)**	Data that would be meaningful for the analysis of a given estimand but was not collected. It should be distinguished from data that does not exist or data that is not considered meaningful because of an intercurrent event.
Treatment policy strategy **Source: E9(R1)**	The occurrence of the intercurrent event is considered irrelevant in defining the treatment effect of interest: the value for the variable of interest is used regardless of whether the intercurrent event occurs.

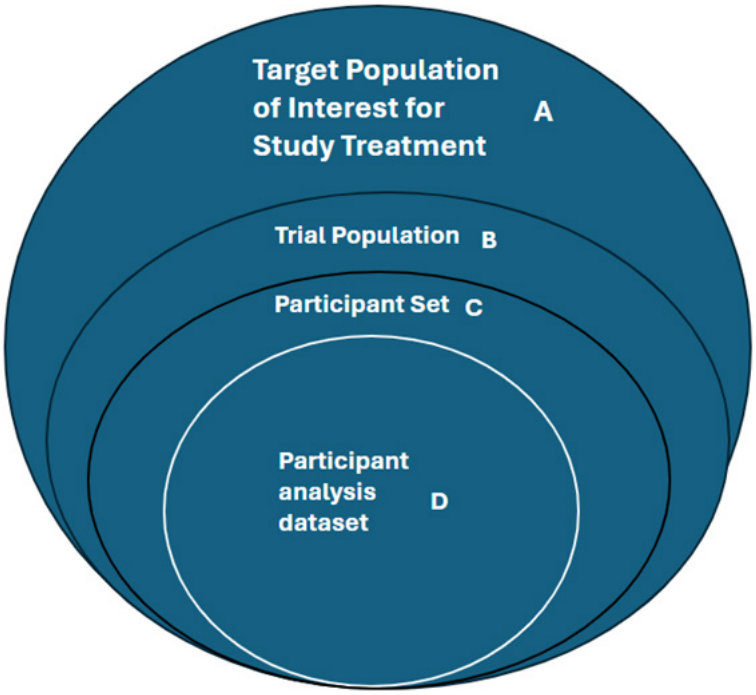
Term	Definition*
Hypothetical strategy **Source: E9(R1)**	A scenario is envisaged in which the intercurrent event would not occur: the value of the variable to reflect the clinical question of interest is the value which the variable would have taken in the hypothetical scenario defined.
Composite variable strategy **Source: E9(R1)**	An intercurrent event is considered to be informative about the subject's outcome and is therefore incorporated into the definition of the variable.
While on treatment strategy **Source: E9(R1)**	Response to treatment prior to the occurrence of the intercurrent event is of interest.
Principal stratum strategy **Source: E9(R1)**	The target population might be taken to be the 'principal stratum' in which an intercurrent event would occur. Alternatively, the target population might be taken to be the principal stratum in which an intercurrent event would not occur.
Principal stratification **Source: E9(R1)**	Classification of subjects according to the potential occurrence of an intercurrent event on all treatments. With two treatments, there are four principal strata with respect to a given intercurrent event: subjects who would not experience the event on either treatment, subjects who would experience the event on treatment A but not B, subjects who would experience the event on treatment B but not A, and subjects who would experience the event on both treatments. In this document, a principal stratum refers to any of the strata (or combination of strata) defined by principal stratification.

*All definitions sourced from ICH E9, E9(R1) or CDISC.

3.3 Commentary on Glossary Terms

The ICH E9 guideline (from 1998) speaks about analysis sets and considers these to be a set of subjects whose data will be included in the main analysis. Two main analysis sets were used in the past: FAS and PP (also revisited in the E9(R1) Addendum). FAS includes as many subjects as possible (almost all enrolled and randomised subjects/participants) and all their collected outcome values (as many as possible of the original/actual collected values), while PP includes those subjects without any violation to protocol criteria (with all their original actual collected values). With E9(R1), intercurrent events and strategies for intercurrent events were introduced. Consequently, the data for the main analysis could be used from all randomised participants (e.g. from FAS) but not all their actual collected data is used, depending on the intercurrent events and strategies for intercurrent events. It may be that only some of their measurements can be used – all participants contributing with at least a portion of their original values collected – while some of the remaining values (collected or not) may not be used but other values (derived, imputed, etc.) could be used. For this reason, a new term – participant analysis dataset – has been introduced in this paper.

The pictogram below describes the flow of terms from 'target population' to actual 'participant analysis dataset'.



A = Human Beings with a specific disease of interest.

B = Participants from A who enter the trial

C = Participants from B who are contributing to an analysis corresponding to an estimand (included in an analysis, without (yet) specifying which of their specific measurements are included for estimation).

[!] Subtle but important difference between 'analysis set' and 'participant analysis dataset' [!]
Analysis set = which trial participants e.g., FAS, PP with all of their available measurements

D = Measurements (original/collected or derived/imputed) from participants in C, for the estimation of a precise treatment effect corresponding to a specific analysis linked to a trial objective and an Estimand.

4. Context

ICH E9 Statistical Principles for Clinical Trials [ICH E9, 1998] was finalised in February 1998, meeting the need for a succinct document on statistical issues related to clinical trials. The guidance was written primarily to attempt to harmonise the principles of statistical methodology applied to clinical trials for marketing applications submitted in Europe, Japan and the United States.

The E9(R1) Addendum has opened new dimensions of pre-specification often driven by the need for more details and granularity to ensure the desired precision, as envisaged by the framework. There is currently a lack of reference documentation describing how the estimands framework may be implemented in the data structures, taking into account consistent implementation practices, and analysing to what extent the implementation is supported by and/or may impact on the existing data standards. This white paper has been initiated to address those gaps.

The E9(R1) addendum describes the thinking process that would ensure alignment between all steps, from formulating the trial objective, through estimand to estimates and sensitivity estimators. Adapting this depicted process (Figure 1, E9(R1) Addendum), we insert the 'Dataset derivation' sub step between estimand and estimators (Figure 1, below).

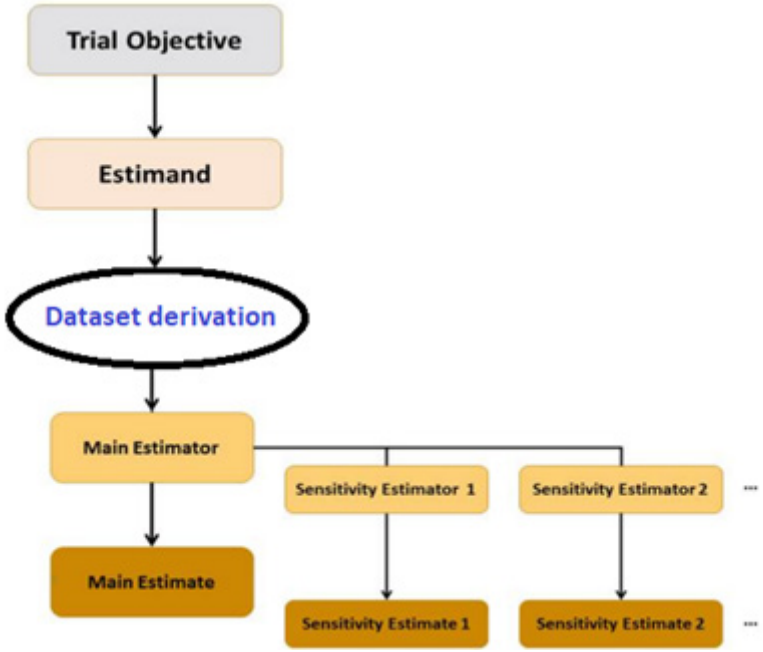


Figure 1: Aligning target of estimation, method of estimation, and sensitivity analysis for a given trial objective.

Figure 2 illustrates the potential impact considered and mapped for data collection, tabulation and analysis, with a summary of this impact. The estimands framework will affect all levels of documentation.

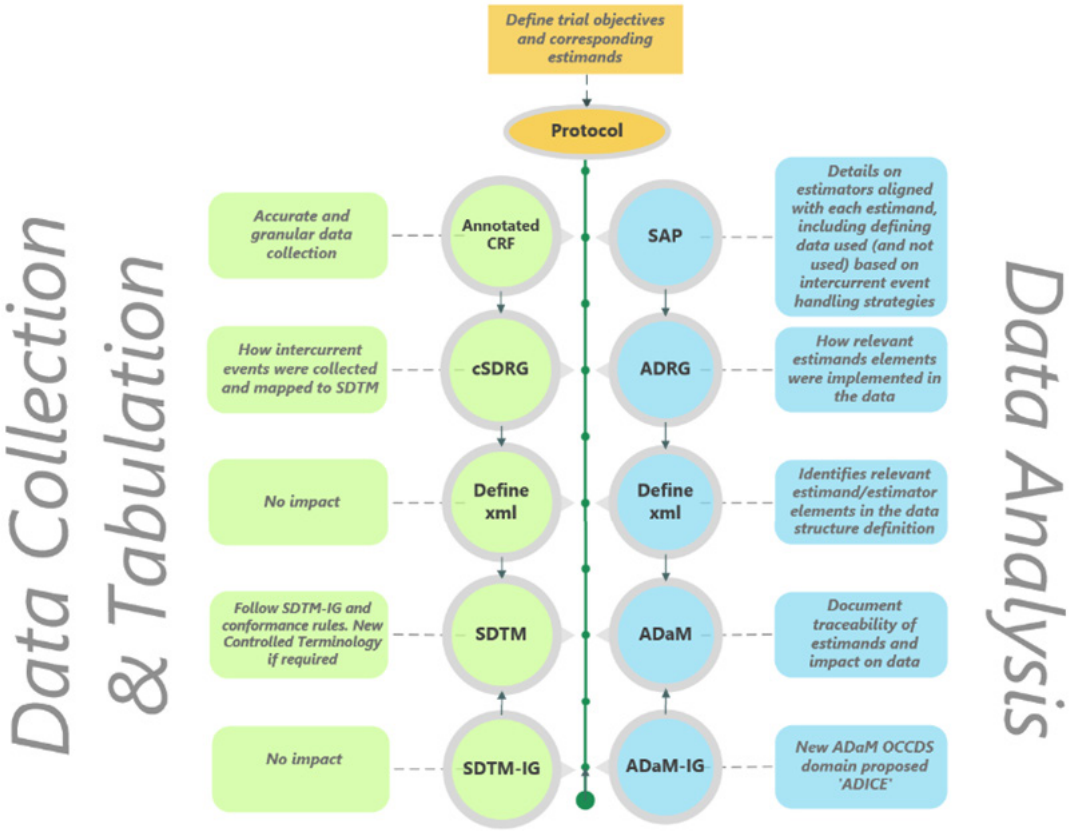


Figure 2: Documentation to Data. The flow is organised according to the logical documentation hierarchy, from the perspective of the reviewer, rather than a sequential generation order.

5. Data Collection and Tabulation

The key intercurrent events observed during clinical trials are primarily related to the treatment itself, including treatment discontinuation or interruption, the use of additional or alternative treatments such as rescue medication or prohibited medication, and terminal events such as death. Accurate collection of intercurrent events is critical in defining estimands and constructing the estimations, as outlined in ICH E9(R1). In addition, the intercurrent events themselves are important information to evaluate the benefit and risk of a new treatment [Akacha et al., 2017; Qu et al., 2023]. However, many current CRFs do not provide sufficient support for capturing intercurrent events; consequently, it is necessary to enhance CRF standards to improve the accuracy of data collection. This section addresses the principle of data collection, which encompasses not only estimands but also aims to enhance overall data collection practices. It is important to note that depending on the planned estimates it may be critical to continue to measure outcome after any individual intercurrent event.

The estimands framework is not expected to impact on SDTM. Data collected from CRFs should be mapped to the corresponding SDTM domains following the CDISC SDTMIG and Conformance Rules. However, the details of how intercurrent events are collected and mapped to the SDTM domains and variables should be explained in the cSDRG. There is no impact on the SDTM Define-XML file.

The CRF and SDTM examples illustrate commonly used approaches and recommendations for collecting and mapping intercurrent events. In this section, the intercurrent events related to treatment deviations and additional/alternative treatments will be the focus. Death and cause of death, which are captured in the Death Details and Disposition CRF, will not be addressed here. The SDTM examples in the paper follow SDTMIG v3.4.

If any intercurrent events of interest cannot be captured using the suggested CRFs outlined in this paper, a specialised CRF may be developed to facilitate their collection. Sponsors should evaluate their studies carefully and adjust these examples by including or removing options as appropriate.

5.1 Direct Consequences of the Treatment
5.1.1 Treatment Discontinuation

Treatment discontinuation is a common intercurrent event. However, the available options in the commonly used CRFs that follow the CDISC standard can be confusing or lack specificity. For example, the options can conflate the reasons for treatment discontinuation (such as adverse events) and who made the decision to discontinue treatment (such as subject withdrawal or physician's decision), or they may not provide enough details (such as technical problems). This confusion often leads to difficulty in selecting the accurate reasons for treatment discontinuation in the CRF, which prevents the collection of underlying reasons.

Qu et al reviewed the reasons for treatment discontinuations for nine Phase II and III studies in basal insulin peglispro and did a post hoc analysis to better understand the types of reasons for premature treatment discontinuations. They reviewed the comments for the original reasons of subject withdrawal, physician decision, and sponsor decision and then classified the underlying reasons of treatment discontinuations into more detailed categories such as travel or relocation, site closure, unsatisfied with study procedure or medication. Based on this research, a list of underlying reasons for early treatment discontinuation is proposed. The explanations and examples are detailed in section 5.1.5.

- ADVERSE EVENT
- APPROVED DRUG AVAILABLE FOR INDICATION
- DEATH
- LACK OF EFFICACY
- LOGISTICAL PROBLEM
- LOST TO FOLLOW-UP
- PREGNANCY
- PROGRESSIVE DISEASE
- PROTOCOL DEVIATION
- SUFFICIENT EFFICACY
- TREATMENT EXPERIENCE CONCERN

To improve the accuracy and specificity of data collection, two primary categories – PROTOCOL DEVIATION and LOGISTICAL PROBLEM – have been further broken down into granular subcategories. It is not recommended to include those terms that are not actual reasons for early discontinuations, such as WITHDRAWAL BY SUBJECT and PHYSICIAN DECISION, reasons that lack specificity, such as TECHNICAL PROBLEMS, as well as OTHER and If 'OTHER', please specify, since they are ambiguous and make it difficult to accurately summarise the actual underlying causes.

Document the participant's status for the treatment period. If the participant discontinued treatment prematurely, record the primary reason for discontinuation.	What was the participant's status? DS.DSDECOD DS.DSTERM	• **COMPLETED** • **ADVERSE EVENT. LINK TO ADVERSE EVENT: _____** • **APPROVED DRUG AVAILABLE FOR INDICATION** • **DEATH** • **LACK OF EFFICACY** • **LOGISTICAL PROBLEM** o CLINICAL TRIAL MATERIAL QUALITY ISSUE OR SHORTAGE o DIFFICULTY TRAVELING TO SITE o GEOPOLITICAL LOGISTICAL RESTRICTIONS o OPERATIONAL ERROR o PERSONAL/FAMILY REASONS NOT RELATED TO EFFICACY OR SAFETY OF THE STUDY INTERVENTION o RELOCATION o SCHEDULE CONFLICTS o STUDY TERMINATION OR SITE CLOSURE o UNSATISFIED WITH STUDY PROCEDURES • **LOST TO FOLLOW-UP** • **PREGNANCY** • **PROGRESSIVE DISEASE** • **PROTOCOL DEVIATION** o DID NOT MEET STUDY ELIGIBILITY CRITERIA AT ENROLLMENT o NONCOMPLIANCE TO STUDY INTERVENTION o NONCOMPLIANCE TO STUDY PROCEDURES o TOOK PROTOCOL-PROHIBITED CONCOMITANT MEDICATIONS • **SUFFICIENT EFFICACY** • **TREATMENT EXPERIENCE CONCERNS** o FEAR OF NEW OR RECURRENT ADVERSE EVENTS o UNSATISFIED WITH STUDY DRUG DELIVERY DEVICES/METHODS

The six primary categories without subcategories will be mapped to both the DSDECOD and DSTERM variables in the SDTM DS domain. For the two categories with subcategories, only the primary categories will be mapped to DSDECOD, while their respective subcategories will be mapped solely to DSTERM in the SDTM DS domain. The eight primary categories follow the extensible CDISC Controlled Terminology NCOMPLT (C66727) for Reason for Completion/Discontinuation. An example of the SDTM DS domain for disposition at treatment epoch is provided below.

DS Example

ds.xpt

Row	STUDYID	DOMAIN	USUBJID	DSTERM	DSDECOD	DSCAT	EPOCH	DSSTDTC
1	ABC456	DS	456103	RELOCATION	LOGISTICAL PROBLEM	DISPOSITION EVENT	TREATMENT	2003-10-15
2	ABC456	DS	456101	LOST TO FOLLOW-UP	LOST TO FOLLOW-UP	DISPOSITION EVENT	TREATMENT	2003-09-21

5.1.2 Treatment Interruption

5.1.2.1 Dose Omission

For orally administered drugs, interruption means that continuous oral dosing was suspended for a period prior to resuming dosing. Four categories shown as bolded text below are recommended for Reason Not Taken, with the LOGISTICAL PROBLEM category having more specific subcategories. A placeholder, <PROTOCOL SPECIFIED>, is provided for adding reasons according to the study protocol.

Indicate if the subject took study medication.	Was the dose administered? **EC.ECOCCUR**	• Yes • No
Indicate why the study treatment was not taken.	Reason Not Taken **EC.ECREASOC** **SUPPEC. QVAL where SUPPEC.QNAM = "RSIPLP" and SUPPEC. QLABEL = "Interrupt reason due to logist. Problem"**	• **ADVERSE EVENT.** List the adverse event ID: _____ • **LACK OF EFFICACY** • **LOGISTICAL PROBLEM** o CLINICAL TRIAL MATERIAL QUALITY ISSUE OR SHORTAGE o DIFFICULTY TRAVELING TO SITE o GEOPOLITICAL LOGISTICAL RESTRICTIONS o OPERATIONAL ERROR o PERSONAL/FAMILY REASONS NOT RELATED TO EFFICACY OR SAFETY OF THE STUDY INTERVENTION o RELOCATION o SCHEDULE CONFLICTS o STUDY TERMINATION OR SITE CLOSURE o UNSATISFIED WITH STUDY PROCEDURES • **PREGNANCY** • **SUFFICIENT EFFICACY** • **TREATMENT EXPERIENCE CONCERNS** o FEAR OF NEW OR RECURRENT ADVERSE EVENTS o UNSATISFIED WITH STUDY DRUG DELIVERY DEVICES/METHOD • **<PROTOCOL SPECIFIED>**
	Start Date **EC.ECSTDTC**	
	Start Date **EC.ECSTDTC**	
	Start Date **EC.ECSTDTC**	
	Start Date **EC.ECSTDTC**	
	Start Date **EC.ECSTDTC**	
	Start Date **EC.ECSTDTC**	
	Start Date **EC.ECSTDTC**	

EC Example

In a double-blind study, participants take two tablets once daily over a period of three weeks. Participant ABC2001 began taking the full dose of study medication on 14 January 2024 and missed taking the study medication for three consecutive days due to a personal reason not related to study treatment. Row 2 shows the period of missing dosing, with start and end dates indicating the duration of the absence of medication intake. The reason for not taking study medication, namely LOGISTICAL PROBLEM, was mapped to variable ECREASOC, with ECOCCUR marked as N.

ec.xpt

Row	STUDYID	DOMAIN	USUBJID	ECSEQ	ECTRT	ECPRESP	ECOCCUR	ECREASOC	ECDOSE	ECDOSU	ECDOSFRQ	EPOCH	ECSTDTC	ECENDTC
1	ABC	EC	ABC2001	1	BOTTLE A	Y	Y		2	TABLET	QD	TREATMENT	2011-01-14	2011-01-23
2	ABC	EC	ABC2001	2	BOTTLE A	Y	N	LOGISTICAL PROBLEM		TABLET	QD	TREATMENT	2011-01-24	2011-01-26
3	ABC	EC	ABC2001	3	BOTTLE A	Y	Y		2	TABLET	QD	TREATMENT	2011-01-27	2011-02-04

The exact reason for the logistical problem for participant ABC2001 was mapped into SUPPEC.

suppec.xpt

Row	STUDYID	RDOMAIN	USUBJID	IDVAR	IDVARVAL	QNAM	QLABEL	QVAL	QORIG
1	ABC	EC	ABC2001	ECSEQ	2	RSIPLP	Interrupt reason due to logist. problem	PERSONAL/FAMILY REASONS NOT RELATED TO EFFICACY OR SAFETY OF THE STUDY DRUG/DEVICE	CRF

5.1.2.2 Infusion Interruption

When administering IV-infused drugs, interruptions may occur during the infusion period. An interruption is defined as the stoppage of the IV infusion during the planned infusion period, which may or may not be resumed. When an interruption occurs, the infusion stop date and time, the reason for the interruption, and the dose administered at the time of interruption should be collected. If the infusion is resumed after a temporary stoppage, a new record is entered in the CRF. This record includes the start and stop dates and times and additional dosing details for the resumed infusion.

Indicate if the infusion was interrupted during administration.	Was the infusion interrupted? **Not submitted**	• Yes • No
Indicate why the infusion was interrupted.	Reason for interruption **EC.ECADJ**	• ADVERSE EVENT. List the adverse event ID: _____ • INFUSION ADMINISTRATION ISSUE • <PROTOCOL SPECIFIED>
Record the date and time when the infusion was started.	Start Date **EC.ECSTDTC**	
	Start Time **EC.ECSTDTC**	
Record the date and time when the infusion was stopped.	Stop Date **EC.ECENDTC**	
	Stop Time **EC.ECENDTC**	

EC Example

An infusion interruption and subsequent resumption occurred during the administration of Drug Z. The planned dosage for each visit was 100 ml, with a 30-minute infusion duration:

- Visit 1: Participant ABC1230 received a 100 ml infusion of Drug Z for 30 minutes.
- Visit 2: During this visit, the infusion was interrupted after 15 minutes (45 ml of Drug Z administered) due to an issue with the infusion administration process. After resolving the issue, the infusion was resumed 20 minutes later, and the participant received the remaining 55 ml of the dose in the following 20 minutes. Consequently, the overall infusion time for visit 2 lasted 55 minutes, and the interruption duration was 20 minutes.

ec.xpt

Row	USUBJID	ECSEQ	ECTRT	ECPRESP	ECOCCUR	ECREASOC	ECDOSE	ECDOSU	ECADJ	VISITNUM	ECSTDTC	ECENDTC
1	ABC1230	1	DRUG Z	Y	Y		100	ML		1	2009-02-13T10:0	2009-02-13T10:30
2	ABC1230	2	DRUG Z	Y	Y		45	ML	INFUSION ADMINISTRATION ISSUE	2	2009-02-20T11:00	2009-02-20T11:15
3	ABC1230	3	DRUG Z	Y	Y		55	ML		2	2009-02-20T11:35	2009-02-20T11:55

5.1.3 Dose Adjustment

Dose adjustment includes dose reduction and increase. In addition to the reasons for the dose adjustment, more specific reasons were collected for LOGISTICAL PROBLEM.

Indicate whether there was a change in dosing.	Was the dose adjusted? **Not submitted**	• Yes • No
If there was a change in dosing, record the reason for the change.	What was the reason the dose was adjusted? **EC.ECADJ** **SUPPEC.QVAL where SUPPEC.QNAM = "RSADJLP" and SUPPEC.QLABEL = "Adjust. reason due to logist. problem"**	• ADVERSE EVENT. List the adverse event ID: _____ • LACK OF EFFICACY • LOGISTICAL PROBLEM o FEAR OF NEW OR RECURRENT ADVERSE EVENTS o OPERATIONAL ERROR • SUFFICIENT EFFICACY • <PROTOCOL SPECIFIED>

EC Example

In a double-blind study, participants take two tablets daily for six months. Due to a LOGISTICAL PROBLEM, participant ABC3004's dosage was initially reduced to one tablet, but it was later increased back to two tablets per day.

ec.xpt

Row	USUBJID	ECSEQ	ECTRT	ECPRESP	ECOCCUR	ECADJ	ECDOSE	ECDOSU	ECDOSFRQ	EPOCH	ECSTDTC	ECENDTC
1	ABC3004	1	BOTTLE A	Y	Y		2	TABLET	QD	TREATMENT	2011-01-14	2011-01-23
2	ABC3004	2	BOTTLE A	Y	Y	LOGISTICAL PROBLEM	1	TABLET	QD	TREATMENT	2011-01-24	2011-01-26
3	ABC3004	3	BOTTLE A	Y	Y		2	TABLET	QD	TREATMENT	2011-01-7	2011-01-31

The specific reason for dose adjustment (reduction) for participant ABC3004 is presented as a supplemental qualifier.

suppec.xpt

Row	STUDYID	RDOMAIN	USUBJID	IDVAR	IDVARVAL	QNAM	QLABEL	QVAL	QORIG
1	ABC	EC	ABC3004	ECSEQ	2	RSADJLP	Adjust. reason due to logist. problem	FEAR OF NEW OR RECURRENT ADVERSE EVENTS	CRF

5.1.4 Treatment Delay

Treatment delay refers to the postponement of a scheduled dose of medication or treatment but is expected to be resumed.

Indicate whether the dose was delayed.	Was the dose delayed? **Not submitted**	• Yes • No
If the dose is delayed, record the reason for the delay.	What was the reason the dose was delayed? **SUPPEC.QVAL where SUPPEC.QNAM = "RSDEL" and SUPPEC.QLABEL = "Reason for Dose Delay"** **SUPPEC.QVAL where SUPPEC.QNAM = "RSDELLP" and SUPPEC.QLABEL = "Delay reason due to logist. problem"**	• **ADVERSE EVENT. List the adverse event ID: _____** • **LOGISTICAL PROBLEM** o CLINICAL TRIAL MATERIAL QUALITY ISSUE OR SHORTAGE o DIFFICULTY TRAVELING TO SITE o GEOPOLITICAL LOGISTICAL RESTRICTIONS o OPERATIONAL ERROR o PERSONAL/FAMILY REASONS NOT RELATED TO EFFICACY OR SAFETY OF THE STUDY INTERVENTION o RELOCATION o SCHEDULE CONFLICTS o STUDY TERMINATION OR SITE CLOSURE o UNSATISFIED WITH STUDY PROCEDURES • **PREGNANCY** • **SUFFICIENT EFFICACY** • **TREATMENT EXPERIENCE CONCERNS** o FEAR OF NEW OR RECURRENT ADVERSE EVENTS o UNSATISFIED WITH STUDY DRUG DELIVERY DEVICES/ METHOD o **<PROTOCOL SPECIFIED>**

It should be noted that ECADJ is not the right variable to capture treatment delays, as this variable holds the reasons behind why a dose was adjusted. An appropriate variable to capture dose delays will be timing variables, e.g. ECSTDTC, and SUPPEC should include the reasons for dose delay.

EC and SUPPEC Example

In a double-blind study, participants take one dose every 28 days (about four weeks). Due to a LOGISTICAL PROBLEM, participant ABC3004's dosage was delayed from 28th day to 42nd day from previous dose.

ec.xpt

Row	USUBJID	ECSEQ	ECTRT	ECPRESP	ECOCCUR	ECDOSE	ECDOSU	ECDOSFRQ	EPOCH	ECSTDTC	ECENDTC
1	ABC3004	1	BOTTLE A	Y	Y	200	mg	EVERY 4 WEEKS	TREATMENT	2011-01-14	2011-01-14
2	ABC3004	2	BOTTLE A	Y	Y	200	mg	EVERY 4 WEEKS	TREATMENT	2011-02-25	2011-02-25

Participant ABC3004 is captured as a supplemental qualifier, with the reason and details for the dose delay.

suppec.xpt

Row	STUDYID	RDOMAIN	USUBJID	IDVAR	IDVARVAL	QNAM	QLABEL	QVAL	QORIG
1	ABC	EC	ABC3004	ECSEQ	2	RSDEL	Reason for Dose Delay	LOGISTICAL PROBLEM	CRF
1	ABC	EC	ABC3004	ECSEQ	2	RSDELLP	Delay reason due to logist. problem	RELOCATION	CRF

5.1.5 Explanation and Examples of Reasons for Treatment Discontinuation, Treatment Interruption, Dose Adjustment and Treatment Delay

SUFFICIENT EFFICACY

Sufficient efficacy refers to participants who discontinue the study intervention when they achieve the desired efficacy results or outcome ahead of the protocol-specified treatment period. Examples include participants achieving remission in major depressive disorder (MDD), participants discontinuing antibiotics for a bacterial infection after symptom alleviation, or participants reaching their weight loss target in a chronic weight management trial.

PROTOCOL DEVIATION

Protocol deviation is a variation from processes or procedures defined in a protocol, as outlined in CDISC Controlled Terminology [NCOMPLT].

- Did not meet study eligibility criteria at enrolment – the participant did not meet study inclusion/exclusion criteria but was inadvertently included in the study.
- Noncompliance to study intervention – the participant was not compliant with study intervention per protocol requirements.
- Noncompliance to study procedures – the participant was not compliant with protocol-required procedures.
- Took protocol-prohibited concomitant meds – the participant took prohibited concomitant medication.

LOGISTICAL PROBLEM

Logistical problems are issues related to the planning, coordination and execution of the clinical trial that lead to complications or disruptions.

- Clinical trial material quality issue or shortage – e.g. supply chain disruptions
- Geopolitical logistical restrictions – e.g. natural disasters, geographical conflicts, or pandemic/epidemic situations
- Operational errors – e.g. site procedure errors, scheduling errors, human errors
- Unsatisfied with study procedures – e.g. the participant thought that the study procedures were too burdensome, that there were too many procedures/measurements.

TREATMENT EXPERIENCE CONCERNS

Treatment experience concerns in a clinical trial are issues or worries participants have regarding their experience with the treatment being studied.

- Unsatisfied with study drug delivery devices/methods – e.g. the participant thought the drug delivery device was too difficult to use
- Fear of new or recurrent adverse events – e.g. the participant was fearful of experiencing a new adverse event or a recurrence of a prior adverse event.

INFUSION ADMINISTRATION ISSUE

Infusion administration issues relate to problems or complications that arise during the process of delivering medication through an infusion. For example, the treatment had to be stopped due to an equipment malfunction with the infusion pump.

<PROTOCOL SPECIFIED>

A placeholder <> is provided for adding reasons for the treatment interruption, dose adjustment and treatment delay terms according to the study protocol.

5.2 Additional/Alternative Treatment

Additional/alternative treatment is another type of commonly seen intercurrent event. This usually includes concomitant medications and procedures (e.g. prohibited medication and procedure, disease-related background therapy) and rescue medications and procedures (e.g. subsequent systemic anti-cancer therapy, radiotherapy, and tumour-directed surgery, treatment for the complications of primary condition developed during study). The example CRFs below illustrate the recommended data collection for precise reasons and timing associated with additional/alternative treatment. Placeholders, <PROTOCOL SPECIFIED >, are provided for adding reasons per study protocol requirement.

5.2.1 Concomitant Medication

In the Concomitant Medication CRF, both the indications and reasons for taking concomitant medications are recorded. The indication is cross-referenced with other CRFs, such as the Adverse Event CRF, to establish a correlation between the concomitant medication and the specific medical condition it addresses.

Indicate if the participant took any concomitant medication/ treatment.	Were any concomitant medications taken? **Not submitted**	• Yes • No
Record only one treatment per line. Provide the full trade name of the medication/ treatment	What was the medication? **CM.CMTRT**	

Record the specific indication for which the medication was taken.	For what indication was the medication taken? **CM.CMINDC** **SUPPCM.QVAL where SUPPCM.QNAM = "AELINK" and SUPPCM.QLABEL = "Related Adverse Event"** **SUPPCM.QVAL where SUPPCM.QNAM = "CELINK" and SUPPCM.QLABEL = "Related Clinical Event"** **SUPPCM.QVAL where SUPPCM.QNAM = "MHLINK" and SUPPCM.QLABEL = "Related Medical History"**	• ADVERSE EVENT. LINK TO ADVERSE EVENT: ____ • CLINICAL EVENT. LINK TO CLINICAL EVENT: ___ • MEDICAL HISTORY. LINK TO MEDICAL HISTORY: ___
Record the specific reason why the medication was taken	For what reason was the medication taken? **SUPPCM.QVAL where SUPPCM.QNAM = "CMREAS" and SUPPCM.QLABEL = "Reason"**	• NON-THERAPEUTIC USE • PROPHYLAXIS FOR <xxx> • REQUIRED CONCOMITANT MEDICATION FOR THE STUDY • VACCINATIONS • <STUDY INDICATION>
	Start Date **CM.CMSTDTC**	
	Is the medication ongoing? **CM.CMENRF or CMENRTPT**	• Yes
	End Date **CM.CMENDTC**	

CM Example

In this example, participant A456101 used methylprednisolone to treat neuropathic pain, while participant A456103 chose SPIKEVAX for COVID-19 prevention.

cm.xpt

Row	STUDYID	DOMAIN	USUBJID	CMSEQ	CMTRT	CMINDC	CMSTDTC	CMENRF	CMENDTC
1	ABC456	CM	A456101	1	METHYLPREDNISOLONE	ADVERSE EVENT	2003-07-21	ONGOING	
2	ABC456	CM	A456103	2	SPIKEVAX		2003-08-15		2003-08-15

suppcm.xpt

Row	STUDYID	RDOMAIN	USUBJID	IDVAR	IDVARVAL	QNAM	QLABEL	QVAL
1	ABC456	CM	A456101	CMSEQ	1	AEILNK	Related Adverse Event	NEUROPATHIC PAIN--18/JUL/2003--GR:GRADE 2
2	ABC456	CM	A456103	CMSEQ	2	CMREAS	Reason	PROPHYLAXIS FOR COVID-19

ae.xpt

Row	DOMAIN	USUBJID	AESEQ	AETERM	AEDECOD	AESTDTC	AETOXGR
1	AE	A456101	5	NEUROPATHIC PAIN	Neuralgia	2003-07-18	GRADE 2

relrec.xpt

Row	STUDYID	RDOMAIN	USUBJID	IDVAR	IDVARVAL	RELID
1	ABC456	AE	A456101	AESEQ	5	1
2	ABC456	CM	A456101	CMSEQ	1	1

5.2.2 Concomitant Procedure

Both the indications and reasons for performing concomitant procedures are recorded in the Procedure CRF. The indication for a procedure is correlated with other CRFs, such as the Adverse Event CRF, to establish a link between the procedure and the specific medical condition prompting it. Reasons for performing a concomitant procedure unrelated to a medical indication are documented separately within the CRF.

Indicate if the subject had any concomitant procedure.	Were any procedures performed? **Not submitted**	• Yes • No
	Procedure category **PR.PRCAT**	• Diagnostic • Medical • Diagnostic/Medical • Study Related
	Procedure name **PR.PRTRT**	
Record the specific indication for which the procedure was performed.	For what indication was the procedure performed? **PR.PRINDC** **SUPPPR.QVAL where SUPPPR.QNAM = "AELINK" and SUPPPR.QLABEL = "Related Adverse Event"** **SUPPPR.QVAL where SUPPPR.QNAM = "CELINK" and SUPPPR.QLABEL = "Related Clinical Event"** **SUPPPR.QVAL where SUPPPR.QNAM = "MHLINK" and SUPPPR.QLABEL = "Related Medical History"**	• ADVERSE EVENT. LINK TO ADVERSE EVENT: ____ • CLINICAL EVENT. LINK TO CLINICAL EVENT: ___ • MEDICAL HISTORY. LINK TO MEDICAL HISTORY: ___
Record the specific reason why the procedure was performed	For what reason was the procedure performed? **SUPPPR.QVAL where SUPPPR.QNAM = "PRREAS" and SUPPPR.QLABEL = "Reason"**	• NON-THERAPEUTIC USE PROPHYLAXIS FOR <xxxx> • <STUDY INDICATION>
	Start Date **PR.PRSTDTC**	
	End date **PR.PRENDTC**	

PR Example

Laparotomy was performed to diagnose suspected ileal obstruction in participant A456102, and angioplasty was performed to improve coronary artery disease in participant A456104.

pr.xpt

Row	STUDYID	DOMAIN	USUBJID	PRSEQ	PRCAT	PRTRT	PRINDC	PRSTDTC	PRENDTC
1	ABC456	PR	A456102	5	DIAGNOSTIC	LAPAROTOMY	ADVERSE EVENT	2003-10-02	2003-10-02
2	ABC456	PR	A456104	9	MEDICAL	ANGIOPLASTY		2003-04-15	2003-04-15

supppr.xpt

Row	STUDYID	RDOMAIN	USUBJID	IDVAR	IDVARVAL	QNAM	QLABEL	QVAL
1	ABC456	PR	A456102	PRSEQ	5	AELINK	Related Adverse Event	ILEAL OBSTRUCTION--02/OCT/2003--GR:GRADE 4
2	ABC456	PR	A456104	PRSEQ	9	PRREAS	Reason	DISEASE IMPROVEMENT

ae.xpt

Row	DOMAIN	USUBJID	AESEQ	AETERM	AEDECOD	AESTDTC	AETOXGR
1	AE	A456102	13	ILEAL OBSTRUCTION	Small intestinal obstruction	2003-10-02	GRADE 4

relrec.xpt

Row	STUDYID	RDOMAIN	USUBJID	IDVAR	IDVARVAL	RELID
1	ABC456	AE	A456102	AESEQ	13	1
2	ABC456	PR	A456102	PRSEQ	5	1

5.2.2.1 Subsequent Cancer Therapy – Surgery

Subsequent tumour-directed surgeries are performed any time after the first dose of the study drug. Record the specific reason why the surgery was performed, e.g. curative tumour resection.

	Category for surgery **PR.PRCAT**	• Cancer surgeries for disease under study
	What is the surgery? **PR.PRTRT**	
	Relevant period **PR.PRSCAT**	• Subsequent
Record the specific reason why the surgery was performed	What was the reason for the surgery being performed? **SUPPPR.QVAL where SUPPPR.QNAM = "PRREAS" and SUPPPR.QLABEL = "Reason"** **PR.PRINDC**	• TUMOR RESECTION PALLIATIVE • TUMOR RESECTION CURATIVE
	Date of surgery **PR.PRSTDTC**	

PR Example

Participant A456111 received right portal embolisation for tumour treatment.

pr.xpt

Row	STUDYID	DOMAIN	USUBJID	PRSEQ	PRCAT	PRTRT	PRINDC	PRSTDTC	PRENDTC
1	ABC456	PR	A456111	4	CANCER SURGERIES FOR DISEASE UNDER STUDY	RIGHT PORTAL EMBOLISATION		2003-12-02	2003-12-02

supppr.xpt

Row	STUDYID	RDOMAIN	USUBJID	IDVAR	IDVARVAL	QNAM	QLABEL	QVAL
1	ABC456	PR	A456111	PRSEQ	4	PRREAS	Reason	TUMOR RESECTION CURATIVE

5.2.2.2 Subsequent Cancer Therapy – Radiotherapy

Subsequent radiotherapy for tumour treatment administered after the first dose of the study drug. Record the reason why the radiotherapy was administered, e.g. curative.

Category for radiotherapy **PR.PRCAT**	• Radiation therapy for disease under study
What is the radiotherapy? **PR.PRTRT**	
Relevant period **PR.PRSCAT**	• Subsequent
Treatment intent **SUPPPR.QVAL where SUPPPR.QNAM = "TRTINT" and SUPPPR.QLABEL = "Treatment Intent"**	• PALLIATIVE • CURATIVE
Start date **PR.PRSTDTC**	
End date **PR.PRENDTC**	

PR Example

In this example, participant A456131 underwent radiation therapy to the brain, with the goal of alleviating symptoms and enhancing quality of life.

pr.xpt

Row	STUDYID	DOMAIN	USUBJID	PRSEQ	PRCAT	PRTRT	PRSTDTC	PRENDTC
1	ABC456	PR	A456131	4	RADIATION THERAPY FOR DISEASE UNDER STUDY	RADIOTHERAPY OF THE BRAIN AREA	2004-02-02	2004-02-02

supppr.xpt

Row	STUDYID	RDOMAIN	USUBJID	IDVAR	IDVARVAL	QNAM	QLABEL	QVAL
1	ABC456	PR	A456131	PRSEQ	4	TRTINT	Treatment Intent	PALLIATIVE

5.2.3 Explanation and Examples of Reasons for Concomitant Medication and Concomitant Procedure

- Non-therapeutic use – The use of a substance or treatment that is unlikely to produce a diagnostic, preventative or therapeutic benefit. This can include recreational use or misuse/abuse of the substance.
- Prophylaxis – Measures taken to prevent the onset of an illness, the recurrence of a condition, or to promote overall wellness. Examples include taking vitamins to boost immunity against viral infections or using antihistamines to prevent allergic reactions.
- Required concomitant medication for the study – Medications participants must take in conjunction with the study treatment as specified by the study protocol. For example, in a clinical trial for a new chemotherapy drug, participants might be required to take antiemetic medications to prevent nausea and vomiting, which are common side effects of chemotherapy.
- <Study indication> – A placeholder is provided for adding study-specific indications, such as treatment of signs or symptoms of the condition(s) under study, rescue therapy and bridging therapy.

5.3 Study Discontinuation

The reasons for study discontinuation are relevant to estimation and missing data imputation. Most treatment discontinuations (such as due to adverse events or lack of efficacy) should not prevent participants from continuing the clinical trial, having any procedures performed, or their data being collected. Participants are generally encouraged to stay in the study, even if they will discontinue or have discontinued treatment to minimise missing values [National Research Council, 2010]. Reasons for treatment and study discontinuations should be collected in separate CRFs. Depending on the study design, more granularities may be needed for reasons for study discontinuation, similar to the approach recommended for study treatment discontinuations. It is important to discuss with the health authority reviewer the options that should be included in this CRF.

5.4 Clinical Study Data Reviewer's Guide (cSDRG)

The cSDRG supports traceability and allows health authorities to identify and review intercurrent events in SDTM. The cSDRG completion guidelines [PHUSE cSDRG 2019] provide guidelines on how to document estimands and intercurrent events under sections 3, 'Participant Data Description', and 3.1, 'Overview'. It is recommended to use this section to describe intercurrent events associated with clinical questions of interest, as well as how intercurrent events are collected and how intercurrent events are mapped to corresponding SDTM domains and variables. In the cSDRG template, the questions intercurrent events can be specified in the table template below.

Intercurrent Events

Intercurrent Event(s) collected in the study	In which CRF forms were details of intercurrent events collected?	In which SDTM domains (and variables) were intercurrent events mapped?

6. Data Analysis

6.1 General Considerations

The ICH E9(R1) estimands framework is intended to cover most clinical trial objectives and corresponding clinical questions described in the protocol and SAP, therefore impacting on 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 Addendum mentions that: *"Clarity is introduced by carefully defining the treatment effect of interest in a way that determines both the* ***population of subjects*** *to be included in the* ***estimation*** *of that treatment effect* ***and the observations from each subject to be included in the analysis considering the occurrence of intercurrent events****."* That extra clarity needs translation into new requirements in the analysis datasets for proper support of the estimands framework.

Based on the Analysis Data Model (ADaM) guidelines, the ADaM estimands implementation framework described here has been designed to facilitate the understanding and traceability of estimands components. The implementation is straightforward and flexible enough to support a broad range of analysis situations. The implementation in analysis datasets will be accompanied by new estimands implementation sections in the ADRG. The new requirements supported by the ADaM estimands implementation framework are:

- **Intercurrent Events:** ways to organise, identify and document intercurrent events, their relationship with each estimand, and the related handling strategy
- **IDatapoints:** ways to document datapoints impacted by intercurrent events
- **Analysis Set:** support for principal stratum-based analysis sets.

Regarding the estimators, these correspond to the statistical analyses performed on and supported by the ADaM datasets. The implementation framework builds upon and complements existing ADaMIG features to support statistical analyses. In other words, all existing features of the ADaMIG are acknowledged and no existing ADaM feature is prevented or discouraged from being used. In some situations, the ADaM estimands implementation framework may offer additional ways of supporting statistical analyses, especially with regards to participant and records (datapoints) selection.

Please keep in mind that this white paper and the estimands implementation framework lay the foundations of the estimands support. It does not intend to address all implementation needs and situations. Follow-up publications and white papers may address more complex needs and situations.

6.2 Implementation of E9(R1) Estimands Framework in ADaM

6.2.1 Dataset-Level Implementation

The datasets supporting the E9(R1) estimands framework implementation in ADaM are presented here. These datasets can be divided into three groups: datasets defining the participant analysis datasets in relation to estimands' population definitions, datasets gathering the intercurrent events, and datasets supporting the statistical analyses (i.e. estimators) related to the estimands.

Figure 3 illustrates a possible data flow from SDTM to ADSL and ADICE (the dataset holding the intercurrent events) and then to other ADaM datasets. This assumes there is a single dataset named ADICE gathering all intercurrent events in one place. When possible, the ADSL and ADICE datasets are built at the beginning of the analysis data flow to serve as support for documenting the impact of intercurrent events into the other ADaM datasets supporting the statistical analyses, though more complex situations can occur. In some cases, intercurrent events may need to be derived from other analysis datasets instead of used/derived directly from the collected data. In these cases, these ADaM datasets will have an impact on ADSL and ADICE, and the data flow may be more complex. More complex data flows are common in ADaM and may be required, e.g. ADSL or ADICE may depend on other ADaM datasets for more complex intercurrent events. The topic is mentioned in the ADaM Implementation Guide (section 3.2 paragraphs 4–5) and the ADaMIG in general does not recommend one way or another to address such cases. The situation is no different for intercurrent events than for other ADaM situations and will not be further discussed in this white paper because it is not specific to the estimands implementation. The datasets will be further discussed below.

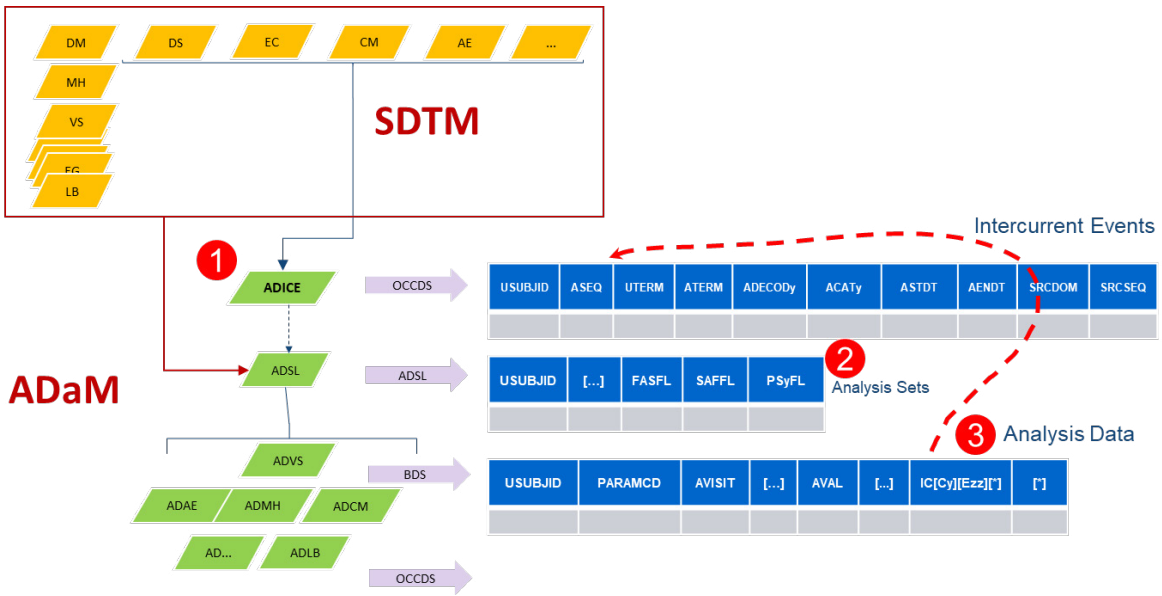


Figure 3: Illustrative data flow from SDTM to ADICE (Intercurrent Events Analysis Dataset) and other ADaM datasets, and use of estimands variable terminology. Note that this is just an example flow, and the precise flow may differ across studies.

The ADaM estimands implementation framework builds upon the ADaMIG and OCCDSIG. Consequently, all features described in the IGs are available and can be used. Additional variables are proposed here to complement the current IGs and to offer specific support to the documentation of estimands.

6.2.1.1 Subject-Level Analysis Dataset (ADSL)

The ADSL dataset is used as usual. The only estimands specific addition is the support for principal stratum-based analysis sets. Refer to 6.2.2 Variable-Level Implementation for more details.

6.2.1.2 Intercurrent Events Analysis Dataset(s)

Analysis datasets supporting the generation of analysis and displays should allow analysts 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 organised and consolidated in a structure facilitating their identification and documentation.

Intercurrent events data is a collection of intercurrent events occurrences, recording the name of the intercurrent event, along with the start and end date/time and relevant identification, traceability, and classification information, including standardised name/category per estimand and handling strategy per estimand. Such data is a typical use case for the Occurrence Data Structure (OCCDS) class. Consequently, it is proposed to organise the intercurrent events data in a dedicated ADICE structure, as a sub-class of the OCCDS class.

This white paper recommends implementing the ADICE structure as a single dedicated ADICE dataset. From a usage and review perspective, it will generally be easier to have all intercurrent events consolidated in a single dataset. However, depending on the needs of the implementers, alternative approaches to a single dedicated ADICE dataset aligned with this framework could be adopted, such as:

- Including the ADICE structure into an existing OCCDS dataset, e.g. a dataset already built to collect events.
- Using several OCCDS datasets to document the intercurrent events.
    - The framework and its documentation features support such cases of multiple intercurrent events documentation datasets. Refer to the *D variable in 6.2.2 Variable-Level Implementation for more details.
- Adding the intercurrent events information directly into ADSL. This approach will not be further discussed in this paper and would only potentially be suitable for the simplest cases of intercurrent events, such as single occurrences of single events.

Dataset(s) implementing the ADICE structure will collect intercurrent events from all applicable sources. That could be events, interventions, or findings domains from SDTM, and some intercurrent events may also be derived (e.g. observation of a findings domain reaching a certain threshold). For more complex cases, intercurrent events may also be sourced from other ADaM datasets.

The OCCDS structure allows the mapping of the original data into a flexible and easily applicable data structure that can be tailored to individual study needs. It is possible to keep source variables from SDTM domains such as source term, source intervention or source coding per ADaM OCCDSIG. Row identifier variables (--SEQ, SRCDOM, SRCSEQ) point to the respective record in the source dataset, which enables developers, validators and reviewers to have the full traceability to the source of an intercurrent event.

Table 1: ADICE Define-XML Metadata

Dataset	Description	Class – Subclass	Structure	Purpose	Keys	Documentation	Location
ADICE[1]	Intercurrent Events Analysis Dataset[1]	OCCURRENCE DATA STRUCTURE – INTERCURRENT EVENTS	One record per subject per intercurrent event	Analysis	STUDYID, USUBJID, ATERM, ASTDT[2]	Presents the consolidated lists of intercurrent events related to the different estimands and the strategy to handle them. Based on [...]	adice.xpt

1. The name and label could be different, and several datasets could be used.
2. Alternative identifiers other than ATERM and ASTDT could be used. See 6.2.2 Variable-Level Implementation.

6.2.1.3 Analysis Datasets Supporting the Estimators

As discussed, analysis datasets should allow analysts to identify datapoints impacted by intercurrent events and trace back to those intercurrent events. It is also useful to identify the records relevant to each estimand and its estimators in a consistent way.

The ADaM estimands implementation framework addresses more specifically the topic of identifying datapoints impacted by intercurrent events in analysis, with options to flag them and to trace back to the impacting intercurrent event. This is achieved using a few new additional variables. Details are provided in section 6.2.2 Variable-Level Implementation.

6.2.2 Variable-Level Implementation

The variables used in the ADaM estimands implementation framework are presented here.

The *ADaM variables lists* in Tables 2, 3 and 4 present the main variables relevant for the estimands framework, grouped according to the three types of datasets presented in section 6.2.1 (Dataset-Level Implementation). It contains a mix of existing ADaMIG/OCCDSIG variables relevant to estimands implementation and a few new variables, alongside explanations of how they could be used to support the estimands framework implementation. The table below is a starting point, and implementers may add any variables deemed necessary to their study, following the ADaMIG.

The variables list will be followed by implementation considerations.

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

- Participant-level variables (principal stratum flags)
- Variables to document intercurrent events and their relationship with estimands
- Variables to document datapoints affected by intercurrent events

A number of variables, especially from the 'Intercurrent event handling strategy' and 'Intercurrent events impacting datapoints' categories here below, use terminologies of the type value versus blank. A non-blank value denotes a strategy applicable to an intercurrent event or a datapoint impacted by an intercurrent event, while a blank value denotes absence of applicable strategy or absence of impact. These variables are all sponsor derived, and the authors envision that for all practical implementation purposes, the sponsor will define rules to decide whether a strategy applies or whether a datapoint is impacted. The authors have not identified a use case where absence of decision would make sense to be documented and therefore have neither presented nor illustrated such case in the terminologies. Should such a use case occur, implementers are free to adjust terminologies as needed to represent the undecidable cases.

Table 2: ADSL Variables List

Variable	Label	Type	Codelist/ Controlled Terms	Core	CDISC Notes
Analysis set flags					
PSyFL	Principal Stratum y Set Flag	Char	YN	Cond	Flags subjects who are part of the principal stratum y, where y is an index of the stratum. It is used when some estimands make use of principal stratum strategies for handling intercurrent events. There could be more than one principal stratum, e.g. different estimands may use a different principal stratum. Required when principal stratum strategy is used.

Table 3: ADICE Structure Variables List

Variable	Label	Type	Codelist/ Controlled Terms	Core	CDISC Notes
Identifiers					
STUDYID	Study Identifier	Char		Req	
USUBJID	Unique Subject Identifier	Char		Req	
Sequence numbers					
ASEQ		Num		Req	Unique record number within a subject. Within a subject, each intercurrent event record is assigned a unique value.
ICEzzGID	Intercurrent Events Grouping zz ID			*Perm*	*Identifier used to group intercurrent events jointly affecting a datapoint. More than one ICEzzGID variable would be needed only in the situation where some intercurrent events could be part of multiple groupings. This variable is reserved for future use not detailed in this white paper.*
Record topic (event)					
*TERM	{Reported Term}	Char		Cond [2]	Original intercurrent event term.
*TRT	{Reported Name of Drug, Med, or Therapy}	Char		Cond [2]	Original intercurrent event name, when the intercurrent event is a treatment.
ATERM	Analysis Term	Char		Cond [2]	Analysis term describing the intercurrent event. The most granular description of the intercurrent event, close or identical to the source term/name of the event. This variable is especially useful when: • There are intercurrent events that are not directly an SDTM-reported event or intervention, e.g. a lab finding above some threshold, an AE that is severe. In such cases, an intercurrent event is derived, e.g. lab test <xxx> above <yyy> threshold, <aeterm> with grade <y>. • In general, when there are multiple sources of intercurrent event from different SDTM domain classes – such as events, interventions, findings, e.g. if occurrence of some AEs or intake of some concomitant medications are intercurrent events – then ATERM is used and could contain either an AE or a medication. When present, it must be filled for all records.
Record start/end date and time					
ASTDT	Analysis Start Date	Num		Cond [4]	Source start date of the intercurrent event in numerical format. One of ASTDT/ASTDTM must be present.
ASTDTM	Analysis Start Datetime	Num		Cond [4]	Source start datetime of the intercurrent event in numerical format. One of ASTDT/ASTDTM must be present.
AENDT	Analysis End Date	Num		Perm	Source end date of the intercurrent event in numerical format. Included if the intercurrent event end date is relevant to assess the impact of the intercurrent event on datapoints.
AENDTM	Analysis End Datetime	Num		Perm	Source end datetime of the intercurrent event in numerical format. Included if the intercurrent event end datetime is relevant to assess the impact of the intercurrent event on datapoints.

Source code and classifications					
*DECOD	Dictionary-Derived Term	Char	*	Perm	Coded term/name of the intercurrent event from the SDTM source dataset.
Source code and classifications					
ADECODy	Analysis Dictionary Derived Term {y}	Char	*	Perm	Coded version of the intercurrent event, at the more granular level needed according to the intercurrent event definition, per protocol/SAP. It is used to present the intercurrent events in a standardised way, related to the intercurrent event definition and policies. Writers of the white paper foresee that typically one such variable will be used in most situations. However, implementers are free to add ones if they have a need to provide different labels to intercurrent events, e.g. different labels for different estimands or tables/listings.
ACATy	Analysis Category {y}	Char	*	Perm	Categorisation of the intercurrent events. Useful when there are different levels of granularity of intercurrent event across estimands, e.g. some estimands may differentiate "Treatment Discontinuation due to Adverse Events" and "Treatment Discontinuation due to Lack of Efficacy", while others may be interested only in "Treatment Discontinuation" in general. In that case, the more granular labelling would go to an ADECODy variable and the less granular, higher-level grouping to an ACATy variable.
Intercurrent event handling strategy					
ESTzz*STP [1]	Estimand zz* planned handling strategy	Char	(ICESTRG) [3]	Req	Documents the planned strategies for handling the intercurrent events related to estimand zz*, as described in the protocol and/or analysis plan. Blank if the intercurrent event is not related to estimand zz*.
ESTzz*STA [1]	Estimand zz* actual handling strategy	Char	(ICESTRG) [3]	Req	Documents the actual strategies for handling the intercurrent events related to estimand zz*. Blank if the intercurrent event is not related to estimand zz* or if the intercurrent event handling strategy is masked by the strategy of another intercurrent event that has a higher precedence. Initially, ESTzz*STA is filled as ESTzz*STP. Then, in a second step, the other intercurrent events for the same estimand are considered, subject by subject, along with their strategy and priority rules. Typically, for a given subject, if an intercurrent event is preceded by another one AND that one has a higher precedence in terms of handling strategy, the handling strategy of that intercurrent event will prevail and mask the strategy of the current intercurrent event. In that case, ESTzz*STA of that event will be set to blank. Note that priority rules are decided and documented by the sponsor.
Traceability					
--SEQ	Sequence Number	Num		Cond [5]	Single domain source of all intercurrent events. One of --SEQ or the pair SRCDOM/SRCSEQ is required to point to source record for the intercurrent event.
SRCDOM	Source Data	Char		Cond [5]	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	Source Sequence Number	Num		Cond [5]	Sequence number of the intercurrent event record in the parent domain. Normally the value of --SEQ or of ASEQ if the parent is another ADaM dataset. One of --SEQ or the pair SRCDOM/SRCSEQ is required to point to source record for the intercurrent event.

Notes:

1. zz*: denotes an estimand number that is used consistently across all datasets (one estimand always gets the same number) relating to the protocol/SAP/ADRG estimands numbering sequence.
2. One of *TERM/*TRT/ATERM must be present and filled for all records as the topic.
   a. One of the variables *TERM/*TRT could be used alone, without ATERM as the topic.
      i. *TERM: when all intercurrent events come from events domains
      ii. *TRT: when all intercurrent events come from interventions domains

b. ATERM could be used as the topic in all situations (for consistency) and must be used when the intercurrent events are based on findings, mix of domain of different classes, involve derivations (e.g. AE with some severity grade). ATERM can be a copy of any of *TERM/*TRT, but also *DECOD, or a derived term.
c. When ATERM is used, *TERM and *TRT may be used as support, and ATERM must be filled for all records. *TERM, *TRT may be missing for some records.

3. ICESTRG is a suggested codelist name to define the data handling strategy names. Such a terminology is not yet part of the official CDISC Terminology. It would include values such as “TREATMENT POLICY”, “HYPOTHETICAL”, “COMPOSITE”, “WHILE ON TREATMENT” and “PRINCIPAL STRATUM” mentioned in the ICH E9(R1). That terminology would be extensible. As explained in the ICH E9(R1), that list is not exhaustive and other strategies could be defined.
4. At least one variable documenting the start of the intercurrent event must be provided.
5. Traceability variables must be provided, either --SEQ or SRCDOM and SRCVAR. --SEQ may be used when the source of intercurrent events is a single SDTM domain. In other situations, SRCDOM and SRCVAR will be used.

Table 4: Analysis Datasets Supporting the Estimators Variables List

Intercurrent events impacting on datapoints – per estimand					
ICEzz*S [1]	Impacting ICE for Est. zz* Seq. Num.	Num		Perm	Point to the intercurrent event(s) impacting on the datapoint for estimand zz* estimations. It depends on the priority rules when several intercurrent events can impact on the same datapoint. The variable is filled with the identifier of the intercurrent event impacting on the datapoint for estimations; that is typically the value of ASEQ from the intercurrent event record in the source intercurrent events dataset. It is left blank when the datapoint is not impacted by any intercurrent event. This variable may also depend on the strategy defined for each intercurrent event that can impact on estimand zz*, per implementer needs/decision. Refer to the implementation consideration section for more details on documenting the impact of intercurrent events on datapoints.
ICEzz*D [1]	Impacting ICE for Est. zz* Src. Dom.	Char		Cond	Source dataset holding the intercurrent event(s) referred to by ICEzz*S. Must be present and filled only if there is more than one intercurrent event dataset referred to from the analysis dataset. When there is only one source dataset holding the intercurrent event, that dataset should be mentioned in the Define-XML and ADRG; if nothing is specified anywhere, that dataset is assumed to be ADICE by default.
ICEzz*V [1]	Impacting ICE for Est. zz* Src. Var.	Char		Cond	Source variable holding the intercurrent event(s) identifier pointed to by ICEzz*S. Must be present and filled only if there is more than one identifier variable referred to from the analysis dataset. When there is only one identifier variable for the intercurrent events, that identifier variable should be mentioned in the Define-XML and ADRG; if nothing is specified anywhere, that variable is assumed to be ASEQ by default.
ICEzz*F [1]	Impacting ICE for Est. zz* Flag	Char	(Y)	Perm	Flag if the datapoint is impacted by an intercurrent event related to estimand zz*. It depends on the strategy defined for each intercurrent event that can impact estimand zz* and on the priority rules when several intercurrent events can impact on the same datapoint. The variable is filled with "Y" if there is at least one intercurrent event impacting on the datapoint, taking into consideration the strategies and priority rules; else left blank when the datapoint is not impacted by any intercurrent event.
ICEzz*N [1]	Impacting ICE for Est. zz* Num. Flag	Num	(1)	Perm	Numerical version of ICEz*F.
Intercurrent events impacting on datapoints – per intercurrent event categorisation modalities					

ICCyS [2]	Impacting ICE Cat. Val. y Seq. Num.	Num		Perm	Point to the intercurrent event(s) impacting on the datapoint, considering only intercurrent events that are labelled by the y^{th} modality of the labelling variable. In practice, one naming/categorisation variable is selected in the intercurrent events dataset (e.g. ADECOD1 or ACAT1 from ADICE). Based on the selected naming/categorisation variable from the intercurrent events dataset, one ICCyS variable is added to the analysis dataset for each modality of that naming/categorisation variable – the index y represents the different modalities of that naming/categorisation variable. As an example, ADICE.ADECOD1 is used as the labelling variable. It has three values in ADICE: "Event A", "Event B", "Event C". Then the three variables (ICC1S, ICC2S, ICC3S) will be created: ICC1S relating to intercurrent events labelled as "Event A", ICC2S relating to intercurrent events labelled as "Event B", ICC3S relating to intercurrent events labelled as "Event C". The variable ICCyS is filled by considering only the intercurrent events labelled by the y^{th} modality of the labelling variable in the intercurrent events dataset. It is filled with the identifier of the intercurrent event impacting on the datapoint (the identifier is typically the value of ASEQ from the intercurrent event record in the intercurrent events dataset); it is left blank when the datapoint is not impacted by any intercurrent event labelled by the y^{th} modality of the labelling variable. Refer to the implementation consideration section for more details on documenting the impact of intercurrent events on datapoints. Based on the example above, ICC1S will only consider impacting on intercurrent events having ADICE.ADECOD1 = "Event A". This variable will normally not depend on strategies associated with intercurrent events considering that it is independent of specific estimands to which strategies are related. If used, there must be one ICCyS variable per modality of the labelling variable. The same labelling variable is used for the ICCyS and ICCyF variables, and "y" indexes are attributed in the same way.
ICCDOM	Impacting ICE by Cat. Val. Src. Dom.	Char		Cond	Source dataset holding the intercurrent event(s) referred to by the ICCyS variables. Must be present and filled only if there is more than one intercurrent event dataset referred to from the analysis dataset. When there is only one source dataset holding the intercurrent events, that dataset should be mentioned in the Define-XML and ADRG; if nothing is specified anywhere, that dataset is assumed to be ADICE by default. By design, a single ICCDOM variable is used for all ICCyS variables.
ICCVAR	Impacting ICE by Cat. Val.Src. Var.	Char		Cond	Source variable holding the intercurrent event(s) identifier pointed to by the ICCyS variables. Must be present and filled only if there is more than one identifier variable referred to from the analysis dataset. When there is only one identifier variable for the intercurrent events, that identifier variable should be mentioned in the Define-XML and ADRG; if nothing is specified anywhere, that variable is assumed to be ASEQ by default. By design, a single ICCVAR variable is used for all ICCyS variables.
ICCyF [2]	Impacting ICE Cat. Val. Y Flag	Char	(Y)	Per	Flags if the datapoint is impacted by an intercurrent event labelled by the y^{th} modality of the labelling variable. Set to "Y" if the datapoint is impacted by such an intercurrent event, else leave blank. See ICCyS for details on assigning the y index to create the set of ICCyF variables. This variable will normally not depend on strategies associated with intercurrent events considering that it is independent of specific estimands to which strategies are related. If used, there must be one ICCyF variable per modality of the labelling variable. The same labelling variable is used for the ICCyS and ICCyF variables, and "y" indexes are attributed in the same way.
ICCyN [2]	Impacting ICE Cat. Val. Y Num. Flag	Num	(1)	Perm	Numerical version of ICCyF.

Intercurrent events impacting on datapoints – per estimand, per intercurrent event categorisation value					
ICCyEzz*S [1, 2]	Imp. ICE Cat. Val. y for Est. zz* Seq.	Num		Perm	Point to the intercurrent event(s) impacting on the datapoint, considering only intercurrent events related to estimand zz* and labelled by the y[th] modality of the labelling variable. These variables work like the ICCyS variables. The difference is that the labelling variable need not be the same for all estimands as for the ICCyS variable. The labelling variable can be selected independently for each estimand zz*. Intercurrent events that must be considered are those that are related to estimand zz* and are labelled by the y[th] modality of the labelling variable selected for estimand zz*. This variable may also depend on the strategy defined for each intercurrent event that can impact on estimand zz*, per implementer needs/decision. See ICCyS for more details. For a given estimand zz*: if used, there must be one ICCyEzz*S variable per modality of the labelling variable for a given estimand zz*. The same labelling variable is used for the ICCyEzz*S and ICCyEzz*F variables, and "y" indexes are attributed in the same way.
ICCEzz*D [1]	Imp. ICE by Cat. Val. For Est. zz* Dom.	Char		Cond	Source dataset holding the intercurrent event(s) referred to by the ICCyEzz*S variables. Must be present and filled only if there is more than one intercurrent event dataset referred to from the analysis dataset. When there is only one source dataset holding the intercurrent event, that dataset should be mentioned in the Define-XML and the ADRG; if nothing is specified anywhere, that dataset is assumed to be ADICE by default. By design, a single ICCEzz*D variable is used for all ICCyEzz*S variables.
ICCEzz*V [1]	Imp. ICE by Cat. Val. For Est. zz* Var.	Char		Cond	Source variable holding the intercurrent event(s) identifier pointed to by the ICCyEzz*S variables. Must be present and filled only if there is more than one identifier variable referred to from the analysis dataset. When there is only one identifier variable for the intercurrent events, that identifier variable should be mentioned in the Define-XML and the ADRG; if nothing is specified anywhere, that variable is assumed to be ASEQ by default. By design, a single ICCEzz*V variable is used for all ICCyEzz*S variables.
ICCyEzz*F [1, 2]	Imp. ICE Cat. Val. Y for Est. zz* Flag	Char	(Y)	Perm	Flag if the datapoint is impacted by an intercurrent event labelled by the y[th] modality of the labelling variable, considering only intercurrent events related to estimand zz*. Set to "Y" if the datapoint is impacted by such an intercurrent event, else leave blank. See ICCyEzz*S for details on values of the labelling variable on how to create the set of ICCyEzz*F variables. This variable may also depend on the strategy defined for each intercurrent event that can impact on estimand zz*, per implementer needs/decision. For a given estimand zz*: if used, there must be one ICCyEzz*F variable per modality of the labelling variable. The same labelling variable is used for the ICCyEzz*S and ICCyEzz*F variables, and "y" indexes are attributed in the same way.
ICCyEzz*N [1, 2]	Imp. ICE Cat. Val. y for Est. zz* N.Flag	Num	(1)	Perm	Numerical version of ICCyEzz*F.
Analysis variables					
ANLzzFL	Analysis Flag {zz}	Char	Y	Cond	Analysis variable per ADaMIG. Per ADaMIG rule, it is related to analyses (i.e. estimators). It is optional, only required if extra selection of records is needed for some analyses that cannot be performed with existing variables. Note that the zz is used as usual here and related to analysis needs. It is not tied to the estimand number. The zz index of the analysis flag has its usual meaning; that is, analysis related. It is not tied to the estimands numbering. There could be one zz value per estimator, or the variable could be shared across several estimators, or an analysis flag might not be used at all. Eventually, the record selection criteria for each estimator will be detailed in the ARM and/or ADRG.

Notes:

1. zz*: denotes an estimand number that is used consistently across all datasets (one estimand always gets the same number) relating to the protocol/SAP/ADRG estimands numbering sequence.
2. y represents a modality of a selected variable categorising the intercurrent events; there are as many ICCy* variables as there are modalities of the selected labelling variable. The implementer is free to choose a suitable variable to label the intercurrent events.

6.2.2.1 Implementation Considerations

6.2.2.1.1 Datapoints Impacted by an Intercurrent Event

The framework helps identify datapoints impacted by an intercurrent event. 'Impacted' is used here in a very general way, meaning that the interpretation and consequently the possible usage of a datapoint in an analysis is influenced by the presence of an intercurrent event.

The framework will go as far as helping users to document if a datapoint is impacted by an intercurrent event, which event, and which data handling strategy applies.

The framework offers a range of variables for documenting impacted datapoints and traceability back to the impacting intercurrent event(s). Which variables to use depends on the needs of the implementer in terms of traceability/documentation and of further processing to support analysis.

What does 'impact' mean for filling traceability variables and flags?

The word 'impact' is used in the most general way in the framework, leaving implementers some flexibility to further specify the impact concept according to their needs, with a reminder to document in Define-XML/ADRG the exact definition they have adopted. The general notion is that an intercurrent event impacts on a datapoint if it has the potential to affect its interpretation or existence. The concept of impact, especially to assess which datapoints are potentially impacted, goes beyond the simple notion of co-occurrence and may depend on the trial design, treatment, datapoint and intercurrent event definition. Implementers may also find useful for some variables such as impact flags to document the *actual impact* of an intercurrent event on a datapoint – 'actual impact' meaning to decide based on strategies associated with the estimand and intercurrent event if the datapoint can be used in the analyses or should be replaced/removed. As an example, a strategy like 'Treatment policy' means that the datapoint will be used as is, even if potentially impacted by the occurrence of an intercurrent event, which means that the intercurrent event has no actual impact on the datapoint. A strategy like 'Hypothetical' means that the datapoint impacted by an intercurrent event will be replaced/removed from analyses, which means that there is an actual impact on the datapoint.

Some general indication to help selecting the proper variables:

Choosing the flag and/or traceability variables

- The impact traceability variables (ICCyS/N, ICCyEzz*S, ICEzz*S) are most useful for relating datapoints to impacting on intercurrent events, especially potential impacts (see topic before). These allow for linking a datapoint back to the intercurrent event in ADICE, and strategies, and can serve as an intermediate step to help decide and document the actual impact based on the data handling strategies.
- The impact flag variables (ICCyF/N, ICCyEzz*F/N, ICEzz*F/N) are useful to identify datapoints impacted by intercurrent events. Focus is on the impact aspect of the intercurrent event on the datapoint. As explained above, the exact notion of impact depends on sponsor needs/decision and will typically involve some form of actual impact. Such flags are most useful as support for further operations, like the selection of datapoints to include in analyses or to replace by imputed values.
- Choosing between the three sets of impact variables:
    - Per intercurrent event categorisation modalities (ICCyS/F): useful to document all intercurrent events impacting on a datapoint, regardless of the estimands, strategies and priorities. This is because there is one variable per type of intercurrent event (i.e. per modality of the intercurrent event categorisation variable) across all estimands. These variables are most useful when the same intercurrent events apply to all estimands. These variables, being per intercurrent event type, can document impacts from different categories in parallel and need not consider priority rules amongst intercurrent event types.
    - Per estimand, per intercurrent event categorisation modalities (ICCyEzz*S/F): these variables work in the same way as (ICCyS/F) but are specific to an estimand and will be most useful when the intercurrent events differ per estimand, because this set of variables is indexed per estimand and can use different labelling variables/rules per estimand. These variables, especially the flags, may also consider the associated strategies to document the actual impact on datapoints.
    - Per estimand (ICEzz*S/F): these variables are useful when there is a need to document one intercurrent event impacting on a datapoint for a given estimand, considering priority rules. That is, the intercurrent event that will drive the data handling strategy for the datapoint for a given estimand. These variables, especially the flags, would typically also consider the associated strategies to document the actual impact on datapoints.

6.2.2.1.2 Selecting Records for Analysis

While the framework helps identify and document datapoints impacted by intercurrent events, it will not drive decisions on the fate of these datapoints and the related documentation. In other words, it will not tell which datapoint to keep, remove or replace for the analyses and it does not provide variables such as selections or actions flags. That part is left to the implementers, who can rely on all mechanisms offered by the ADaM IG.

However, some of the variables added in the framework, especially the intercurrent events impacting on flags – such as ICCyF, ICCyEzzF, ICEzzF – may offer new options to the implementers to help select records relevant for the analysis, or identify those that are being dropped/replaced.

6.2.2.1.3 Imputation

Imputation is used here to describe the modelling technique by which variables/variable outcomes are imputed/created based on a statistical model. Multiple imputation can be used for the imputation of missing data (please see missing data definition in the glossary), specifically replacing missing values with plausible values [Li et al., 2015]. Multiple imputation can also be used to impute datapoints (possibly) impacted by intercurrent events, when the intercurrent events are addressed with a hypothetical strategy (where the original value post-intercurrent event, even if available, is replaced by another imputed one under the hypothetical scenario envisaged, and, if not available, then subsequent (missing) values are imputed also to reflect the hypothetical scenario envisaged). Despite similar techniques and naming, these two imputation situations are different, and this should be carefully considered by the reader, also in conjunction with the imputation of outcome values to implement a composite variable strategy in a stochastic fashion (please see composite variable strategy in E9(R1)).

6.3 Analysis Data Reviewer's Guide (ADRG)

Updates to the ADRG [PHUSE ADRG, 2019] to offer better support to the estimands framework are presented here. Only sections relevant to the estimands implementation will be discussed. This is based on the latest ADRG version published by PHUSE at the time of writing this white paper. Similar to CDISC controlled terminology, these updates have been proposed to the PHUSE Management of ODS Regulatory Referenced Deliverables Project, to be considered in a future version of the template. The sections will show how the existing ADRG document can be updated to provide additional explanations related to the estimands implementation in ADaM and will also introduce a new 'Estimands and Estimators' section to the ADRG. Each section will be presented with an introductory explanation followed by completion instructions, as applicable, provided within square brackets: [...].

6.3.1. Section 3.1 Estimands and Estimators

This is a new section proposed for addition to the ADRG document template. The purpose of this section is to group in a single location key information related to estimands and estimators' implementation. This is a central piece of documentation to link estimands and estimators' definitions in the protocol and SAP with their implementation in the analyses datasets and results. This section is presented as a table.

Please note that some of the information presented in this section may exist in Analysis Results Metadata. However, Analysis Results Metadata is not systematically submitted/requested in regulatory submissions and does not fulfil the same purpose or contain the entire set of information related to estimands implementations. The intent of this section is to gather all relevant information related to estimands implementation in a single location that serves as a convenient reference to consult.

3. Analysis Considerations Related to Multiple Analysis Datasets

3.1 Estimands and Estimators

[To complete the table:

Add one section per estimand. Sections are organised to follow estimands order and numbering in the protocol/SAP; the <X: estimand> represents the estimand numbering and name, as it appears in the protocol/SAP. The estimand section contains relevant information at the estimand level, which is valid across all estimators of that estimand.

As necessary, within each estimand section, add a sub-section per estimator. Sub-section ordering and name follow estimators ordering and name as stated in the SAP; the <X.y: estimator> represents the estimand ID, estimator ID and name, starting with <X>.0: main for the main estimator and following with the sensitivity analyses estimators. The estimator sub-sections contain only information specific to each estimator and can either complement or supersede information present in the parent estimand section. Any information related to the estimand and valid across all estimators will be reported in the estimand section, while information specific to an estimator will be reported in the estimator specific sub-section.

The location of the information items in the table below may change between the estimand sections and the estimator or sub-sections, depending on the study specificities. E.g. if the analysis dataset is different for some estimators, it may appear in the respective estimator's sub-sections.

Case of similar estimands: in some situations, studies may have several estimands that are mostly similar except for key elements like target variables. In those situations, some shortcuts using references are possible to avoid repeats. E.g. if estimands 1 to 5 share the exact same intercurrent events, when completing the 'Intercurrent Event dataset(s) and variables' record in estimands sections 2 to 5, you may simply state: 'Same as estimand 1'.]

Estimand/Estimator ID	Descriptor	Description
<X: name>	Protocol	Protocol reference: <section (page) in protocol where estimand is described>
	SAP	SAP reference: <section (page) in SAP where estimand is described>
	Analysis dataset	Dataset name: <dataset supporting the analyses for the estimand> Intercurrent event(s) impact variable(s): <variable for identification of endpoints impacted by the intercurrent event(s): ICCyS/ICCyEzzS/ICEzzS ...> Treatment modalities: <list of modalities of the treatment variable being compared or ALL> Endpoint variable: <variable being analysed> Timing variable: <timing measurement, in case of repeated measures over time> Covariable(s): <co-variables relevant to the analyses if any> Additional dataset: <details if extra datasets like ADSL need to be merged with the analysis dataset>
	Analysis records	Analysis records selection clause: <where clause in terms of analysis dataset/ ADSL participant-level variables>
	Population-level summary	Summary statistic: <name of the summary statistic, reference to SAP section/ relevant for details>
	Intercurrent event dataset(s) and variables	Dataset(s) name: <dataset(s) containing the intercurrent event(s) relevant to the estimand> Intercurrent event source name variable: <variable containing the intercurrent event term. This is the more granular description of the intercurrent event(s), as it would appear in the raw data or based upon the derivation rule (for derived intercurrent events). Intercurrent event coded name/group variable and modalities: <variable containing the intercurrent event coded name and, if needed, group. This could hold the coded name of the intercurrent event or a grouping relevant to the estimator> Estimand strategy variable: <variable describing the intercurrent handling strategy for this estimand> Strategies: <provide the strategy considered for this estimand for each intercurrent event modality>
<X.0: main>	Protocol	Protocol reference: <section (page) in protocol where the estimator is described>
	SAP	SAP reference: <section (page) in SAP where the estimator is described>
	Analysis record set	Analysis records: <criteria to select records that are part of the analysis>
	Analysis description	Analysis method: <method expressed in terms of analysis dataset variables, to make sure all datasets and variables involved in the analysis are identified> Analysis details: <provide the analysis details. It could be a reference to the analysis results metadata or a similar document. Details of the analysis procedure could be provided here in absence of other dedicated documents>
	Results	Table: <table ID (page) in the CSR where the estimator results are presented>
<X.y: sensitivity y>		
...		<fill for each estimand/estimator>

6.3.2. Section 3.2 Core Variables

If participant-level estimands selection flags were used, they would be listed as part of the core variables in this section.

3.2 Core Variables

Core variables are those that are represented across all/most analysis datasets.

[Principal stratum analysis set(s) PSyFL would be listed if used in the study]

Variable Name	Variable Description
STUDYID	Study identifier used for this protocol
USUBJID	Unique subject identifier
.....	.....
PSyFL	*Principal Stratum y Set Flag*

6.3.3. Section 3.6 Imputation/Derivation Methods

Complete this section if any imputation rules may affect the estimators.

3.6 Imputation/Derivation Methods

[Extra topics that could be added regarding the estimands framework implementation:

- Discussion on the rationale for the selection of intercurrent events impact traceability variables/flags, or both, in analysis datasets (*S and/or *F/N variables).
- Discussion on type of intercurrent events impact traceability variables/flags used in analysis datasets (ICCY*, ICCyEzz*, ICEzz*) and on specific rules for computing those variables = when applicable across multiple datasets.
- Description of exclusion/imputation/derivation methods used to support estimands and intercurrent events related to data handling strategies in relation to intended analyses (e.g. hypothetical strategy) that are used in multiple analysis datasets. Include priority rules for assessing impact of intercurrent events.]

6.3.4. Section 4.2 Data Dependencies

In this section present dependencies of the intercurrent event dataset(s) on their respective input datasets and add the intercurrent event dataset(s) to the dependencies of other analysis datasets where applicable.

4. Analysis Data Creation and Processing Issues

4. **Data Dependencies**

[Dependency table or flowchart diagram is displayed here and includes applicable dependencies of ADSL, intercurrent events dataset(s), e.g. ADICE, and all analysis datasets.]

6.3.5. Section 5.1 Overview

This section contains leading questions, similar to those proposed in the cSDRG document, to draw attention to the estimands implementation. It is recognised to be a summary of key information provided in the new section 3.1, and the information provided should be consistent.

5. Analysis Dataset Descriptions

5.1 Overview

[The following questions, which are extracts (i.e. repeat information) from the table in section 3.1 Estimands and Estimators, would be added.]

• Were there any analysis datasets created to support the ICH (E9)R1 estimands framework?

<Yes/No> [If yes, provide additional details by answering the following questions.]

1. What dataset(s) are used for storing the intercurrent events?
2. What datasets and variables are used to support estimands analyses?
3. Is there any additional information regarding implementation of the estimands framework?
   [You may add a sentence like: Please refer to section 3.1 for more details.]

6.3.6. Section 5.2 Analysis Datasets

This section should be updated to include the intercurrent events dataset(s). Add a sub-section for each intercurrent event dataset by providing relevant information on the traceability, handling strategy and imputation dates as necessary. The ADSL sub-section could be updated if participant-level estimands selection flags were used. And, finally, sections regarding the analysis datasets supporting the estimands-related analyses could be updated to describe estimands' relevant variables such as estimands records selection flags and intercurrent events impact variables. This section and sub-section will be used to provide any additional information that was not provided in overview section 3.1 or in the Define-XML, typically with more detailed explanations.

5.2 Analysis Datasets

Dataset Dataset Label	Class	Efficacy (E)/ Safety (S)/ Immunogenicity (I)	Baseline or other subject characteristics	PK/PD	Primary Objective	Structure
ADSL Subject-Level Analysis Dataset	ADSL		X			One observation per subject
[ADICE] *[Intercurrent Events Analysis Dataset]*	*OCCDS*	*E/S*		*[X]*	*[X]*	*One observation per subject per intercurrent event*
.....	.....					.....
[ADxxxx] *[Analysis Dataset Label]*	*[BDS/ OCCDS]*	*E/S*	*[X]*	*[X]*	*[X]*	*One observation per subject [per ...]*

5.2.1 ADSL – Subject-Level Analysis Dataset

The analysis set flag variables are defined in ADSL and copied together with the variables listed in section 3.2 into other analysis datasets as needed. [More details on the construction of subject-level estimands related variables (PSyFL) could be provided here. Typically, details that would not fit in the overview section 3.1 or in the Define-XML.]

5.2.2 ADICE – Intercurrent Events Analysis Dataset [would be adjusted if more than one dataset was used or if the name was different]

The ADICE dataset contains one observation per subject per intercurrent event. It is derived from [provide source datasets]. This dataset consolidates all the intercurrent events information.

[A more detailed explanation of ADICE could be provided here to complement the Define-XML if necessary. E.g. the source of the intercurrent events and, if some are derived, the derivation method may be described in this section.]

5.2.3 ADxxx – <label>

[A more detailed explanation of the analysis datasets and of relevant estimands implementation variables could be provided here to complement the Define-XML if necessary. E.g. a more detailed description could be provided here on topics such as:

- *Which sets of intercurrent event variables have been selected and why (flag and/or traceability, per estimand/per modality/per estimand per modality).*
- *Rules to decide which datapoints are impacted by which intercurrent events, including priority rules when several intercurrent events impact on a datapoint.*
- *How the intercurrent events impact is translated into the data, in relation to the data handling strategy and supported analyses (exclusion, replacement, computations of composite datapoints).*

7. Summary and Conclusion

Section 5 (Data Collection and Tabulation) explores the crucial aspects of data collection and tabulation in the context of clinical trials, specifically focusing on intercurrent events related to treatment discontinuation, interruption and additional/alternative treatments. The need for improved accuracy for the underlying reasons of intercurrent events in data collection is emphasised and recommendations for CRF design are provided. It is important to note that depending on the planned estimates it may be critical to continue to measure

outcome after any individual intercurrent event. There is no impact on SDTM datasets in the estimands framework, but the associated SDTM domains should be mapped in accordance with the SDTMIG and follow conformance rules. The estimands framework affects all levels of documentation and one such document is the cSDRG, which provides traceability. The cSDRG is recommended to describe intercurrent events associated with the clinical question of interest, as well as how intercurrent events are collected, and how they are mapped to corresponding SDTM domains and variables.

Section 6 (Data Analysis) gets to the heart of estimands implementation. Following general considerations, the ADaM estimands implementation framework is outlined at the dataset and variable levels. It cannot be emphasised enough that the ADaM estimands implementation framework builds upon the ADaMIG and OCCDSIG. This enables all existing features described in the IGs, while an additional dataset and variables have been proposed to complement the current IGs and to offer specific support to the documentation of estimands. A new ADICE dataset is proposed to organise the intercurrent events data in a dedicated structure, as a sub-class of the OCCDS class. Traceability and documentation are essential principles for ADaM datasets, so variables supporting traceability are proposed along with updates to the ADRG for estimands implementation framework coverage.

The illustrative example shows that the E9(R1) framework can be implemented at CDISC level. The described principles can guide and facilitate estimands implementation using CDASH, SDTM and ADaM. It is helpful and clarifying to use estimands across all levels of clinical research, from protocol to estimation, from eCRF to ADaM, to ensure harmonisation between statisticians, clinicians and statistical programmers, beyond the envisaged stakeholders listed in the addendum. The project team plans to investigate further deliverables that will assist implementers of estimands through more complex examples and the relationship of estimands to other data-related clinical trial conduct activities (e.g. Risk- Based Monitoring).

8. Disclaimer

The opinions expressed in this document are those of the authors and should not be construed to represent the opinions of PHUSE members, respective companies/organisations or regulators' views or policies. The content in this document should not be interpreted as a data standard and/or information required by regulatory authorities.

9. References

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