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Implementation of the ICH E9(R1) Estimands Framework Using Data Standards

- Senior Manager of Biostatistics at Fortrea with 18+ years of experience supporting global clinical trials.
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- As a PHUSE working group co-lead for ICH E9(R1) estimands, she frequently present practical insights at PHUSE events and other industry forums.
- Her expertise includes estimands, imputation methods, sensitivity analyses, and advanced statistical methodologies.
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All examples contained within this presentation are examples of how to implement the E9(R1) estimands framework within data collection, tabulation and analysis following data standards. They should not be considered as examples of how to appropriately implement the estimands framework within an individual clinical study.

Overview of Estimand Framework E9 (R1)

Estimand Attributes

Treatment

Population

Variable (Endpoint)

Intercurrent Events

Population level summary

Intercurrent Events (ICE)

Treatment discontinuation due to LOE

Terminal events (death)

Use of prohibited concomitant medication, rescue therapy, etc.

Treatment discontinuation due to safety

Switching Treatment

Strategies to handle ICE

Treatment Policy

Hypothetical

Composite

While on treatment

Principal stratum

Estimands implementation needs in Data Standards

Variable (Endpoint), Target Population and Treatment condition

- SDTM has ways to collect such information.
- ADaM can represent such elements: topic, analysis parameters, “population” flags (*), treatments.

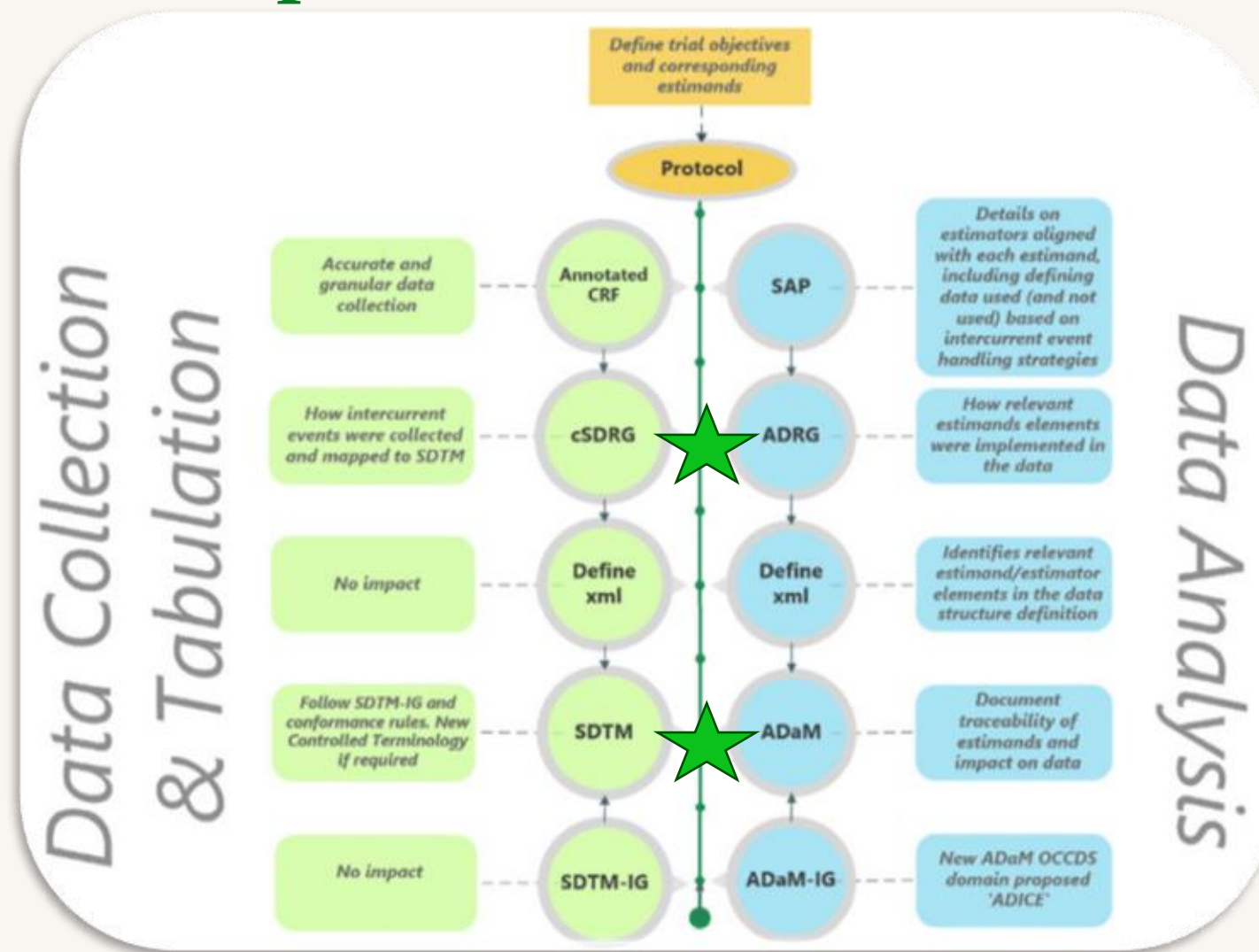
Population Level Summary

- ADaM is designed to support analyses: uses ADAM for the analysis (estimator part).
- Results/summary are related to Analysis Results Standards (ARS) scope. Version 1.0 released in 2023 does not include estimands specific features nor terminology (e.g. statistics ontology)

Strategies of Intercurrent events

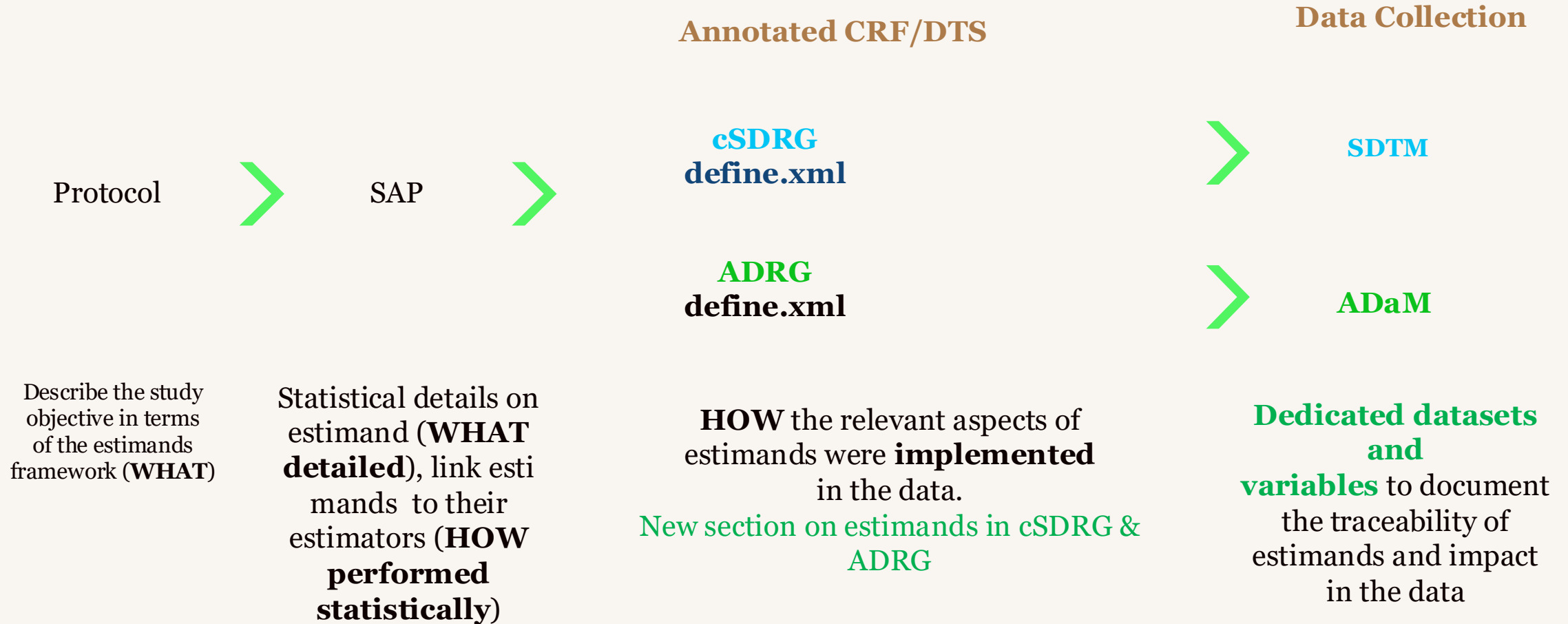
- SDTM has ways to collect information defining the intercurrent events (treatment alteration/discontinuation, concomitant medications, ...). Not to identify/label them as intercurrent events necessarily - though not necessarily needed.
- ADaM does not have specific structure to represent intercurrent events and relationship between intercurrent events and endpoints.

Estimand Implementation Framework in data



Documentation to Data

Get **sufficiently detailed answers** during collection



Case Study – Estimand 1

Treatment conditions

- Assignment to drug X vs placebo, at the selected dose and frequency of administration, regardless of treatment discontinuation due to AE or LoE, and as if patients would not discontinue treatment due to geopolitical logistical restrictions

Target population

- Patients with a diagnosis of MDD in a current major depressive episode with at least moderate symptom severity

Endpoint

- Change from baseline to Week 8 in the total score of the 17-item version of Hamilton Depression Rating Scale (HDRS)

Population-level summary

- Difference in treatment means

Intercurrent Events

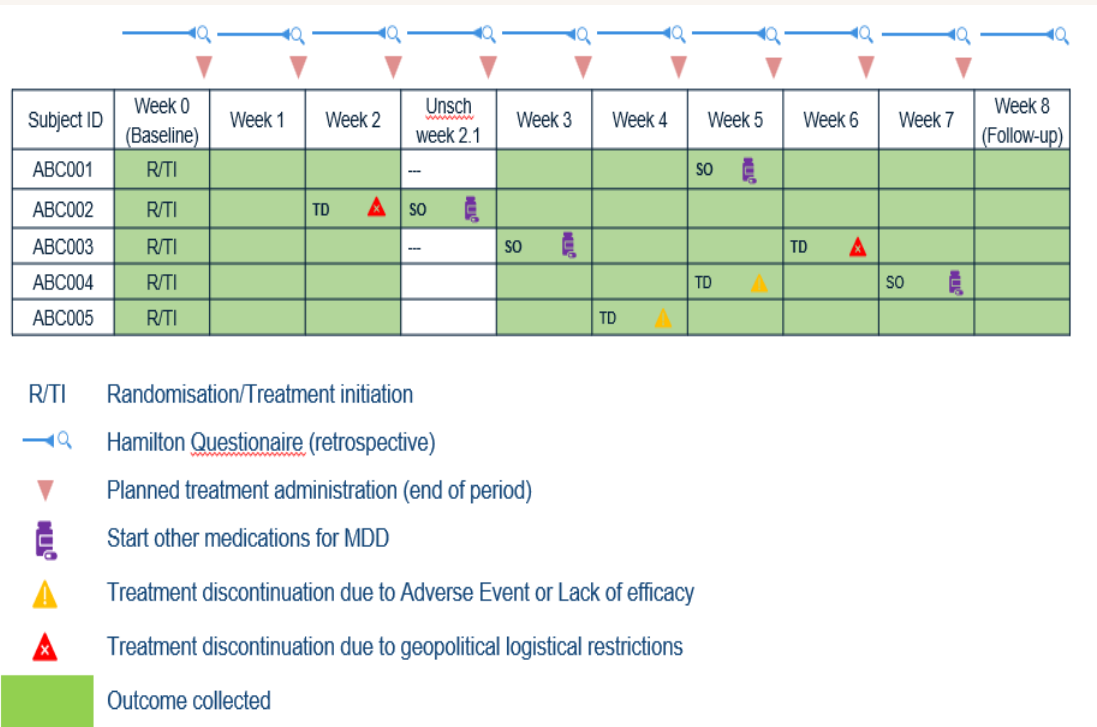
- Use of other MDD medications (SOx)
- Treatment discontinuation due to Adverse events or Lack of Efficacy (TD)
- Treatment discontinuation due to geopolitical logistical restrictions (LOG).

Strategies for Intercurrent events

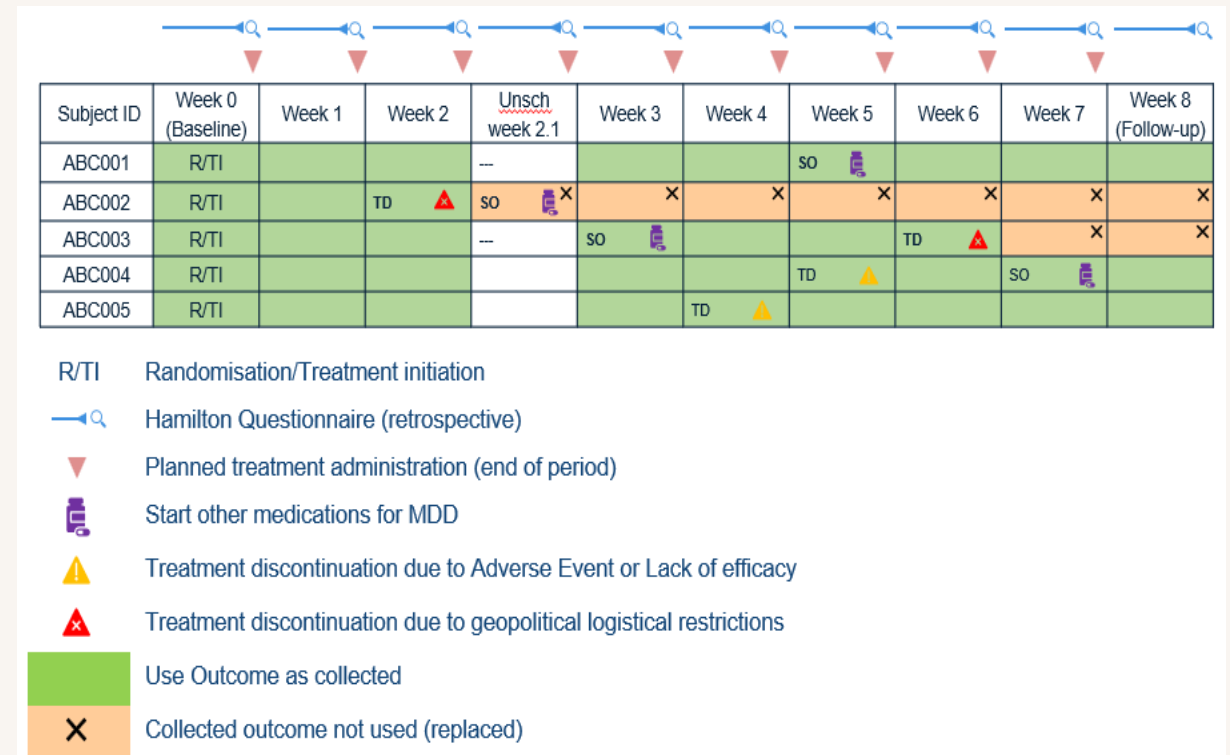
- Treatment policy strategy is used for use of other MDD medications (SOx)
- Treatment policy strategy is used for treatment discontinuation due to Adverse events or Lack of Efficacy (TD)
- Hypothetical strategy is used for treatment discontinuation due to geopolitical logistical restrictions (LOG).

Data flow - Estimand 1

General Data flows – Estimands 1



Data flows – intercurrent events impact with estimands 1 related data handling strategies



Data Collection & Tabulation – Summary

Data Collection

- Accuracy, Granularity, Completeness
- Sponsors should assess study designs

Codelist

- **Proposals shared with CDISC (CDASH/CT)**
- **Recommendations for new terms**

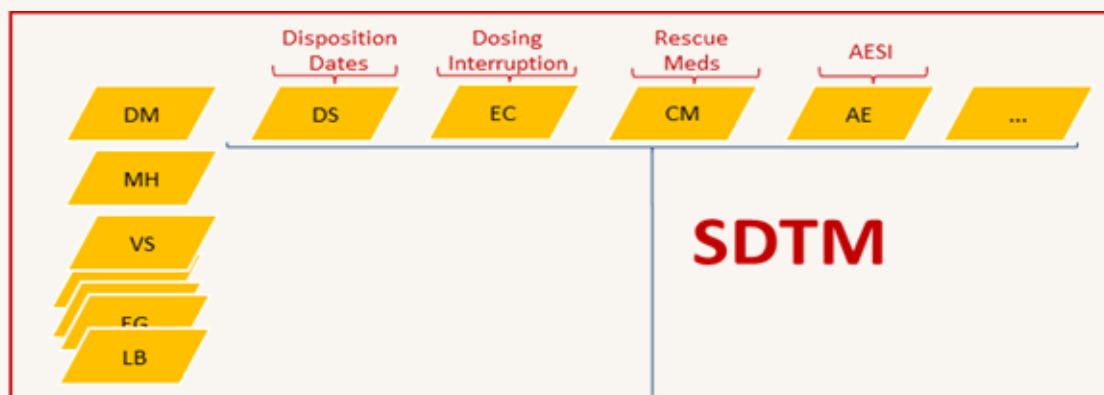
SDTM

- Estimands framework has no impact
- Follow SDTM IG & Conformance Rules

cSDRG

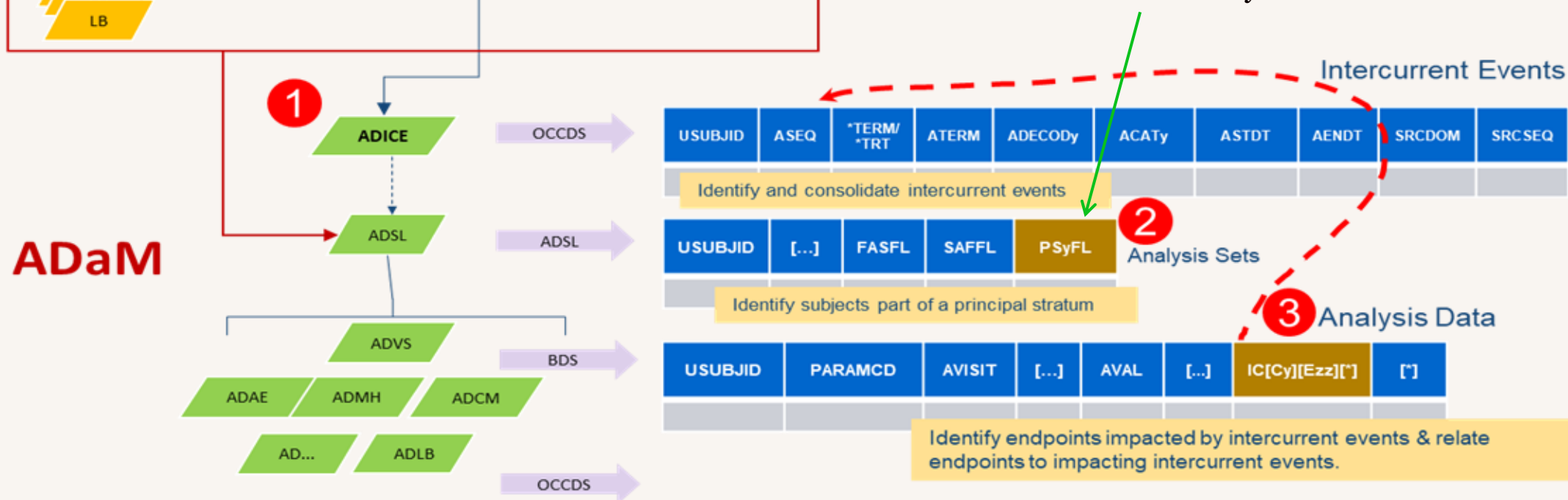
- **Subsection for Intercurrent Events**
- **Define, collection and mapping**

ADaM Implementation - Overview



If principal stratum strategy is used, principal stratum flag(s) can be added to ADSL (New flag) along with FAS, SAF, etc.

More than one principal stratum may be added according to analysis needs.



ADICE (Intercurrent Events Analysis Dataset) – Part I

Name	Label	Type	Core	Notes
Identifiers				
STUDYID	Study Identifier	Char	Req	
USUBJID	Unique Participant Identifier	Char	Req	
Sequence numbers				
ASEQ		Num	Req	Unique number per participant, per intercurrent event
Record topic (event)				
*TERM	{Reported Term}	Char	Cond	At least one original term variable required.
*TRT	{Reported Name of Drug, Med, or Therapy}	Char	Cond	
ATERM	Analysis Term	Char	Cond	ATERM is specially useful when combining multiple source datasets/domains and/or having derived events.
Record start/end date and time				
ASTDT	Analysis Start Date	Num	Cond	Start date of the intercurrent event. or
ASTDTM	Analysis Start Datetime	Num	Cond	Start datetime of the intercurrent event.
AENDT	Analysis End Date	Num	Perm	End date of the intercurrent event
AENDTM	Analysis End Datetime	Num	Perm	End datetime of the intercurrent event
Traceability				
--SEQ	Sequence Number	Num	Cond	When a single domain is source of all intercurrent events.
SRCDOM	Source Data	Char	Cond	Name of the parent dataset holding the intercurrent event (when source is a dataset or multiple domains, datasets) .
SRCSEQ	Source Sequence Number	Num	Cond	Sequence number of the intercurrent event record in parent domain. Normally value of --SEQ or of ASEQ if the parent is another ADaM dataset.

ADICE (Intercurrent Events Analysis Dataset) – Part I

Row	DOMAIN	USUBJID	DSSEQ	DSTERM	DSDECOD	DSCAT	EPOCH	DSSTDTC
3	DS	ABC002	3	GEOLOGICAL LOGISTICAL RESTRICTIONS	LOGISTICAL PROBLEM	DISPOSITION EVENT	TREATMENT	2022-03-30
7	DS	ABC003	3	GEOLOGICAL LOGISTICAL RESTRICTIONS	LOGISTICAL PROBLEM	DISPOSITION EVENT	TREATMENT	2022-04-27
11	DS	ABC004	3	SUICIDAL THOUGHTS	ADVERSE EVENT	DISPOSITION EVENT	TREATMENT	2022-04-20
15	DS	ABC005	3	LACK OF EFFICACY	LACK OF EFFICACY	DISPOSITION EVENT	TREATMENT	2022-04-13

Row	DOMAIN	USUBJID	CMSEQ	CMTRT	CMDECOD	CMCAT	CMSCAT	CMINDC	EPOCH	CMSTDTC	CMENRF
1	CM	ABC001	1	DULOXETINUM	DULOXETINE	ANTIDEPRESSANTS	ANTIDEPRESSANT MEDICATION/ THERAPY FOR CURRENT EPISODE	RESCUE THERAPY	TREATMENT	2022-04-20	ONGOING
2	CM	ABC002	1	FLUOXETINUM	FLUOXETINE	ANTIDEPRESSANTS	ANTIDEPRESSANT MEDICATION/ THERAPY FOR CURRENT EPISODE	RESCUE THERAPY	TREATMENT	2022-04-03	ONGOING
3	CM	ABC003	1	LORAZEP	LORAZEPAM	ANTIDEPRESSANTS	ANTIDEPRESSANT MEDICATION/ THERAPY FOR CURRENT EPISODE	RESCUE THERAPY	TREATMENT	2022-04-06	ONGOING
3	CM	ABC004	1	FLUOXETINUM	FLUOXETINE	ANTIDEPRESSANTS	ANTIDEPRESSANT MEDICATION/ THERAPY FOR CURRENT EPISODE	RESCUE THERAPY	TREATMENT	2022-05-04	ONGOING

Intercurrent events

- Treatment discontinuation due to lack of efficacy
- Treatment discontinuation due to Adverse event
- Treatment discontinuation due to logistical issues
- Starting other pharmacological treatments for MDD

Unique sequence number of the event within a subject

ADICE

USUBJID	ASEQ	TRTP	ATERM	ASTDT	AENDT	SRCDOM	SRCSEQ
ABC001	1	Drug X	DULOXETINE	2022-04-20		CM	1
ABC002	1	Placebo	LOGISTICAL PROBLEM	2022-03-30		DS	3
ABC002	2	Placebo	FLUOXETINE	2022-04-03		CM	1
ABC003	1	Drug X	LORAZEPAM	2022-04-06		CM	1
ABC003	2	Drug X	LOGISTICAL PROBLEM	2022-04-27		DS	3
ABC004	1	Placebo	ADVERSE EVENT	2022-04-20		DS	3
ABC004	2	Placebo	FLUOXETINE	2022-05-04		CM	1
ABC005	1	Placebo	LACK OF EFFICACY	2022-04-13		DS	3

ADICE (Intercurrent Events Analysis Dataset) – Part II

Name	Label	Terminology	Core	Notes
Coding and classifications				
*DECOD	Dictionary-Derived Term	*	Perm	Coded term/name of the intercurrent event from the SDTM source dataset.
ADECODy	Analysis Dictionary Derived Term {y}	*	Perm	Coded version of the intercurrent event , at the more granular level: per protocol/SAP. Useful for reporting, summaries. Normally one variable; unless intercurrent events are named differently per estimand.
ACATy	Analysis Category {y}	*	Perm	Categorisation of the intercurrent events . Useful when there are different levels of granularity of intercurrent event across estimands.
Intercurrent event handling strategy				
ESTzz*STP ¹	Estimand zz* planned handling strategy	(ICESTRG) ²	Req	Planned 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.
ESTzz*STA	Estimand zz* actual handling strategy	(ICESTRG)	Req	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.

zz*: represent the estimand number zz across all datasets. Indexes need not be created sequentially but aligned with numbering in protocol/IAP.

ICESTRG: intercurrent event data handling strategy codelist

ADICE (Intercurrent Events Analysis Dataset) – Part II

USUBJID	ASEQ	TRTA	ATERM	ADECOD1	ACAT1	ASTDT	AENDT	EST01STP	EST01STA	SRCDOM	SRCSEQ
ABC001	1	Drug X	DULOXETINE	Starting other pharmacological treatments	Starting other pharmacological treatments	2022-04-20		TREATMENT POLICY		CM	1
ABC002	1	Placebo	LOGISTICAL PROBLEM	Treatment discontinuation due to a geopolitical logistical restriction	Treatment discontinuation due to a geopolitical logistical restriction	2022-03-30		HYPOTHETICAL	HYPOTHETICAL	DS	3
ABC002	2	Placebo	FLUOXETINE	Starting other pharmacological treatments	Starting other pharmacological treatments	2022-04-03		TREATMENT POLICY		CM	1
ABC003	1	Drug X	LORAZEPAM	Starting other pharmacological treatments	Starting other pharmacological treatments	2022-04-06		TREATMENT POLICY		CM	1
ABC003	2	Drug X	LOGISTICAL PROBLEM	Treatment discontinuation due to a geopolitical logistical restriction	Treatment discontinuation due to a geopolitical logistical restriction	2022-04-27		HYPOTHETICAL	HYPOTHETICAL	DS	3
ABC004	1	Placebo	ADVERSE EVENT	Treatment discontinuation due to adverse events	Treatment discontinuation due to AE/LoE	2022-04-20		TREATMENT POLICY		DS	3
ABC004	2	Placebo	FLUOXETINE	Starting other pharmacological treatments	Starting other pharmacological treatments	2022-05-04		TREATMENT POLICY		CM	1
ABC005	1	Placebo	LACK OF EFFICACY	Treatment discontinuation due to lack of efficacy	Treatment discontinuation due to AE/LoE	2022-04-13		TREATMENT POLICY		DS	3

Standardised name of the intercurrent event, per protocol/SAP wording

Categorisation of intercurrent event (grouping), considering data preparation/analysis needs

Planned strategy, per protocol/SAP

Actual strategy, per protocol/SAP

Typically one standardised name across estimands.

One or more categories could be added, depending on estimands needs

Handling strategy is documented per estimand ESTzz*STP/A -> index per estimand.

Three intercurrent event categories:

- Starting other pharmacological treatments: **Treatment policy**
- Treatment discontinuation due to AE or Lack of efficacy: **Treatment policy**
- Treatment discontinuation due to a geopolitical logistical restriction: **Hypothetical strategy**

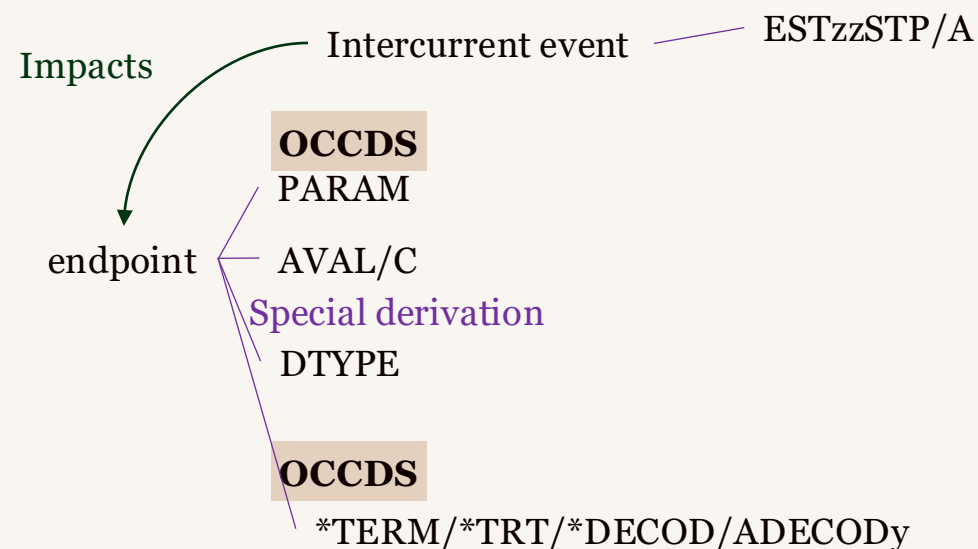
Priorities: in case treatment discontinuation due to logistical issues with

Analysis datasets – Overview

Basic need: identify endpoints impacted by intercurrent events.

- **Impacted** means that the intercurrent event can impact the endpoint existence, usage, interpretation.
- **Identification** will only identify endpoints, it does not tell the fate of the endpoint

Associated handling strategy



There are 3 identification methods available in the implementation framework to identify endpoints impacted by intercurrent events

- 1) Identifying intercurrent events impacting an endpoint
per intercurrent event categorisation modalities
 - Multiple intercurrent events (one per modality) can be documented as impacting an endpoint.
 - Granularity depends on the selection of the categorisation variable in the intercurrent events dataset – ADICE.
 - Same categorisation applies across all estimands.
- 2) Identifying intercurrent events impacting an endpoint
per intercurrent event categorisation modalities, per estimand
 - Similar to 1) but the categorisation variable / impact rule is defined per estimand.
 - Useful when different intercurrent event and/or intercurrent events categorisations apply to different estimands.
- 3) Identifying intercurrent events impacting an endpoint
per estimand
 - Documenting *one* intercurrent event (at most) impacting an endpoint, per estimand. Assumes priority rule in case of multiple intercurrent events impacting an endpoint.

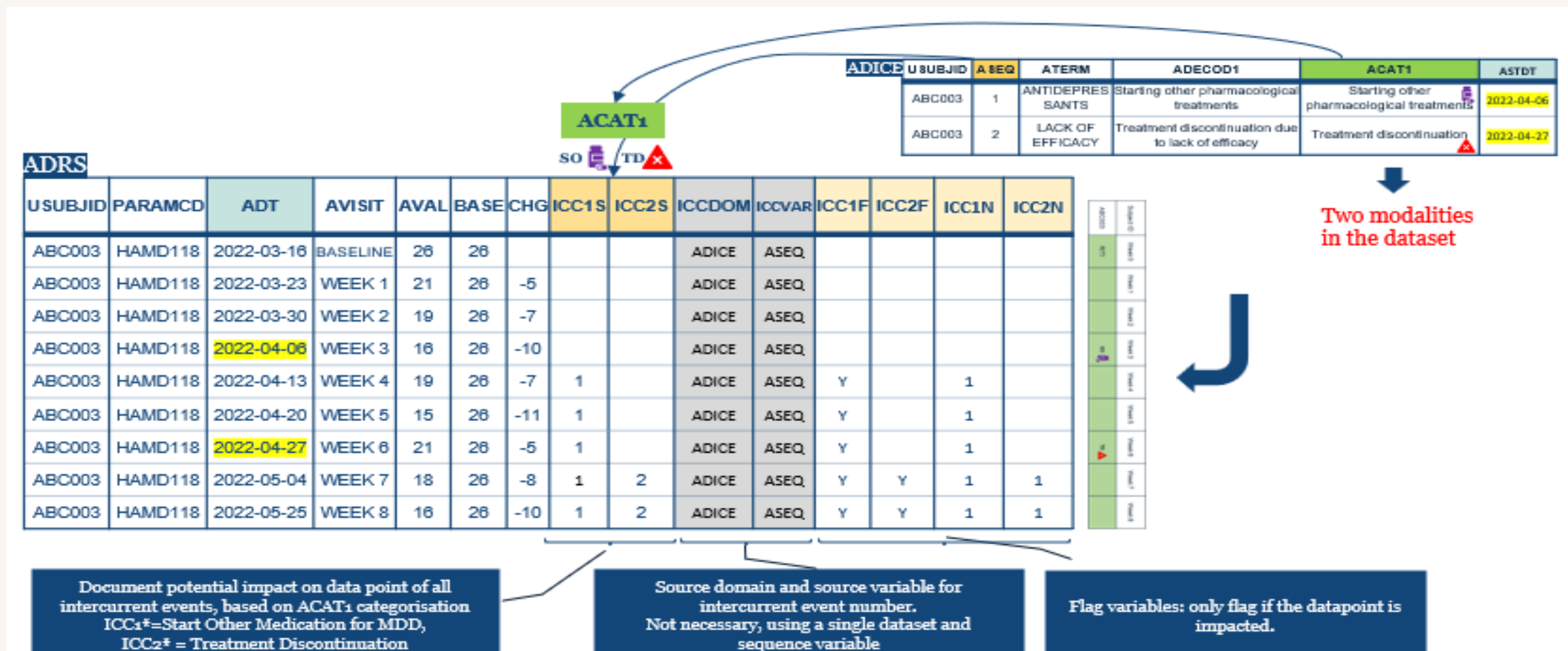
Analysis datasets – Impact Variables Example details per intercurrent event categorisation modalities

- Extra variables that can be added to any BDS/OCCDS/ADaM Other dataset to relate datapoints to intercurrent events

Name	Label	Type	Terminology	Core	Notes
ICCyS	Impacting ICE Cat. Val. y Seq. Num.	Num		Perm	Point to the intercurrent event(s) impacting the datapoint, considering only intercurrent events that are labelled by the y th modality of the naming/categorisation variable.
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 are more than one intercurrent event dataset referred to from the analysis dataset.
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 are more than one identifier variable referred to from the analysis dataset.
ICCyF	Impacting ICE Cat. Val. Y Flag	Char	(Y)	Per	Flag 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. If used, there must be one ICCyF variable per modality of the labelling variable.
ICCyN	Impacting ICE Cat. Val. Y Num. Flag	Numr	(1)	Perm	Numerical version of ICCyF.

- Index y represent the yth modality of the naming / categorisation variable in the intercurrent event dataset (ADICE).
- In case two events categorised with the same modality impact a datapoint, only one can be documented in the scheme.
Selection rule to be described by implementer; e.g, first occurrence is documented or most recent occurrence before the endpoint.

Analysis datasets – Impact Variables Example details per intercurrent event categorisation modalities



Analysis datasets – Impact Variables Structure per intercurrent event categorisation modalities, per estimand

- Extra variables that can be added to any BDS/OCCDS/ADaM Other dataset to relate datapoints to intercurrent events

Name	Label	Type	Terminology	Core	Notes
ICCyEzz*S	Imp. ICE Cat. Val. Y for Est. zz* Seq.	Num		Perm	Point to the intercurrent event(s) impacting the datapoint, considering only intercurrent events related to estimand zz* and labelled by the y th modality of the labelling variable for the estimand.
ICCEzz*D	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. Only when multiple intercurrent datasets are used for estimand zz.
ICCEzz*V	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. Only when multiple intercurrent variables are used for estimand zz.
ICCyEzz*F	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 for estimand zz, considering only intercurrent events related to estimand zz*. Set to "Y" if the datapoint is impacted by such an intercurrent event, else leave blank.
ICCyEzz*N	Imp. ICE Cat. Val. y for Est. zz* N.Flag	Numr	(1)	Perm	Numerical version of ICCyEzz*F.

Index y represent the yth modality of the naming / categorisation variable in the intercurrent event dataset (ADICE) for estimand zz*. **y is an index that has context within the zz* index.**

Analysis datasets – Impact Variables Structure per intercurrent event categorisation modalities, per estimand

ADICE

USUBJID	ASEQ	ATERM	ADECOD1	ACAT1	ASTDT	EST01STP
ABC003	1	ANTIDEPRES SANTS	Starting other pharmacological treatments	Starting other pharmacological treatments	2022-04-06	HYPOTHETICAL
ABC003	2	LACK OF EFFICACY	Treatment discontinuation due to lack of efficacy	Treatment discontinuation	2022-04-27	TREATMENT POLICY

ACAT1

SO  TD 

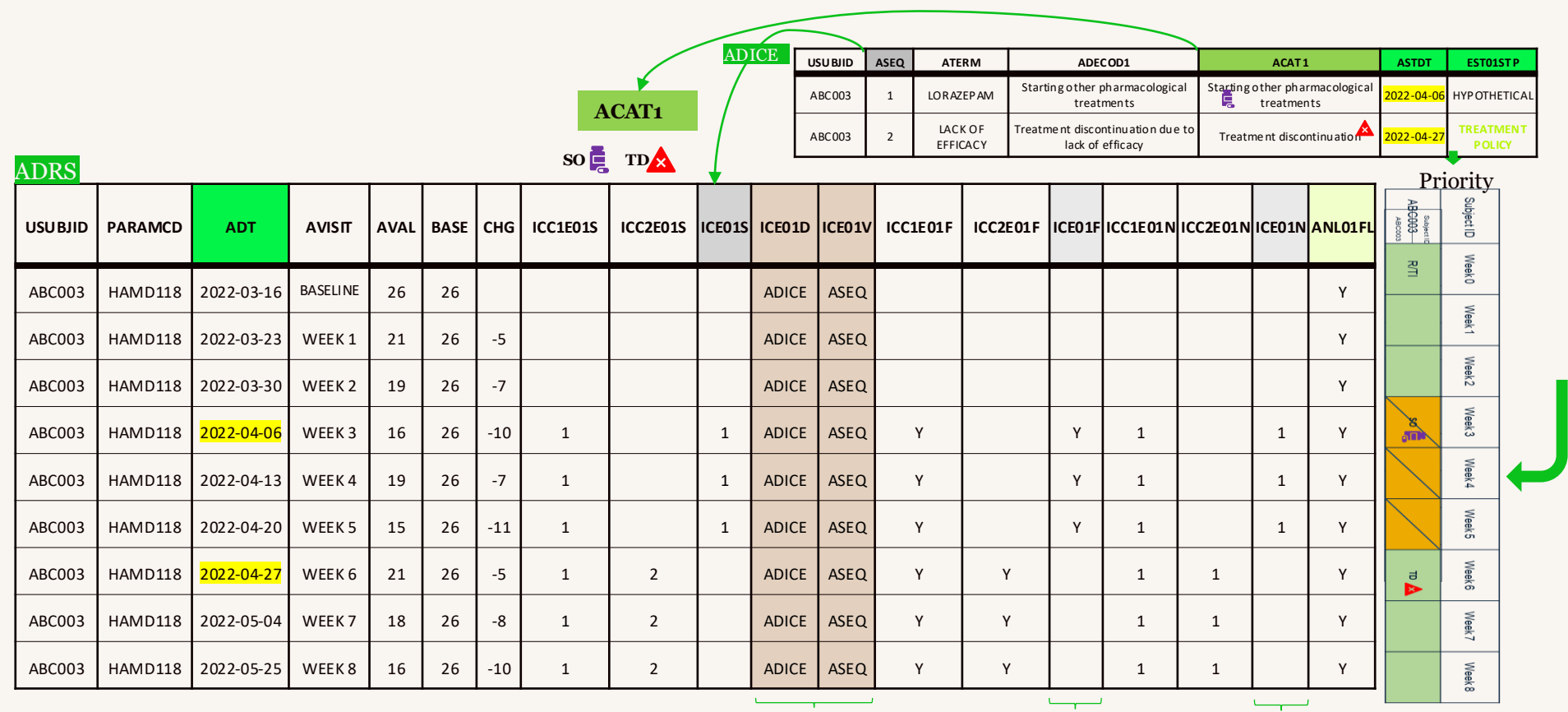
ADRS

USUBJID	PARAMCD	ADT	AVISIT	AVAL	BASE	CHG	ICC1E01S	ICC2E01S	ICCE01D	ICCE01V	ICC1E01F	ICC1E01N	ICC2E01F	ICC2E01N
ABC003	HAMD118	2022-03-16	BASELINE	26	26				ADICE	ASEQ				
ABC003	HAMD118	2022-03-23	WEEK 1	21	26	-5			ADICE	ASEQ				
ABC003	HAMD118	2022-03-30	WEEK 2	19	26	-7			ADICE	ASEQ				
ABC003	HAMD118	2022-04-06	WEEK 3	16	26	-10	1		ADICE	ASEQ	Y	1		
ABC003	HAMD118	2022-04-13	WEEK 4	19	26	-7	1		ADICE	ASEQ	Y	1		
ABC003	HAMD118	2022-04-20	WEEK 5	15	26	-11	1		ADICE	ASEQ	Y	1		
ABC003	HAMD118	2022-04-27	WEEK 6	21	26	-5	1	2	ADICE	ASEQ	Y	1	Y	1
ABC003	HAMD118	2022-05-04	WEEK 7	18	26	-8	1	2	ADICE	ASEQ	Y	1	Y	1
ABC003	HAMD118	2022-05-25	WEEK 8	16	26	-10	1	2	ADICE	ASEQ	Y	1	Y	1

Two applicable modalities in the dataset

In this simple example, the impact variables per category modalities, per estimand are identical to those per category modalities. This is because the same naming/categorisation is used (ACAT1) and both modalities are applicable to estimand 1 (see EST01STP)

Analysis datasets – Impact Variables Example detailed per estimand



There is one impact variable per estimand, which assumes that in case of multiple intercurrent events impacting an endpoint, priority rules are defined.
For estimand 1, Treatment policy handling strategy has presedence over hypothetical strategy.

ADRG Updates Overview

- **NEW section: 3.1 Estimands and Estimators** : synthetic view of estimands and estimators implementation in one place.

Estimand / Estimator ID	Descriptor	Description
1.1: Main estimator	Reference	Protocol Reference: see section 9.3.2.2 SAP reference: see section 1.1, 4.2.2.
	Analysis dataset	Analysis records: ICE01F <= "Y" and ANL01FL = "Y"
	Analysis description	Analysis method: Mixed Effects Repeated Measures Model (MMRM): CHG ~ BASE TRT01PN AVISIT TRT01PN*AVISIT, with measure repeated on USUBJID over AVISIT. Treatment effect estimated through Least Square Mean difference on TRT01PN*AVISIT Analysis details: Please refer SAP Table 8.x.x.x
	Results	Table: Please refer CSR Table 8.x.x.x

- **UPDATE section: 5.1 Overview:**
summary question on estimands

5.1 Overview

- Were there any analysis datasets created to support ICH (E9) R1 estimands framework? <Yes/No>
(if Yes, answer the following questions)
 - What dataset(s) is/are used for storing the intercurrent events?
 - <insert additional text here>
 - What datasets and variables are used to support estimands analyses?
 - <insert additional text here>
 - Is there any additional information regarding implementation of estimands framework?
 - <insert additional text here>

- **RECOMEND section 5.2 Analysis Datasets:**
describe intercurrent dataset(s) ADICE structure
and any datasets with datapoints affected by intercurrent events
as necessary. (e.g. records selection/replacements per handling strategies).

	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					One observation per subject per intercurrent event
ADHDRS Hamilton Depression Scale Analysis dataset	BDS	X				X	One observation per subject per subject, per parameter, per analysis visit
.....							

ADaM Implementation - Summary

ADICE

- New data structure for consistent documentation of all intercurrent events
- Support harmonized workflows

New ADaM Variables

- ADSL: new analysis set flags
- BDS/OCCDS/ADaM Other: new record level variables for intercurrent event traceability and impact

Guidance

- Building upon existing ADaM-IG that already addresses analysis features (estimations)

ADRG

- New section for estimands and estimators implementation

Project Team

- AbbVie - Lauren Shinaberry
- Amgen - Matt Baldwin
- Bayer - Banoo Madhanagopal, Jonathan Siegel, Mindy Mo, Oliver Wirtz
- Biogen - Marian Mitroiu
- Bristol Myers Squibb - Xiaohan Zou
- Eli Lilly - Elisa Gomez, Yongming Qu, Zongjun Zhang, Robin White
- Gilead - Dong Xi
- Johnson & Johnson - Lori Van Meter, Alexandra Cochinaire, Nilani Liyanage, Rosanne Lane
- Merck Group - Cedric Davister
- Novartis - Elena Polverejan, Samson Ghebremariam
- Novo Nordisk - Sujitha Susan John
- Roche - Chris Price

References

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2. ICH E9(R1) Estimands and Sensitivity Analysis in Clinical Trials - Training Module 1: Summary
3. Polverejan E, O'Kelly M, Hefting N, Norton JD, Lim P, Walton MK. Defining Clinical Trial Estimands: A Practical Guide for Study Teams with Examples Based on a Psychiatric Disorder. Ther Innov Regul Sci. 2023 Sep;57(5):911-939. doi: 10.1007/s43441-023-00524-2. Epub 2023 May 27. PMID: 37244885; PMCID: PMC10224760.
4. PSI Online Estimand Workshop March2025; PHUSE Implementation of Estimands using Data standards project team, Cedric Davister, Senior Data Standards Manager, Clinical Measurement Sciences, Merck KGaA and Alexandra Cochinaire, Manager Clinical Data Standards, Johnson & Johnson
5. White paper publication May 19, 2025
 - Main white paper
 - appendix/example



Thank you