Estimands implementation using data standards

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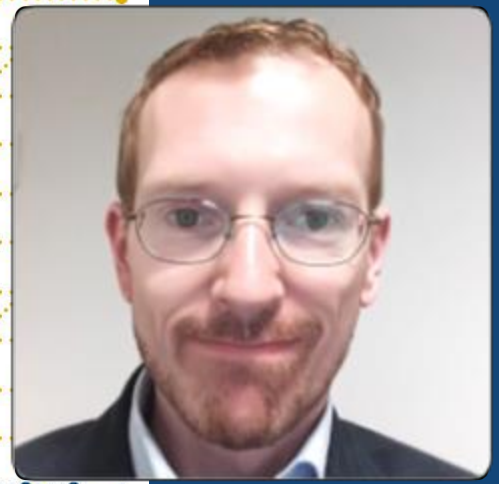
Meet the Speakers



Cedric Davister

Title: Senior Data Standards Manager

Organization: Merck KGaA

Cedric has been working in the pharma industry, in biostatistics and data management, for the last 15+ years; and for almost as long involved with the use of the CDISC standards. Cedric is responsible for the ADaM and TFL standards at Merck KGaA. In the data standards community, Cedric has been involved most recently with the Analysis Results Standard and is currently working on the consolidated ADaMIG team, and on the PHUSE Estimands implementation project.

Alexandra Cochinaire

Title: Lead Clinical Data Standards

Organization: Johnson & Johnson

Alexandra has a diverse background with experience in statistics, statistical programming and clinical data standards. Having worked for both pharmaceutical companies and CROs, her expertise covers various phases of clinical trials from analysis, reporting to regulatory submission across different therapeutic areas.

In her current role at Johnson & Johnson, she supports the Immunology team developing standard templates compliant with CDISC and fit for purpose in collaboration with study programmers and statisticians.

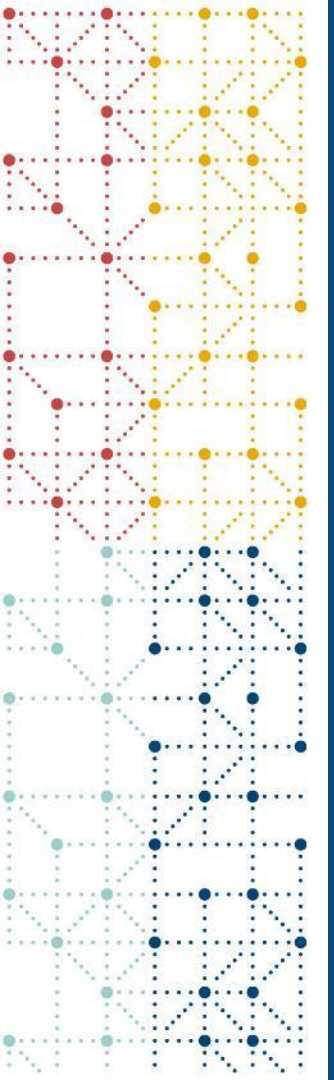
Disclaimer and Disclosures

- *The views and opinions expressed in this presentation are those of the author(s) and do not necessarily reflect the official policy or position of CDISC.*

- *The authors have no real or apparent conflicts of interest to report.*

Agenda

1. Introduction
2. Data Analysis (ADaM, ADRG)
3. Data Analysis - Example
4. Conclusion and Next Steps



1. Introduction

The PHUSE project and Estimands definition

About the project

ICH E9(R1)

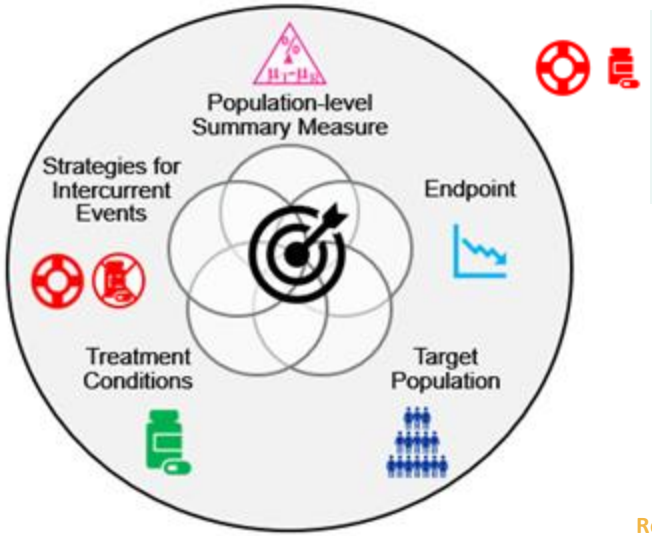
- Addendum to the Guideline on Statistical Principles for Clinical Trials **(ICHE9)** on **Estimands and Sensitivity Analysis in Clinical Trials (R1)**[1,2]: finalized in November 2019 (Step 4)
- Has been or is in the process of being adopted by Health Authorities
- Covers the important multidisciplinary considerations relating to the implementation of the ICH E9(R1) estimands framework for clinical trial planning, design, conduct, analysis and interpretation
- **The technical implementation in the data flow was not in scope**

PHUSE Project

- **Create a White Paper**[3,4] **providing recommendations and best practices to implement the estimands framework in data, based on industry standards**
- Assemble data standards and estimands experts, relevant stakeholders
- Cross-industry, data standards organisations (CDISC) and regulatory agencies (FDA) effort
- Collaboration with CDISC and EIWG (Estimands Implementation Working Group)

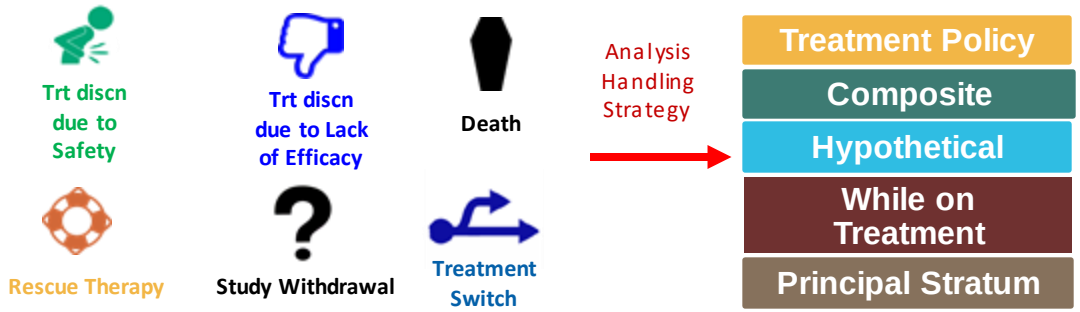
What are Estimands?

Estimands
A precise description of the treatment effect reflecting the clinical question posed by the trial objective. The estimand consists of 5 components:



Intercurrent Events

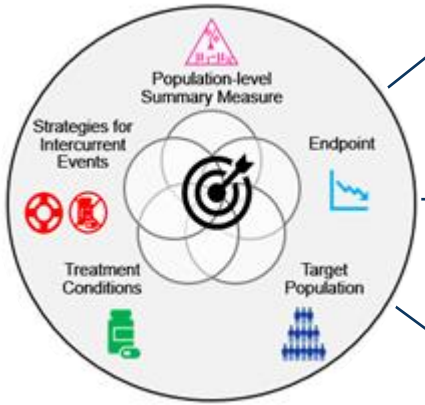
Events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest



5 Strategies for Intercurrent Events[2]

Treatment Policy	Composite	Hypothetical	While on Treatment	Principal Stratum
• Occurrence of the intercurrent event is irrelevant • Value for the variable of interest is used regardless of whether the intercurrent event occurs	• Intercurrent event considered to be informative about the patient's outcome • Incorporated into the definition of the variable	• Scenario in which event does not occur • Disregard data collected after start of event	• Response to treatment prior to the occurrence of the intercurrent event is of interest • Outcome after intercurrent event is considered irrelevant	• As part of target population definition • Population is defined by those in whom the intercurrent event would or would not occur

Estimands Impact on Analysis



Analysis & data

- Mapping intercurrent events
- Analysis sets and estimand-based analyses
- Identifying data points impacted by intercurrent events, traceability, handling strategy

Documentation & Traceability

- Consistent documentation of the estimands implementation - ADRG
- Traceability from protocol/SAP to the data.

Flexible Solutions

- Based on user needs
- Proposed examples in white paper

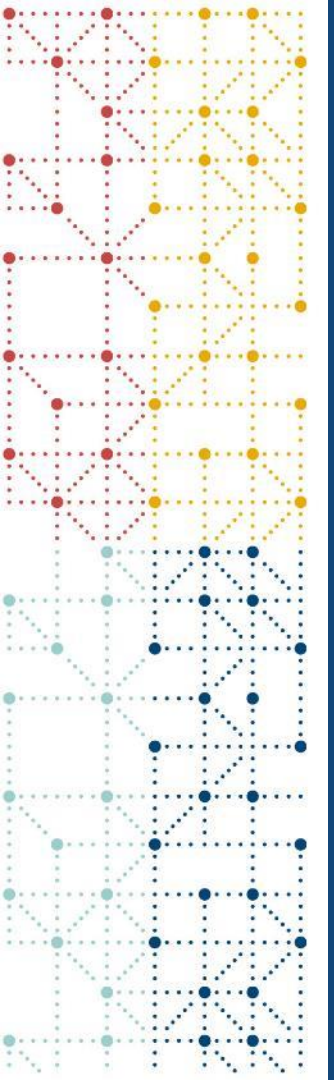
Design principles

- Estimands: broad application scope, relatively new topic

ADaM implementation framework: balance flexibility and consistency

ADaM
New data structure and variables cover key use cases
Flexible, pick what is needed.

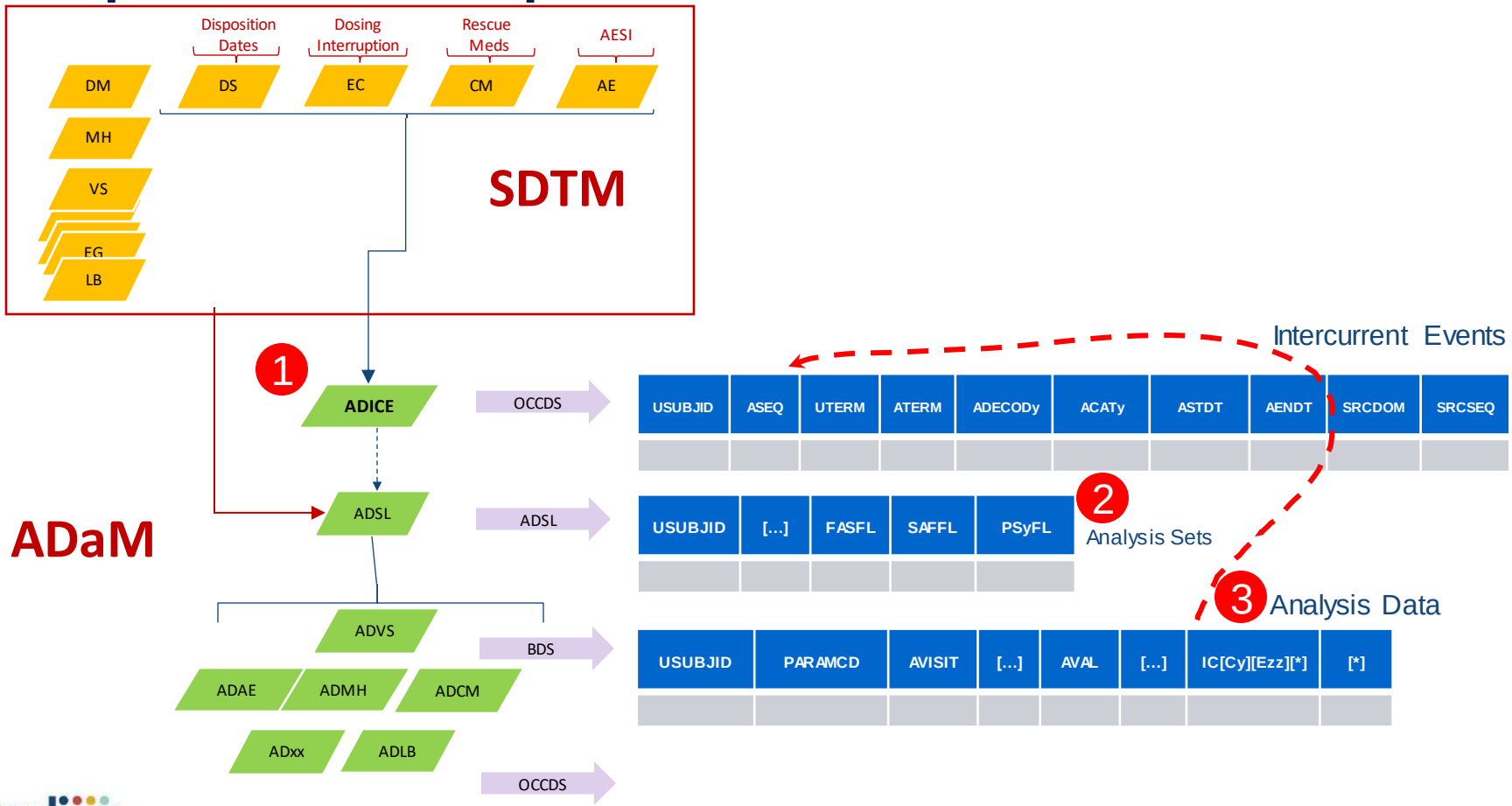
ADRG
New section to document estimands implementation strategy.
Consistent documentation



2. Analysis Data (ADaM, ADRG)

Analysis Data Implementation Recommendations

Proposed ADaM Implementation - Overview



NEW Intercurrent Events Data structure (OCCDS-ICE)

- Optional and supportive data structure to consolidate all intercurrent events
- Facilitates traceability and the referencing of intercurrent events from other datasets
- Built from multiple sources (typically SDTM domains)
- OCCDS structure: one record per subject, per intercurrent event

ADICE ← recommend one dataset (InterCurrent Events Analysis Dataset)

USUBJID	ASEQ	ATERM	ADECODy	ACATy	ASTDT(M)	AENDT(M)	SRCDOM	SRCSEQ	[…]

- Key features:
  - Naming/Categorisation: ATERM / ADECODy / ACATy : original name/ standardised names / categories of intercurrent events – actual selection of variables depending on trial/analyses needs.
  - Traceability: ASEQ to refer to records in ADICE; SRCDOM, SRCSEQ to point to source records

- Under consideration:
  - Documenting the actual/planned strategy associated with the intercurrent events, per estimand
  - Documenting the intercurrent event impact rules and impact start/end dates (impact start/end may differ from event start/end)
  - Grouping intercurrent events

NEW ADSL variables

Analysis sets: add supports for principal stratum strategies

- **PSyFL (**Principal Stratum y Set Flag): subject in principal stratum y.
  - ► set of subjects with/without occurrence of an intercurrent event

USUBJID	[…]	FASFL	SAFFL	PSyFL	[...]

NEW Analysis Datasets Variables (BDS, OCCDS, ADaM OTHER)

- Extra variables that can be added to any BDS/OCCDS/ADaM Other dataset to relate data points to intercurrent events
  - **IC[Cy][Ezz]*[S]* (Impact. [ICE class y][for estimand zz] *Seq.*)**: Link the intercurrent event(s) and datapoints.
    - ► point to the identifier of an intercurrent event (typically ***ASEQ)*** impacting the datapoint.
  - ICCyS: identify intercurrent events impacting the interpretation/usage of the datapoint. y is an index based on the values of *one* of the ADECODy/ACATy variables from ADICE.
  - ICEzzS: identify the one intercurrent event impacting the usage of the datapoint for estimand zz, based on the strategy. Assumes priority rules.
  - ICCyEzzS: for more complex cases, refine ICCy* per estimand. E.g. use a different ADECODy/ACATy variable per estimand.

USUBJID	PARAMCD	AVISIT	[…]	AVAL	[...]	IC[Cy][Ezz][*]

Extra suffixes ***[D] Dom., [V] Var., [F] flag, [N] Fl. N***

- Under consideration
  - Indicator to document action on the record (e.g. use/drop/replace) in relation to estimand zz.
  - Record type: original record, imputed record (missing value), replaced record (intercurrent event strategy).

ADRG – updates

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

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

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

3. Analysis Data - Example

Analysis Data Example

Examples – Analysis Data - case description

Question of interest leading to estimand 01[4,5]:

What is the treatment effect of

drug monotherapy X versus placebo

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

in patients with Major Depressive Disorder (MDD),

regardless of treatment adherence and as if there were no other antidepressant medications available administered concomitantly with study treatment ?

Example – Estimands in Major Depressive Disorder[4,5]

Treatment conditions	• Assignment to drug X vs placebo, at the selected dose and frequency of administration, regardless of treatment discontinuation and as if other pharmacological treatments for MDD were not available
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
Strategies for Intercurrent events	• **Treatment policy** strategy is used for any treatment discontinuation (**TD**) • **Hypothetical strategy** is used for addressing starting other pharmacological treatments for MDD (**SO**) - Priority of Treatment policy over Hypothetical strategy in case both would be applicable.

Examples – Analysis Data - case description

Subject ID	Week 0	Week 1	Week 2	Unsch week 2.1	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8
ABC001	R/TI			---			SO			
ABC002	R/TI		TD	SO						
ABC003	R/TI			---	SO			TD		

Outcome collected

Start other medications for MDD

Treatment discontinuation

Examples – Analysis Data - case description

Subject ID	Week 0	Week 1	Week 2	Unsch week 2.1	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8
ABC001	R/TI			---			SO			
ABC002	R/TI		TD	SO						
ABC003	R/TI			---	SO			TD		

Outcome collected
/ Replacement outcome data following hypothetical strategy

Start other medications for MDD

Treatment discontinuation

Hypothetical strategy: disregard data collected after start of event (remove/replace)

Treatment policy: use data regardless of event (confounded with treatment). *Has priority over other intercurrent events in this study.*

Examples – Analysis Data - ADICE

USUBJID	ASEQ	ATERM	ADECOD1	ACAT1	ASTDT	AENDT	EST01STP	EST01STA	SRCDOM	SRCSEQ
ABC001	1	DULOXETINE	Starting other pharmacological treatments	Starting other pharmacological treatments	20APR2022		Hypothetical	Hypothetical	CM	1
ABC002	1	ADVERSE EVENT	Treatment discontinuation due to adverse events	Treatment discontinuation	30MAR2022		Treatment Policy	Treatment Policy	DS	3
ABC002	2	FLUOXETINE	Starting other pharmacological treatments	Starting other pharmacological treatments	03APR2022		Hypothetical		CM	1
ABC003	1	LORAZEPAM	Starting other pharmacological treatments	Starting other pharmacological treatments	06APR2022	20APR2022	Hypothetical	Hypothetical	CM	1
ABC003	2	LACK OF EFFICACY	Treatment discontinuation due to lack of efficacy	Treatment discontinuation	27APR2022		Treatment Policy	Treatment Policy	DS	3

Unique sequence number of the event within a subject

Term/treatment from SDTM source domain, for traceability.

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

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

Start/End Date(time) derived from SDTM --STDTC/--ENDTC variables

Planned strategy, per protocol/SAP

Actual strategy, considering priority rules (treatment policy has precedence per SAP)

Examples – Analysis Data - ADHDRS

USUBJID	PARAMCD	ADT	AVISIT	AVAL	BASE	CHG	ICC01S	ICC02S	ICE01S	ANL01FL	E01AC
ABC001	HDRS	16MAR2022	BASELINE	25	25					Y	USE
ABC001	HDRS	23MAR2022	WEEK 1	26	25	1				Y	USE
ABC001	HDRS	30MAR2022	WEEK 2	24	25	-1				Y	USE
ABC001	HDRS	06JUN2022	WEEK 3	23	25	-2				Y	USE
ABC001	HDRS	13APR2022	WEEK 4	19	25	-6				Y	USE
ABC001	HDRS	20APR2022	WEEK 5	18	25	-7	1		1	Y	REPLACE
ABC001	HDRS	27APR2022	WEEK 6	23	25	-2	1		1	Y	REPLACE
ABC001	HDRS	04MAY2022	WEEK 7	21	25	-4	1		1	Y	REPLACE
ABC001	HDRS	25MAY2022	WEEK 8	16	25	-9	1		1	Y	REPLACE
ABC002	HDRS	16MAR2022	BASELINE	31	31					Y	USE
ABC002	HDRS	23MAR2022	WEEK 1	31	31	0				Y	USE
ABC002	HDRS	30MAR2022	WEEK 2	30	31	-1		1		Y	USE
ABC002	HDRS	03APR2022	WEEK 2 UNSCHEDULED	16	31	-15	2	1			USE
ABC002	HDRS	06JUN2022	WEEK 3	30	31	-1	2	1		Y	USE
ABC002	HDRS	13APR2022	WEEK 4	32	31	1	2	1		Y	USE
ABC002	HDRS	20APR2022	WEEK 5	30	31	-1	2	1		Y	USE
ABC002	HDRS	27APR2022	WEEK 6	34	31	3	2	1		Y	USE
ABC002	HDRS	04MAY2022	WEEK 7	29	31	-2	2	1		Y	USE
ABC002	HDRS	25MAY2022	WEEK 8	28	31	-3	2	1		Y	USE
ABC003	HDRS	16MAR2022	BASELINE	26	26					Y	USE
ABC003	HDRS	23MAR2022	WEEK 1	21	26	-5				Y	USE
ABC003	HDRS	30MAR2022	WEEK 2	19	26	-7				Y	USE
ABC003	HDRS	06APR2022	WEEK 3	16	26	-10	1		1	Y	REPLACE
ABC003	HDRS	13APR2022	WEEK 4	19	26	-7	1		1	Y	REPLACE
ABC003	HDRS	20APR2022	WEEK 5	15	26	-11	1		1	Y	REPLACE
ABC003	HDRS	27APR2022	WEEK 6	21	26	-5	1	2		Y	USE
ABC003	HDRS	04MAY2022	WEEK 7	18	26	-8	1	2		Y	USE
ABC003	HDRS	25MAY2022	WEEK 8	16	26	-10	1	2		Y	USE

Examples – Analysis Data - ADHDRS

SO TD

USUBJID	PARAMCD	ADT	AVISIT	AVAL	BASE	CHG	ICC01S	ICC02S	ICE01S	ANL01FL	E01AC
ABC003	HDRS	16MAR2022	BASELINE	26	26					Y	USE
ABC003	HDRS	23MAR2022	WEEK 1	21	26	-5				Y	USE
ABC003	HDRS	30MAR2022	WEEK 2	19	26	-7				Y	USE
ABC003	HDRS	06APR2022	WEEK 3	16	26	-10	1		1	Y	REPLACE
ABC003	HDRS	13APR2022	WEEK 4	19	26	-7	1		1	Y	REPLACE
ABC003	HDRS	20APR2022	WEEK 5	15	26	-11	1		1	Y	REPLACE
ABC003	HDRS	27APR2022	WEEK 6	21	26	-5	1	2		Y	USE
ABC003	HDRS	04MAY2022	WEEK 7	18	26	-8	1	2		Y	USE
ABC003	HDRS	25MAY2022	WEEK 8	16	26	-10	1	2		Y	USE

Document potential impact on data point of all intercurrent events, based on ACAT1 categorisation ICC01=Start Other Medicaton for MDD, ICC02 = Treatment Discontinuation

Document effective impact for estimand 1, i.e. considering priority rule and handling strategy

ADRG – updates – new section 3.1 + misc updates

3. Analysis Considerations Related to Multiple Analysis Datasets

3.1 Estimands and Estimators

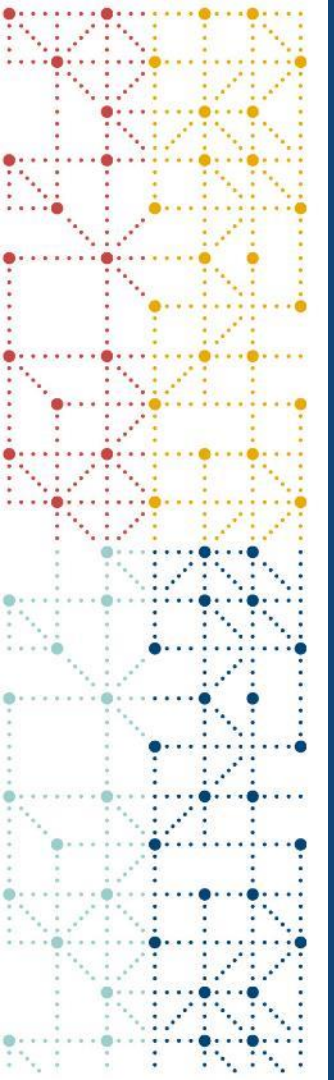
Estimand / Estimator ID	Descriptor	Description
1: Estimand 01 (E1)	Protocol SAP	Protocol reference: see section 3. SAP reference: see section 1.1.
	Analysis dataset	Dataset name: ADHDRS ICE impact variable(s):ICE01S, ICC01S, ICC02S. Treatment variable: TRT01P, TRT01PN Treatment modalities: Placebo (1), Drug X (2) Endpoint variable: CHG where PARAM = “HAMD1 - Total Score” Timing variable: AVISIT (only scheduled visit are considered for the estimations) from “BASELINE / WEEK 0” to “WEEK 7’" Covariable(s): BASE Additional dataset: none.
	Analysis set	Full analysis set, see SAP section 3. Analysis Sets. FASFL=“Y”
	Population level summary	Summary statistic: difference in treatment means
	Intercurrent Event dataset(s) and variables	Dataset(s) name: ADICE ICE source name variable: ATERM ICE coded name/group variable and modalities: ACAT1(Treatment discontinuation, Starting other pharmacological treatments) Estimand strategy variable: EST01STA Strategies: •ACAT1(Treatment discontinuation): Treatment Policy •ACAT1(Starting other pharmacological treatments): Hypothetical

ADRG – updates – new section 3.1 + misc updates

3. Analysis Considerations Related to Multiple Analysis Datasets

3.1 Estimands and Estimators

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: EST01RFL = "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



4. Conclusion

Final thoughts and next steps in the project

Analysis Data - 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: 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

Conclusion

Broad community engagement is key to success

Cross-functional interaction critical

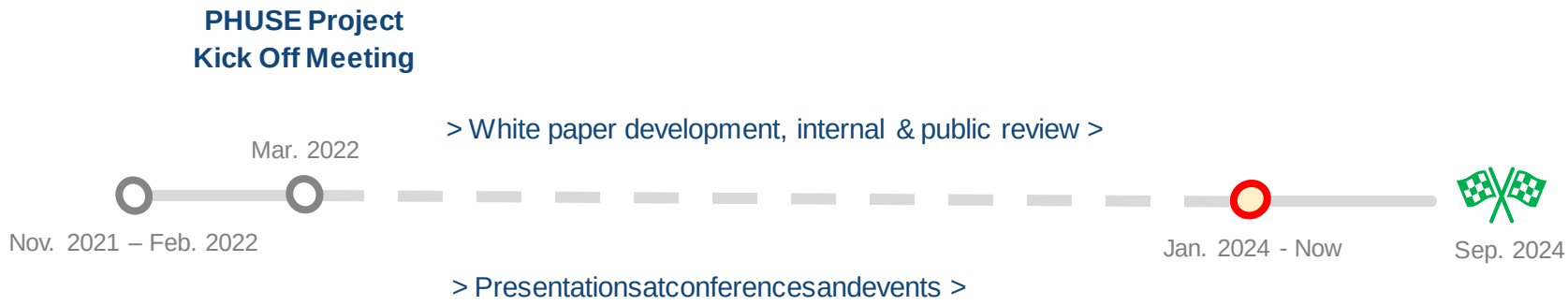
Different implementation approaches may be appropriate

Need to update/extend existing data standards

Consistent implementation of estimands is beneficial

White paper is a first step to lay foundations

Project history and next steps



Build team: Industry, SDOs and FDA

Broad representativity

Finalise the white paper
Work on review comments (100+)
+ Collaboration with EIWG*

Constant engagement with the community, seeking feedbacks

* Estimands Implementation Working Group

Thank You!

e-mail: workinggroups@phuse.global

PHUSE Advance Hub: Implementation of Estimands (ICH E9 R1) using Data Standards

References

1. ICH E9(R1) Addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). Updated Nov 20, 2019.

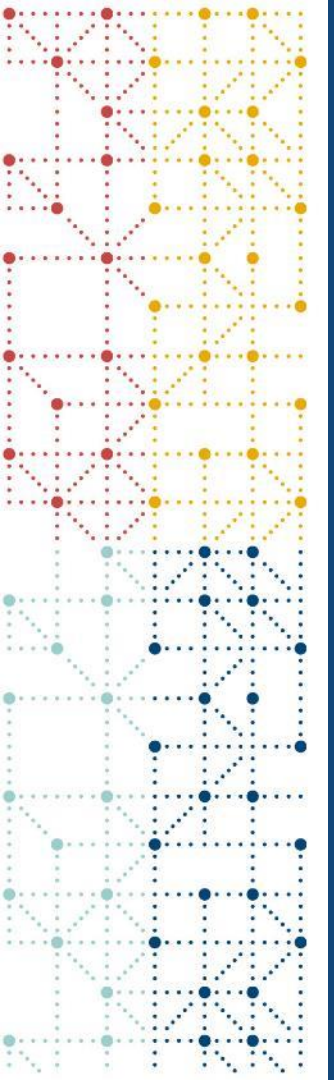
2. ICH E9(R1) Estimands and Sensitivity Analysis in Clinical Trials - Training Module 1: Summary

3. PHUSE Estimands Implementation white paper (public review draft)

4. and Appendix examples (public review draft)

5. 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.

6. PHUSE deliverables (future release area)

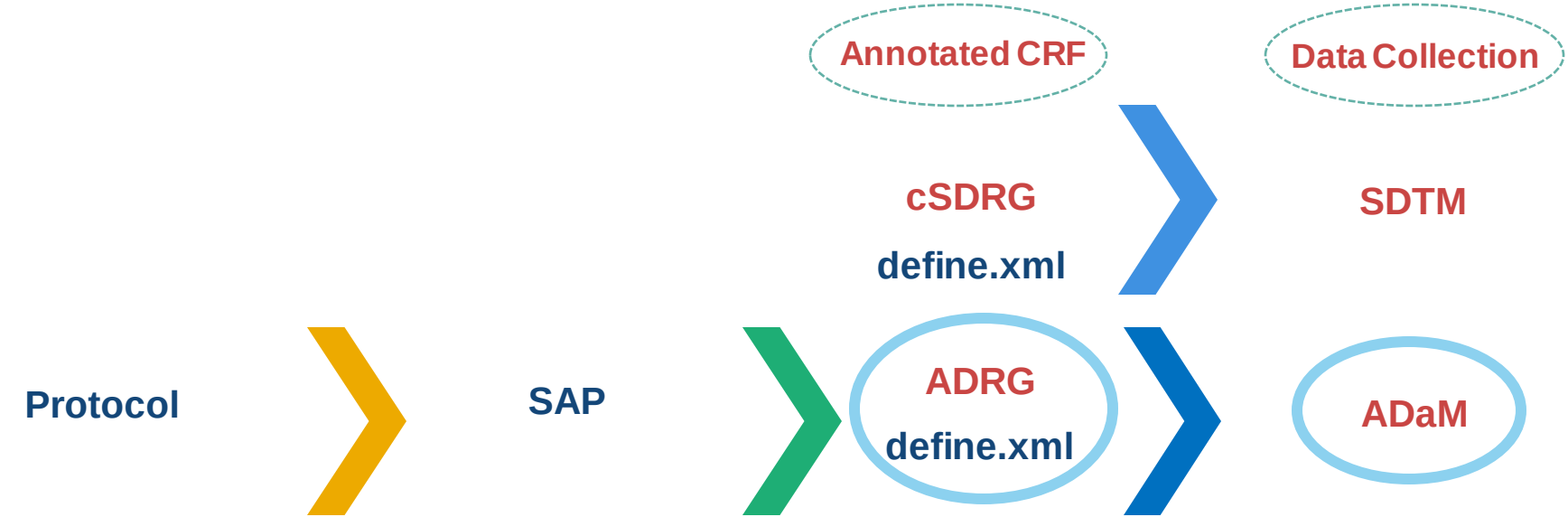


BACKUP

Extra material

Documentation to Data

Get **sufficiently detailed answers** during collection



Describe the study objective in terms of the estimands framework (**WHAT**)

Statistical details on estimand (**WHAT detailed**), link estimandst o their estimators (**HOW performed statistically**)

HOW the relevant aspects of estimands were **implemented** in the data. New section on estimands in CSDRG & ADRG

Dedicated datasets and variables to document the traceability of estimands and impact in the data

Data Collection and Tabulation - Overall recommendations

Accurate collection of intercurrent events is critical to support estimands approach and constructing the estimators

Granular collection is important to precisely asses intercurrent events; especially reasons for treatment discontinuations and use of concomitant medications, the main sources of intercurrent events

Complete collection of data points with respect to handling strategy of intercurrent events is key to make proper estimations of the effect of interest

Data collection enhancements enable to use the most appropriate strategies to handle intercurrent events based on the underlying reasons

Data Collection & Tabulation - Summary

Data Collection	• Accuracy and Granularity • 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

Next steps to prepare the final white paper

- Finalise the Build a document that is effective and meets stakeholders needs
  - Add all clarifications and precisions based on the public review feedbacks: 100+ comments
  - Collaboration with EIWG to finalise the design of the analysis datasets

- What to expect compared to the public review draft:
  1. Overall: cleaning and clarifying the current text to better convey the message/mechanics of the framework – but no fundamental changes in proposed framework (bulk of changes).
  2. Section 5 CRF: some refinement/discussions on terminology but no structural change (to confirm by sub-team 1).
  3. Section 6 Analysis: no structural changes considered, very likely tweaks/replacement of some variables, e.g. ESTzz(R)FL.
  4. Example: possible some adjustment to reflect FDA feedback and section 6 variable tweaks.
  5. Intermediate ADaM datasets: combining datapoints and intercurrent events records to provide a timeline view.