{2023-NOV-15}

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

Revision History

Version	Date	Summary
1.0	2023-11-15	Initial Version

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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."*. While 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, it does not provide recommendations for the E9(R1) implementation at a data standards level. Furthermore, the scientific community of trialists, especially statisticians, from pharma industry and Regulatory Agencies have been extremely active in recent years in the dimension of understanding the meaning of estimands, how to formulate clinical questions and build estimand constructs, what estimands currently exist, how the estimands framework could be used to account for COVID-19 pandemic possible impact on trials run during the pandemic, 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 within 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 Reviewers 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].
- 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 within an individual clinical study

3: Definitions:

3.1Acronyms 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
CRF	Case Report Form
CT	Controlled Terminology
ICH	International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
EIWG	Estimands Implementation Working Group
OCCDS	Occurrence Data Structure
SDTM	Study Data Tabulation Model
SDTMIG	Study Data Tabulation Model Implementation Guide

3.2 Glossary

Term	Definition*
Estimand	A precise description of the treatment effect reflecting the clinical question posed by a given clinical trial objective. It summarizes at a population level what the outcomes would be in the same patients under different treatment conditions being compared.
Estimate	A numerical value computed by an estimator.
Estimator	A method of analysis to compute an estimate of the estimand using clinical trial data.
Intercurrent Events	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	Data that would be meaningful for the analysis of a given estimand but were not collected. They should be distinguished from data that do not exist or data that are not considered meaningful because of an intercurrent event.
Treatment Policy Strategy	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 or not the Intercurrent event occurs.
Hypothetical Strategy	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	An intercurrent event is considered in itself to be informative about the patient's outcome and is therefore incorporated into the definition of the variable.
While On Treatment Strategy	Response to treatment prior to the occurrence of the intercurrent event is of interest.
Principal Stratum Strategy	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	Classification of subjects according to the potential occurrence of an

Stratification	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(R1).

4: Context:

ICH E9 - Statistical Principles for Clinical Trials [ICH E9, 1998] was finalized 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 harmonize 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 complexity, often driven by more details and (much)/ more 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, considering consistent implementation practices, and analysing to what extent the implementation is supported by and/or may impact the existing data standards. This white paper has been initiated to address those gaps.

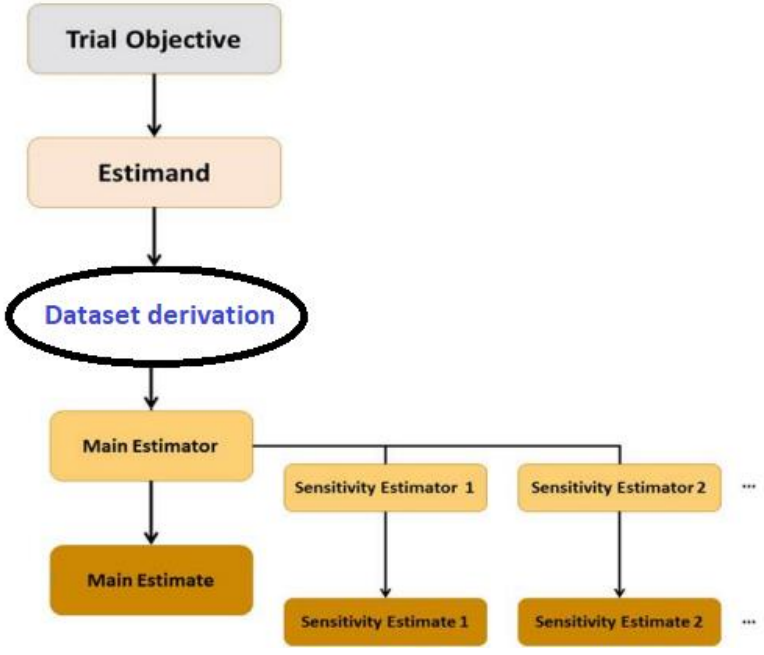

Figure 1: Aligning target of estimation, method of estimation, and sensitivity analysis, for a given trial objective

Figure 2 illustrates the potential impacts studied and mapped for data collection, tabulation, and

analysis, with a summary of these impacts. The estimands framework will affect all levels of documentation. The flow is organized according to the logical documentation hierarchy, from the perspective of the reviewer, rather than a sequential generation order.

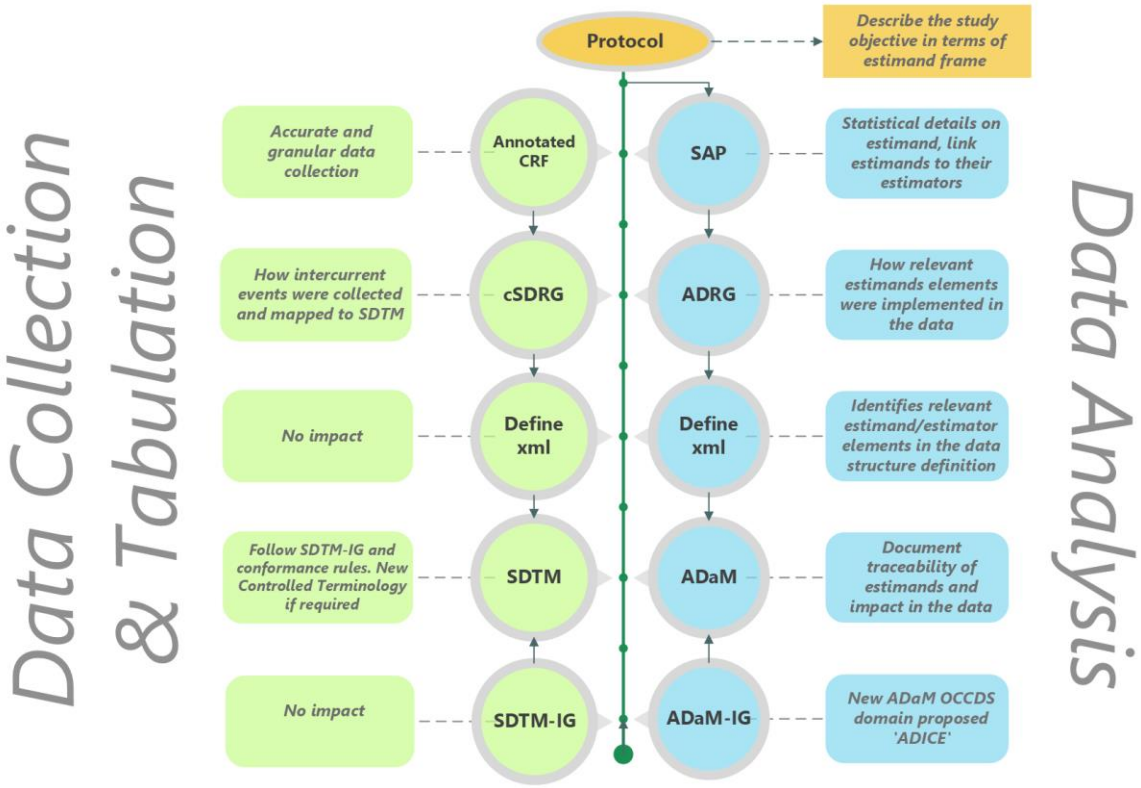

Figure 2: Documentation to Data. The flow is organized according to the logical documentation hierarchy, from the perspective of the reviewer, rather than a sequential generation order.

5: Data Collection & Tabulation:

The most frequently observed intercurrent events during clinical trials are direct consequences of the treatment itself such as treatment discontinuation or interruption, the use of additional or alternative treatments like 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., 2021]. However, 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. In this section, the intercurrent events related to treatment deviations and additional/alternative treatments will be the main focus. Death, which is explicitly captured in the Death Details and Disposition CRF without ambiguity, will not be addressed.

The estimands framework is not expected to impact 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 provided in the Appendix illustrate commonly used approaches and recommendations for collecting and mapping intercurrent events. 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 that prevents the collection of underlying reasons. Recently, Qu et al reviewed the reasons for treatment discontinuations for 9 phase 2 and 3 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, etc.

Based on this research, a list of underlying reasons for early treatment discontinuation, which is grouped into eight primary categories, is recommended. It is recommended to NOT include those that are not actual reasons for early discontinuations, such as "SUBJECT WITHDRAWAL", as well as reasons that lack specificity, such as "TECHNICAL PROBLEMS". In addition, it is not recommended to include "OTHER" and "If 'OTHER', please specify," as they are ambiguous and make it difficult to accurately summarize the actual underlying causes. The eight primary categories include:

- DEATH
- ADVERSE EVENT
- PREGNANCY
- LACK OF EFFICACY
- SUFFICIENT EFFICACY
- PROTOCOL DEVIATION
- LOGISTICAL PROBLEM
- LOST TO FOLLOW UP

To improve the accuracy and specificity of data collection, two primary categories, "PROTOCOL

DEVIATION" and "LOGISTICAL PROBLEM", have been further broken down into granular sub-categories.

Disposition CRF Example

Document the subject's status for trial period. If the subject discontinued treatment prematurely, record the primary reason for discontinuation.	What was the subject's status? **DS.DSDECOD** **DS.DSTERM**	○ **COMPLETED** ○ **DEATH** ○ **ADVERSE EVENT. List the adverse event ID:** **_____** ○ **PREGNANCY** ○ **LACK OF EFFICACY** ○ **SUFFICIENT EFFICACY** ○ **PROTOCOL DEVIATION** ▪ DID NOT MEET STUDY ELIGIBILITY CRITERIA AT ENROLLMENT ▪ TOOK PROTOCOL PROHIBITED CONCOMITANT MEDS ▪ NONCOMPLIANCE TO STUDY PROCEDURES ▪ NONCOMPLIANCE TO STUDY INTERVENTION ○ **LOGISTICAL PROBLEM** ▪ RELOCATION ▪ SCHEDULE CONFLICTS OR DIFFICULTY TRAVELING TO SITE ▪ PERSONAL/FAMILY REASONS NOT RELATED TO EFFICACY OR SAFETY OF THE STUDY DRUG/DEVICE ▪ UNSATISFIED WITH STUDY PROCEDURES ▪ UNSATISFIED WITH STUDY DRUG DELIVERY DEVICES/METHODS ▪ FEAR OF NEW OR RECURRENT ADVERSE EVENTS ▪ STUDY TERMINATION OR SITE CLOSURE ▪ CLINICAL TRIAL MATERIAL QUALITY ISSUE OR SHORTAGE ▪ GEOPOLITICAL LOGISTICAL RESTRICTIONS ▪ OPERATIONAL ERROR ▪ BLIND BROKEN ○ **LOST TO FOLLOW-UP**

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 main 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 are following 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

	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

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.

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 = "REASSPEC" and SUPPEC.QLABEL = "Reason Specify"**	○ **ADVERSE EVENT**. List the adverse event ID: _____ ○ **SUFFICIENT EFFICACY** ○ **PREGNANCY** ○ **LOGISTICAL PROBLEM** • RELOCATION • SCHEDULE CONFLICTS OR DIFFICULTY TRAVELING TO SITE • PERSONAL/FAMILY REASONS NOT RELATED TO EFFICACY OR SAFETY OF THE STUDY DRUG/DEVICE • UNSATISFIED WITH STUDY PROCEDURES • UNSATISFIED WITH STUDY DRUG DELIVERY DEVICES/METHODS • FEAR OF NEW OR RECURRENT ADVERSE EVENTS • STUDY TERMINATION OR SITE CLOSURE • CLINICAL TRIAL MATERIAL QUALITY ISSUE OR SHORTAGE • GEOPOLITICAL LOGISTICAL RESTRICTIONS • OPERATIONAL ERROR
Record date and time when treatment was suspended.	Start Date **EC.ECSTDTC**	
	Start Time **EC.ECSTDTC**	
Record date and	Stop Date	

time when treatment was resumed.	EC.ECENDTC	
	Stop Time EC.ECENDTC	

EC Example

Below is an example of a double-blind study where subjects take two tablets every day for a duration of 12 months. Subject ABC2001 missed taking their study medication for three days because of a personal reason not related to study treatment. The reason for not taking study medication, LOGISTICAL PROBLEM, is mapped to variable ECREASOC, and ECOCCUR is marked as "N".

ec.xpt

	STUDYID	DOMAIN	USUBJID	ECSEQ	ECLNKID	ECTRT	ECPRESP	ECOCCUR	ECREASOC	ECDOSE	ECDOSU	ECDOSFRQ	EPOCH	ECSTDTC	ECENDTC
1	ABC	EC	ABC2001	1	A2-20110114	BOTTLE A	Y	Y		2	TABLET	QD	TREATMENT	2011-01-14	2011-01-23
2	ABC	EC	ABC2001	2	A0-20110124	BOTTLE A	Y	N	LOGISTICAL PROBLEM	0	TABLET	QD	TREATMENT	2011-01-24	2011-01-26
3	ABC	EC	ABC2001	3	A2-20110125	BOTTLE A	Y	Y		2	TABLET	QD	TREATMENT	2011-01-27	2011-01-31

The specific reason for treatment interruption for subject ABC2001 is presented as a supplemental qualifier.

suppec.xpt

	STUDYID	RDOMAIN	USUBJID	IDVAR	IDVARVAL	QNAM	QLABEL	QVAL	QORIG
1	ABC	EC	ABC2001	ECSEQ	2	REASSPEC	Reason Specify	PERSONAL/FAMILY REASONS NOT RELATED TO EFFICACY OR SAFETY OF THE STUDY DRUG/DEVICE	CRF

5.1.3 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, reason for the interruption, and the dose administered at the time of interruption should be collected. If the infusion is resumed, a new exposure page/log line should be triggered to capture the resumed dosing start and stop-date and time, as well as the remainder of the planned dosing as a separate entry.

Indicate if infusion was interrupted during	Was the infusion interrupted?	○ Yes ○ No

administration.	**Not submitted**	
Indicate why infusion was interrupted.	Reason for interruption **EC.ECADJ**	○ ADVERSE EVENT. List the adverse event ID: _____ ○ INFUSION ADMINISTRATION ISSUE
Record date and time when infusion was started.	Start Date **EC.ECSTDTC**	
	Start Time **EC.ECSTDTC**	
Record date and time when infusion was stopped.	Stop Date **EC. ECENDTC**	
	Stop Time **EC.ECENDTC**	

EC Example

The following is an example of an infusion interruption and subsequent resumption during the administration of Drug Z. The planned dosage for each visit was 100 mg, with a 30-minute infusion duration:

- Visit 1: Subject ABC1230 received a 100 mg infusion of Drug Z for 30 minutes.
- Visit 2: During this visit, the infusion was interrupted after 15 minutes (45 mg 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 subject received the remaining 55 mg 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

	USUBJID	ECSEQ	ECLNKGRP	ECTRT	ECPRESP	ECOCCUR	ECREASOC	ECDOSE	ECDOSU	ECADJ	VISITNUM	ECSTDTC	ECENDTC
1	ABC1230	1	V1	DRUG Z	Y	Y		100	MG		1	2009-02-13T10:0	2009-02-13T10:30
2	ABC1230	2	V2	DRUG Z	Y	Y		45	MG	INFUSION ADMINISTRATION ISSUE	2	2009-02-20T11:00	2009-02-20T11:15
3	ABC1230	3	V2	DRUG Z	Y	Y		55	MG		3	2009-02-20T11:35	2009-02-20T11:55

5.1.4 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. A placeholder is provided for adding terms according to the study protocol, such as change in toxicity grade, etc.

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 change.	What was the reason the dose was adjusted? **EC.ECADJ** **SUPPEC.QVAL where SUPPEC.QNAM = "ECADJSPC" and SUPPEC.QLABEL = "Specified Reason for Dose Adjustment"**	○ ADVERSE EVENT. List the adverse event ID: _____ ○ SUFFICIENT EFFICACY ○ LOGISTICAL PROBLEM ▪ FEAR OF NEW OR RECURRENT ADVERSE EVENTS ▪ OPERATIONAL ERROR ○ <PROTOCOL SPECIFIED>

EC Example

The following is an example in a double-blind study where subjects take 2 tablets daily for 6 months. Due to a LOGISTICAL PROBLEM, subject ABC3004's dosage was initially reduced to 1 tablet, but it was later increased back to 2 tablets per day.

ec.xpt

	USUBJID	ECSEQ	ECLNKID	ECTRT	ECPRESP	ECOCCUR	ECADJ	ECDOSE	ECDOSU	ECDOSFRQ	EPOCH	ECSTDTC	ECENDTC
1	ABC3004	1	A2-20110114	BOTTLE A	Y	Y		2	TABLET	QD	TREATMENT	2011-01-14	2011-01-23
2	ABC3004	2	A0-20110124	BOTTLE A	Y	Y	LOGISTICAL PROBLEM	1	TABLET	QD	TREATMENT	2011-01-24	2011-01-26
3	ABC3004	3	A2-20110125	BOTTLE A	Y	Y		2	TABLET	QD	TREATMENT	2011-01-27	2011-01-31

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

suppec.xpt

	STUDYID	RDOMAIN	USUBJID	IDVAR	IDVARVAL	QNAM	QLABEL	QVAL	QORIG
1	ABC	EC	ABC3004	ECSEQ	2	ADJSPEC	Specified reason for dose adjustment	FEAR OF NEW OR RECURRENT ADVERSE EVENTS	CRF

5.1.5 Treatment Delay

A treatment delay is also a type of dose modification.

Indicate whether 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 = "RSNDELAY" and SUPPEC.QLABEL = "Reason for Dose Delay"** **SUPPEC.QVAL where SUPPEC.QNAM = "RSNDELSP" and SUPPEC.QLABEL = "Specified Reason for Dose Delay"**	○ ADVERSE EVENT. List the adverse event ID: _____ ○ SUFFICIENT EFFICACY ○ PREGNANCY ○ LOGISTICAL PROBLEM ▪ RELOCATION ▪ SCHEDULE CONFLICTS OR DIFFICULTY TRAVELING TO SITE ▪ PERSONAL/FAMILY REASONS NOT RELATED TO EFFICACY OR SAFETY OF THE STUDY DRUG/DEVICE ▪ UNSATISFIED WITH STUDY PROCEDURES ▪ UNSATISFIED WITH STUDY DRUG DELIVERY DEVICES/METHODS ▪ FEAR OF NEW OR RECURRENT ADVERSE EVENTS ▪ STUDY TERMINATION OR SITE CLOSURE ▪ CLINICAL TRIAL MATERIAL QUALITY ISSUE OR SHORTAGE ▪ GEOPOLITICAL LOGISTICAL RESTRICTIONS ▪ OPERATIONAL ERROR

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, and SUPPEC should include the reasons for dose delay.

SUPPEC Example

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

suppec.xpt

Row	STUDYID	RDOMAIN	USUBJID	IDVAR	IDVARVAL	QNAM	QLABEL	QVAL	QORIG
1	ABC	EC	ABC3004	ECSEQ	1	RSNDELAY	Reason for Dose Delay	LOGISTICAL PROBLEM	CRF
1	ABC	EC	ABC3004	ECSEQ	1	RSNDELSP	Specified Reason for Dose Delay	RELOCATION	CRF

5.1.6 Definitions and examples of reasons for treatment discontinuation, treatment interruption, infusion interruption, dose adjustment and treatment delay:

Definitions are provided below for the proposed new term of 'Sufficient Efficacy' (in the NCOMPLT codelist) as well as for the granular sub-categories of the existing terms of 'Protocol Deviation' and

Logistical Problem'.

On the CDISC Control Terminology website, a study team can request adding new terms to existing codelists, or adding a new codelist altogether, by accessing the 'New Term Request Page'. In the request, a detailed definition of the new term is submitted, as well as sufficient examples to support the case. Furthermore, it is important to consider that there are no duplicate codelists or terms, and one must explain why the newly proposed codelist or term will not overlap with an already existing codelist or term.

SUFFICIENT EFFICACY:

Sufficient efficacy refers to subjects who prematurely discontinue the study intervention because they are satisfied with their efficacy results or outcome. Examples include subjects achieving remission in major depressive disorder (MDD), subjects discontinuing antibiotics for a bacterial infection after symptom alleviation, subjects reaching their weight loss target in a chronic weight management trial, or subjects achieving amyloid plaque reduction in an Alzheimer's disease trial.

PROTOCOL DEVIATION:

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

LOGISTICAL PROBLEM:

- Unsatisfied with study procedures - e.g., the subject thought that the study procedures were too burdensome, too many procedures/measurements, etc.
- Clinical trial material quality issue or shortage – e.g., supply chain disruptions
- Geopolitical logistical restrictions - e.g., natural disaster, geographical conflicts, or pandemic/epidemic situations
- Operational error - e.g., site procedure errors, scheduling errors, human errors
- Blind broken – an accidental unblinding of study intervention

INFUSION ADMINISTRATION ISSUE:

Examples: During IV infusion, there was an equipment issue with the infusion pump, and the treatment had to be stopped. If the issue could be fixed immediately, the subject might resume treatment after it was resolved.

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 tumor-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.

5.2.1 Concomitant Medication

Indicate if the subject took any concomitant medication/ treatment.	Were any concomitant medications taken? **Not submitted**	○ Yes ○ No
Record only one treatment per line. Provide full trade name of the medication/ treatment	What was the medication? **CM.CMTRT**	
Record specific reasons the medication was taken.	For what indication was the medication taken? **CM.CMINDC**	○ ADVERSE EVENT. LINK TO ADVERSE EVENT: _____ ○ MEDICAL HISTORY. LINK TO MEDICAL HISTORY: _____ ○ CLINICAL EVENT. LINK TO CLINICAL EVENT: _____ ○ PROPHYLAXIS FOR ANTIVIRAL ○ PROPHYLAXIS FOR ANTIFUNGAL ○ PROPHYLAXIS FOR INFECTION ○ PROPHYLAXIS FOR INFUSION REACTION ○ THROMBOPROPHYLAXIS ○ PROPHYLAXIS FOR TUMOR LYSIS SYNDROME ○ VACCINATIONS ○ REQUIRED CONCOMITANT MEDICATION FOR THE STUDY ○ <STUDY INDICATION> ○ RESCUE THERAPY ○ BRIDGING THERAPY ○ NON-THERAPEUTIC USE ○ SUPPORTIVE CARE ○ DIETARY SUPPLEMENT
	Start Date **CM.CMSTDTC**	
	Is the medication ongoing? **CM.CMENRF or CMENRTPT**	○ Yes
	End date **CM.CMENDTC**	

CM Example

cm.xpt

	STUDYID	DOMAIN	USUBJID	CMTRT	CMINDC	CMSTDTC	CMENRF	CMENDTC
1	ABC456	CM	456101	ASPIRIN	PROPHYLAXIS FOR INFECTION	2003-07-21	ONGOING	
2	ABC456	CM	456103	ANTACIDS	RESCUE THERAPY	2003-08-15		2003-09-01

5.2.2 Concomitant Procedure

Indicate if the subject took any concomitant procedure.	Were any procedures performed? **Not submitted**	○ Yes ○ No
	Procedure Category **PR.PRCAT**	○ Diagnostic ○ Therapeutic Procedure ○ Diagnostic and Therapeutic Procedure ○ Study Related
	Procedure Name **PR.PRTRT**	
Record specific reasons the procedure was performed.	For what indication was the procedure performed? **PR.PRINDC**	○ ADVERSE EVENT. LINK TO ADVERSE EVENT: _____ ○ MEDICAL HISTORY. LINK TO MEDICAL HISTORY: ____ ○ CLINICAL EVENT. LINK TO CLINICAL EVENT: ____ ○ <PROPHYLAXIS FOR xxxx> ○ RESCUE THERAPY ○ BRIDGING THERAPY ○ PALLIATIVE ○ CURATIVE ○ DISEASE IMPROVEMENT ○ <STUDY INDICATION>
	Start Date **PR.PRSTDTC**	
	End date **PR.PRENDTC**	

5.2.3 Subsequent Cancer Surgery

Category for surgery **PR.PRCAT**	○ Cancer Surgeries for Disease Under Study
What is the surgery? **PR.PRTRT**	
Relevant Period **PR.PRSCAT**	○ Subsequent

Record specific reasons the surgery was performed.	What was the reason the surgery performed? **PR.PRINDC**	○ TUMOR RESECTION PALLIATIVE ○ TUMOR RESECTION CURATIVE
	Date of Surgery **PR.PRSTDTC**	

5.2.4 Subsequent Radiotherapy

	Category for Radiotherapy **PR.PRCAT**	○ Radiation Therapy for Disease Under Study
	What is the radiotherapy? **PR.PRTRT**	
	Relevant Period **PR.PRSCAT**	○ Subsequent
Record specific reasons the radiotherapy was performed.	What was the intent of the radiotherapy performed? **PR.PRINDC**	○ PALLIATIVE ○ CURATIVE ○ ADJUVANT ○ DISEASE CONTROL
	Start Date **PR.PRSTDTC**	
	End Date **PR.PRENDTC**	

5.2.5 Definitions and Examples

- Prophylaxis - Measure taken to prevent disease, e.g., viral infection, infusion reaction, etc.
- Non-therapeutic use - unlikely to produce a diagnostic, preventative, or therapeutic benefit. Can be recreational use or even abuse.
- Supportive care - palliative care aimed at comfort vs. cure.
- Required concomitant medication for the study - for example, insulin is used in diabetes studies.
- 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 - non-surgical medical intervention intended to treat a subject when: 1) the primary condition under study is failing to improve or is worsening; and/or 2) a complication of the primary condition under study has developed.

- Bridging therapy - therapy intended to serve as a bridge to another stage of therapy or health. For example, heparin is used during a perioperative period for temporary anticoagulation while a subject's regular anticoagulant therapy, such as with warfarin, is suspended.

5.3 Study Discontinuation

In addition, the reasons for study discontinuation are also considered to be relevant to estimands and estimation. ICH E9 (R1) Addendum differentiates the treatment and study discontinuations. The reason for treatment discontinuation but not study discontinuation should be related to potential efficacy and adverse effect of the treatment, or due to logistic reasons that the clinical trial materials cannot be received on time. All these reasons should not prevent subjects continuing the clinical trials to have any procedures performed and data collected. Subjects are generally encouraged to stay in the study even if they will discontinue or have discontinued treatment to minimize missing values [National Research Council 2010]. In other cases, subjects may need to be discontinued from the study due to reasons that prevent them from continuing the study (e.g., relocation), resulting in treatment discontinuations. Therefore, reasons for treatment and study discontinuations can be the same or different. Therefore, they should be collected in separate CRFs. For example, a subject may discontinue the treatment and study due to relocation. Another subject may discontinue treatment due to intolerance to the study medication (an adverse event) and may discontinue the study later due to relocation.

Document the subject's status for the study. If the subject discontinued study prematurely, record the primary reason for discontinuation.	What was the subject's status? **DS.DSDECOD** **DS.DSTERM**	○ **COMPLETED** ○ **ADVERSE EVENT.** LINK TO ADVERSE EVENT: _____ ○ **DEATH** ○ **PREGNANCY** ○ **PROTOCOL DEVIATIONS** • DID NOT MEET STUDY ELIGIBILITY CRITERIA AT ENROLLMENT • NONCOMPLIANCE TO STUDY PROCEDURES ○ **LOGISTICAL PROBLEM** • RELOCATION • SCHEDULE CONFLICTS OR DIFFICULTY TRAVELING TO SITE • PERSONAL/FAMILY REASONS NOT RELATED TO EFFICACY OR SAFETY OF THE STUDY DRUG/DEVICE • UNSATISFIED WITH STUDY PROCEDURES • STUDY TERMINATION OR SITE CLOSURE • CLINICAL TRIAL MATERIAL QUALITY ISSUE OR SHORTAGE • GEOPOLITICAL LOGISTICAL RESTRICTIONS • OPERATIONAL ERROR • BLIND BROKEN ○ **LOST TO FOLLOW-UP**

5.4 Clinical Study Data Reviewer's Guide (cSDRG)

According to the cSDRG completion guidelines [PHUSE cSDRG 2018], 'other data of special interest' can be summarized in "Additional contents of interest" under Section 3. This section would be recommended to describe intercurrent events associated with clinical questions of interest, as well as describe how intercurrent events are collected and explain how intercurrent events are mapped to corresponding SDTM domains and variables. In the cSDRG template, the following questions can be added regarding intercurrent events. There is an option to display the information in a question-and-answer format or in a table format, both options are provided as guidance.

Question and Answer Format

Intercurrent Events:

1. Are intercurrent events collected for this study? If so, what are the intercurrent events considered for implementation of estimands?
2. In which CRF forms were details of intercurrent events collected?
3. In which SDTM domains (and variables) were intercurrent events mapped?
4. What Controlled Terminology was used? Were there any additional terms included in the codelist?

Table Format

Intercurrent Events:

Intercurrent Event collected in the Study	In which CRF forms were details of intercurrent events collected?	In which SDTM domains (and variable) were intercurrent events mapped?	What Controlled Terminology was used? Were there any additional terms included to the codelist?

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 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 translates 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 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 that are supported by the ADaM estimands implementation framework are:

- **Intercurrent Events:** provides ways to organise, identify, and document intercurrent events, their relationship with each estimand and the related handling strategy.
- **Datapoints:** provides ways to document datapoints affected by intercurrent events and if they can be considered for analyses.
- **Population:** support for estimand's specific definition of the population of subjects used for estimations.

Regarding the estimators: these correspond to the statistical analyses that are 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. While in some situations, the ADaM estimands implementation framework may offer additional ways of supporting statistical analyses, especially with regards to subject and records (datapoints) selection.

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 3 groups: datasets supporting the estimand's specific population definitions, datasets gathering the intercurrent events, and datasets supporting the statistical analyses (i.e. estimators) related to the estimands.

Figure 3 illustrates a typical data flow from SDTM to ADSL and ADICE (dataset holding the intercurrent events) and then to other ADaM datasets. This assumes there is a single dataset named ADICE gathering all intercurrent events into one place and the ADSL dataset holds the estimands' specific population definitions. The ADSL and ADICE datasets are ideally built at the very 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. The datasets will be further discussed below.

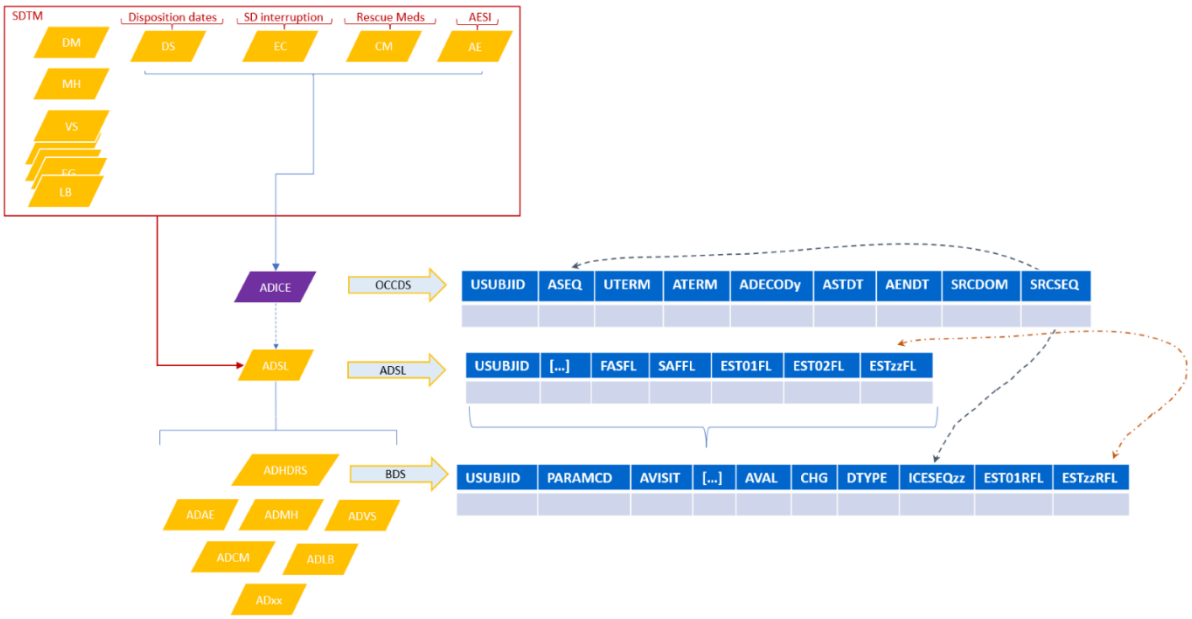

Figure 3: Data flow from SDTM to ADICE (Intercurrent Events Analysis Dataset) and other ADaM datasets, use of estimands variable terminology

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

6.2.1.1 Subject-Level Analysis Dataset (ADSL)

Estimand specific populations will be documented through dedicated subject-level flags in the ADSL dataset. Refer to 6.2.2 variable-level implementation for more details.

6.2.1.2 Intercurrent Events 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 to implement the ADICE structure as a single like named 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 implementors, alternative

approaches to a single dedicated ADICE dataset, aligned with this framework could be adopted, such as

- including the ADICE structure into existing OCCDS dataset, e.g., a dataset already built to collect some 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 ICEDOMzz* 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 most simple 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 finding domain reaching a certain threshold). For more complex cases, intercurrent events may also be sourced from other ADaM dataset.

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 with the use of U* type variables (n.b. U* indicates unmodified). 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[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, several datasets could be used.
2. Alternative identifier other than ATERM, ASTDT could be used, see 6.2.2 variable-level implementation.

6.2.1.3 Analysis Datasets supporting the estimators

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

The ADaM estimands implementation framework addresses the following topics in datasets supporting the statistical analyses:

- Datapoints impacted by an intercurrent event
- Records relevant to all estimand's estimators
- Records relevant to an estimator
- Parameters relevant to an estimator

This will be achieved through the use of existing ADaMIG variables and a few new additional variables. Details will be provided in 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 list* in Table 2 presents the main variables relevant for the estimands framework, grouped according to the 3 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 on 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 3 categories based on purpose:

- Variable to document if a subject is relevant for an estimand (Estimands populations flags)
- Variables to document intercurrent events and their relationship with estimands
- Variables to document datapoints affected by intercurrent events and its impact on estimation (Estimand analysis set record flag)

Table 2: ADaM variables list

Variable	Label	Type	Codelist/ Controlled Terms	Core	CDISC Notes
ADSL					
Population flags					
ESTzz*FL [1, 2]	Estimand zz* Population Flag	Char	YN	Perm	Subject considered for estimand zz* in ADSL. Useful when only a subset of subjects must be considered for the estimand, e.g. selection based on a baseline characteristic, principal stratum strategy. Can be copied into other datasets.
ADICE structure					
Identifiers					
STUDYID	Study Identifier	Char		Req	
USUBJID	Unique Subject Identifier	Char		Req	
Sequence numbers					
ASEQ		Num		Req	Unique number per record, per subject, per intercurrent event
ICEzzGID	Intercurrent Events Grouping zz ID			*Perm*	*Identifier used to group intercurrent events affecting jointly 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 whitepaper.*
Record topic (event)					
--TERM	{Reported Term}	Char		Cond[3]	Original intercurrent event term when there is only one source event domain.
UTERM	Unmodified Reported Term	Char		Cond [3]	Original intercurrent event term when there are multiple source events domains.
--TRT	{Reported Name of Drug, Med, or Therapy}	Char		Cond [3]	Original intercurrent event when there is only one source intervention domain.
UTRT	Unmod. Rep. Name of Drug, Med, or Thrpy.	Char		Cond [3]	Original intercurrent event when there are multiple source intervention domains.
ATERM	Analysis Term	Char		Cond [3]	Analysis term describing the intercurrent event. A more granular description of the intercurrent event, close to the source. This would be used 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 of 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 [5]	Source start date of the intercurrent event in numerical format. One of ASTDT/ASTDTM must be present.
ASTDTM	Analysis Start Datetime	Num		Cond [5]	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	Source coding, single source, useful to support. --DECOD/UDECOD are mutually exclusive.
UDECOD	Dictionary-Derived Term	Char	*	Perm	Source coding, multiple sources. --DECOD/UDECOD are mutually exclusive.
*		Char	*	Perm	Any source classification if relevant for intercurrent event could be included, e.g., AEHLT, AEHLGT, AESOC, ATCy, ATCyCD ....
Source code and classifications					
ADECODy	Analysis Dictionary Derived Term {y}	Char	*	Perm	Coded version of the intercurrent event, at lower level of granularity needed according to intercurrent event definition. Present the intercurrent event in a standardised way, related to the intercurrent event definition and policies. This is the lower level (more granular standard definition) across all estimands. There would be more than one variable such only if an intercurrent even would have a different standardised name for some estimands.
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. One has notion of "Treatment discontinuation due to AE" and "Treatment discontinuation due to Lack of Efficacy".
Intercurrent event handling strategy					
ESTzz*STR [1, 2]	Estimand zz* handling strategy	Char	(ESTSTRAT) [4]	Req	Strategy for handling the intercurrent events related to estimand zz*. Blank if the intercurrent event is not related to estimand zz*. Else filled with the strategy to handle it.
Traceability					
--SEQ	Sequence Number	Num		Cond [6]	Single domain source of all intercurrent event s. One of --SEQ or the pair SRCDOM/SRCSEQ is required to point to source record for the intercurrent event.

SRCDOM	Source Data	Char		Cond [6]	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 [6]	Sequence number of the intercurrent event record in parent domain. Normally 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.
Analysis Datasets supporting the estimators					
Records included in estimand zz* estimations					
ESTzz*RFL [1, 2]	Estimand zz* Record-Level Flag	Char	Y	Perm	Datapoint included for estimand zz* estimation; can appear in ADaM datasets (BDS/OCCDS/OTHER).
Intercurrent event impacting datapoints					
ICESEQzz* [1]	Impacting ICE seq. Num. for Est. zz*	Num		Req	Point to the intercurrent event(s) impacting the datapoint for estimand zz* estimations - it can depend on the strategy defined for each intercurrent event that can impact estimand zz*. The variable is filled with the intercurrent event identifier impacting the datapoint for estimations; that is typically the value of ASEQ from the intercurrent event record. Refer to the implementation consideration section for more details on documenting impact of intercurrent events on datapoints.
ICEDOMzz* [1]	Dataset of Impacting ICE for Est. zz*	Char		Cond	Dataset holding the intercurrent event(s) impacting the datapoint for estimand zz*. Name of the dataset holding the intercurrent events. Must be present and filled only if there is more than one intercurrent event dataset present in the package. This variable can appear in ADaM datasets containing endpoints affected by intercurrent events.
ICEVARzz* [1]	Impac. ICE seq. Num. Var. for Est. zz*	Char		Cond	Variable holding the intercurrent event(s) identifier impacting the datapoint for estimand zz*. Must be present and filled only if the record identifier variable in the intercurrent event dataset can be different from ASEQ.
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 if extra selection of records is needed for some analyses that cannot be performed with existing variables. It could be used instead of or in addition to the ESTzz*RFL. 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 tie 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 may 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. Estimand analysis flags use “EST” as prefix and concurrent numbers to tie all estimands defined in the protocol.
3. One of --TERM/UTERM/--TRT/UTRT/ATERM must be present and filled for all records as the topic.

a. One of the variables --TERM/UTERM/--TRT/UTRT could be used alone, without ATERM as topic.
    i. --TERM: when all intercurrent events come from a single events domain
    ii. UTERM: when all intercurrent events come from events domains
    iii. --TRT: when all intercurrent events come from a single interventions domain
    iv. UTRT: when all intercurrent events come from interventions domains

b. ATERM could be used as topic in all situations (for consistency). And must be used when the intercurrent events are based on findings, mix of domain of different classes, involves derivations (e.g., AE with some severity grade). ATERM can be a copy of any of --TERM/UTERM/--TRT/UTRT, but also --DECOD/UDECOD, or a derived term.

c. --TERM/UTERM are mutually exclusive, and --TRT/UTRT are mutually exclusive.

d. When ATERM is used, --TERM or UTERM and --TRT or UTRT may be used as support, then ATERM must be filled for all records, --TERM/UTERM, --TRT/UTRT may be missing for some records.

4. ESTSTRAT is the controlled terminology for the estimands handling strategies such as “treatment policy”, “hypothetical”, “composite variable”, “while on treatment” and “principal stratum”. The definitive terminology will be developed and published per the CDISC Terminology process.
5. At least one variable documenting the start of the intercurrent event must be provided.
6. 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.

6.2.2.1 Implementation considerations

6.2.2.1.1 Datapoints impacted by an intercurrent event

Variables ICESEQzz* (and ICEDOMzz*/ICEVARzz* if applicable) are useful to identify datapoints impacted by intercurrent events. However, exact rule on how to fill the variable is up to the implementer as no generalized rule on impacted datapoint identification currently exist. The general idea is to identify datapoints affected by an intercurrent event and relate the impacted datapoints to that event.

There is no general guidance on how to document the impact of intercurrent events on datapoints and therefore on how to fill ICESEQzz*.

The rule further considered in this white paper is as follows: when an intercurrent event potentially impacts a datapoint, based on timing of occurrence, populate ICESEQzz* with the ID of that intercurrent event only if the event actually affects the datapoint according to its handling strategy (e.g. hypothetical, composite endpoints strategies). It should be left blank if the event does not have an actual impact (e.g. treatment policy). If multiple intercurrent events occur and potentially affect a datapoint from a timing perspective, refer to the analysis plan to identify the one to consider in priority (there is an assumption that the analysis plan describes priority rules for such cases). Populate ICESEQzz* with the ID of that event if it impacts the datapoint as explained before. When an intercurrent event affects a datapoint, it typically also affects all subsequent datapoints. If that is the case the ICESEQzz* of those datapoints will also be filed with the ID of the intercurrent event. Another rule may be adopted by implementers, depending on analysis/traceability needs. In any case, the logic used to complete the ICESEQzz* variables and consequences for the analysis should be documented in the ADRG and in the define-xml for clarity.

6.2.2.1.2 Records relevant to an estimand's estimations

The ESTzz*RFL variable is used to identify all records relevant to the estimation(s) of the estimand zz*. Relevant to the estimation is intended here across all estimators. Records that would not be included are datapoints not relevant to the estimands and datapoints that could have been relevant but must be excluded due to the occurrence of an intercurrent event affecting them – which is also depending on the handling strategy.

There are currently no rules describing precisely what relevant to estimations means and how the flag must be derived. It is left to the implementer to provide the details and document them in the ADRG and define-xml. However, the rule to derive these flags must be estimator independent – for estimator dependent inclusion flag, the ANLzzFL would be used per ADaMIG.

6.2.2.1.3 Records relevant to an analysis (estimator)

All mechanisms to identify records relevant to an analysis (estimator) available in ADaM are valid. There are no restrictions in the framework. The new estimands specific variables ESTzz*FL and ESTzz*RFL may be used in addition to existing implementation guides mechanisms to facilitate the selection of the analysis records. In particular, the ESTzz*FL variables may be used in addition to or instead of the usual ADaM population flags (corresponding to the ICH analysis set flags, e.g. FASFL, SAFFL) to identify subjects relevant for an estimand (e.g. identify subjects part of a principal stratum), while the ESTzz*RFL

variables may in some case avoid the need for ANLzzFL variables or to complement them. However, the way to identify the relevant records for an analysis is left to the implementer. There are currently no general guidance mandating the use of the ESTzz*FL and ESTzz*RFL variables or described how they must be used. That decision is left to the implementer and should be documented in the ADRG and define-xml.

6.2.2.1.4 Parameters relevant to an analysis (estimators)

In the case where parameters supporting estimands are derived, the derivation may be dependent on the estimator with possibly different derivation rules for the main and sensitivity analyses. In such situations, per usual ADaMIG rules, such parameters would bear different names in the respective analyses.

6.2.2.1.5 Imputation

Imputation is used here to describe the statistical technique by which variables/variable outcomes are imputed/created based on a statistical model. This imputation can be used directly (as used traditionally) for imputation of missing data (please see missing data definition in the glossary). It can also be used to impute datapoints impacted by intercurrent events when the events are handled with a hypothetical strategy. Despite similar techniques and naming, these two imputation situations are different, and this should be carefully considered by the reader.

6.3 Analysis Data Reviewers Guide (ADRG)

Updates to the ADRG [PHUSE ADRG, 2019] to offer a better support to the estimands framework are presented here. Only sections relevant to the estimands implementation will be discussed here. This is based on the latest ADRG version published by PHUSE at the time of writing this whitepaper. Similar to CDISC controlled terminology these updates have been proposed to the PHUSE Management of 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 definition in the protocol and SAP with their implementation in the analyses datasets and results. This section is presented as a table.

3. Analysis Considerations Related to Multiple Analysis Datasets

3.1 Estimands and Estimators

[Add one estimand section <X> per estimand; numbering scheme <X> left to implementer, ideally aligned with protocol/SAP estimands IDs. The estimand section contains relevant information at the estimand level, across all estimators. Optionally, add one estimator subsection <X.y: name> per estimator; numbering scheme <X.y: name> left to implementer, ideally aligned with SAP estimators IDs.

The estimator subsections contain only information specific to the estimators and complement/supersede information from 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 subsection. It is expected that some of the information below will be moved between the estimand section and estimator subsections depending on the study specificities. E.g., if the analysis dataset is identical for all estimators, it will be listed in the estimand section, while if the analysis dataset differs across estimators, it will be reported in each of the estimator subsections.]

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] Estimand record inclusion variable: [variable for inclusion of records related to the estimand: ESTzzRFL] Intercurrent event(s) impact variable(s): [variable for identification of end points impacted by the intercurrent event(s): ICESEQzz] Treatment variable: [name of the variable containing the comparison factor for the estimand] Treatment modalities: [list of modalities of the treatment variable being compared or ALL] Endpoint variable: [variable being analyzed] 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].
	Population	Population selection clause: [where clause in terms of analysis dataset / ADSL variable]
	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)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.y : main/sensitivity >	Protocol	Protocol Reference: [section (page) in protocol here the estimator is described]
	SAP	SAP reference: [section (page) in SAP where the estimator is described]
	Analysis dataset	Analysis records: [criteria to select records part of the analysis]
	Analysis description	Analysis method: [method expressed in terms of analysis dataset variables; it is to make sure that 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 similar document. Details or 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 1>		
…		[fill for each estimand/estimator]

6.3.2. Section 3.2 Core variables

In case subject-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.

Variable Name	Variable Description
STUDYID	Study identifier used for this protocol

USUBJID	Unique subject identifier
…….	……..
*ESTzz*FL*	*Estimand zz Population Flag*

[zz*: denotes an estimand number that is consistently used across all datasets, following the Protocol/SAP numbering sequence for estimands.]

6.3.3. Section 3.6 Imputation/Derivation Methods

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

3.6 Imputation/Derivation Methods

[If date imputation was performed, were there rules that were used in multiple analysis datasets? See individual datasets in section 5.2 for any date imputation rules.]

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 the ones proposed in the cSDRG document, to draw attention to the estimands implementation. It is recognized to be a simplified version of the information provided in the new section 3.1 and the information provided should be consistent.

5. Analysis Dataset Descriptions

5.1 Overview

• Were there any analysis datasets created to support 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. Are there any additional information regarding implementation of estimands framework?

[you may add a sentence like: “Please refer to section 3.1 for more details.”]

6.3.5. 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(s) by providing relevant information on the traceability, handling strategy

and imputation dates as necessary; the ADSL sub-section could be updated if subject-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 like 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 providing more detailed explanations.

5.2 Analysis Datasets

Dataset Dataset Label	Class	Efficacy	Safety	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*	*[X]*	*[X]*		*[X]*	*[X]*	*One observation per subject per intercurrent event*
.....	.....						.....
[ADxxxx] *[Analysis dataset label]*	*[BDS/OCCDS]*	*[X]*	*[X]*	*[X]*	*[X]*	*[X]*	*One observation per subject [per ...]*

5.2.1 ADSL – Subject Level Analysis Dataset

The population indicator 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 (e.g.; ESTzzFL) 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 is used or if name is 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.

[More detailed explanation of ADICE could be provided here to complement the define-xml if necessary.]

Date Imputation Rules

- [If the source of the intercurrent event(s) has partial dates, its start and stop dates were imputed in accordance with the SAP section x.x Handling of Missing Data.]

5.2.3 ADxxx – <label>

[More detailed explanation of the analysis datasets and of relevant estimands implementation variables could be provided here to complement the define-xml if necessary.]

7: Summary and Conclusion:

Section 5 (Data Collection & 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 emphasized and recommendations for CRF design are provided. 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 cSDRG is recommended to describe intercurrent events associated with clinical questions of interest, as well as describe how intercurrent events are collected, and explain how intercurrent events are mapped to corresponding SDTM domains and variables. The estimands framework affects all levels of documentation and one such document is the cSDRG, which provides traceability. The cSDRG describes intercurrent events associated with the clinical question of interest, along with how they are collected, as well as how they are mapped to 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 variables levels. It cannot be emphasized 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 will investigate further deliverables that will assist implementors 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/organizations or Regulator's 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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