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

PHUSE Japan SDE 2023

Chris Price (Roche)

Shahida Tamboli (Fortrea)

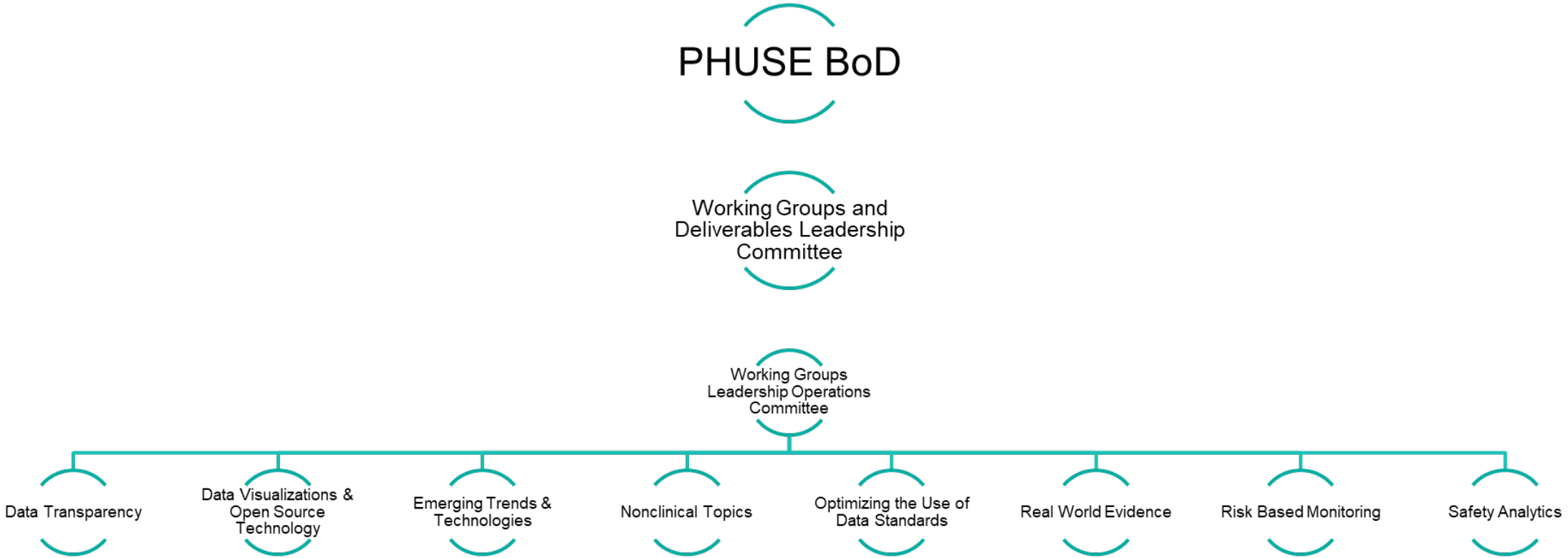
Disclaimers

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

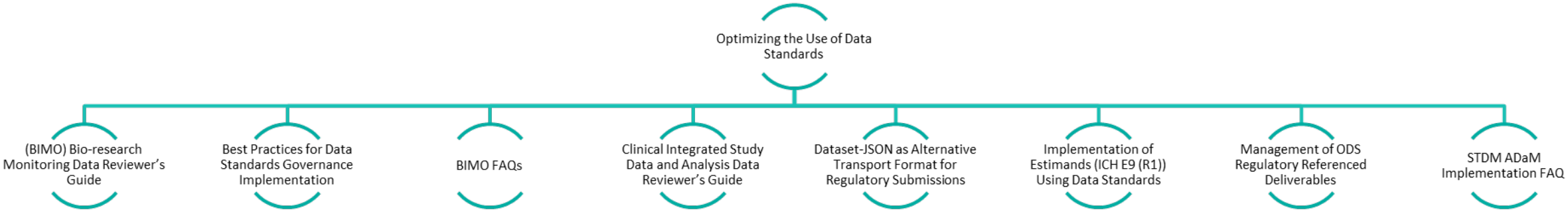
This PHUSE project includes members from PHUSE collaborative partners and stakeholders and is currently ongoing, the final white paper will be shared for public review. Consequently, these recommendations are subject to change upon completion of the public review.

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.

PHUSE Working Groups

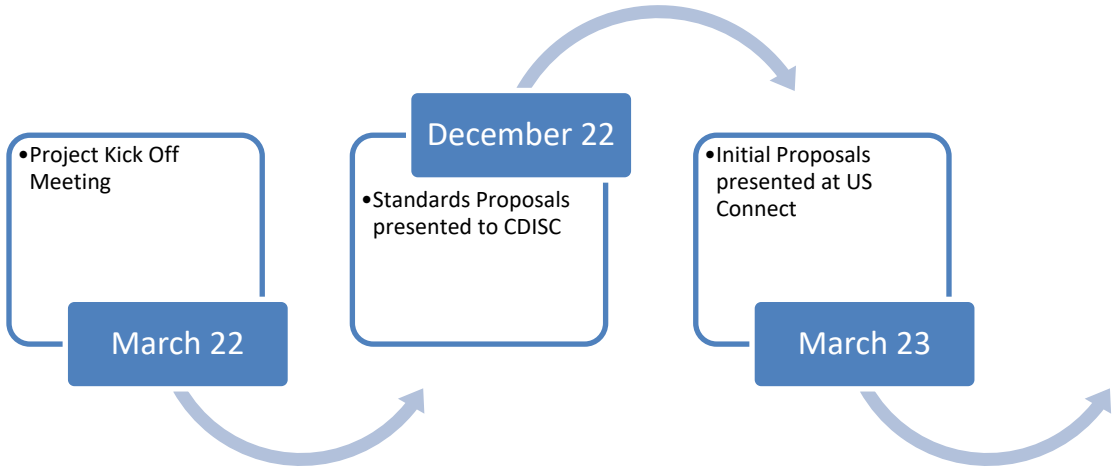


Optimizing the Use of Data Standards



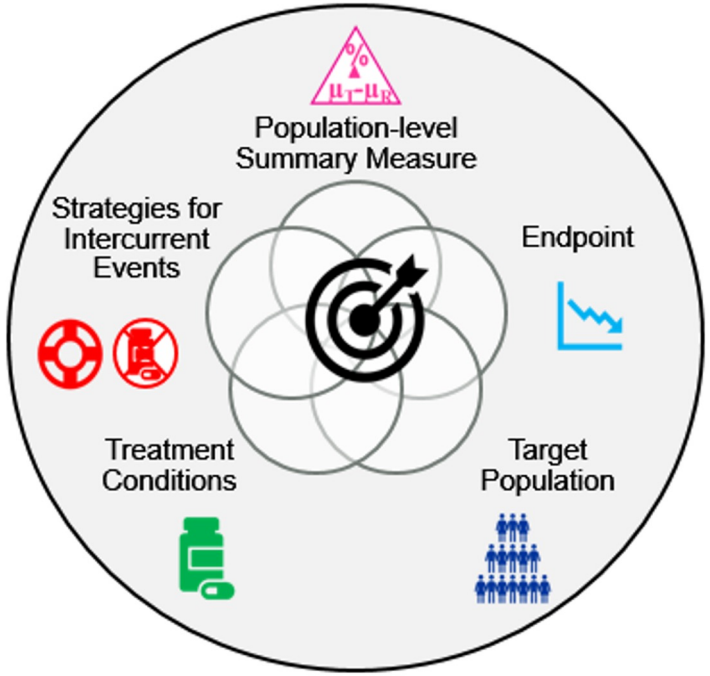
Introduction

Project Team


•Project Kick Off Meeting
March 22
December 22
•Standards Proposals presented to CDISC
•Initial Proposals presented at US Connect
March 23

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:



*Slide courtesy of Roche

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

- Trt discn due to Safety
- Trt discn due to Lack of Efficacy
- Death
- Rescue Therapy
- Study Withdrawal
- Treatment Switch

Analysis Handling Strategy →

- Treatment Policy
- Composite
- Hypothetical
- While on Treatment
- Principal Stratum

Documentation to Data

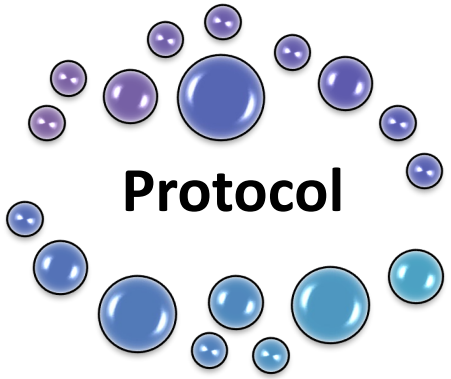
Get **sufficiently detailed answers** during collection

Annotated CRF

Data Collection

cSDRG

SDTM



Protocol

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

SAP

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

ADRG
Define.xml

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

ADaM

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

Data Collection & Tabulation

Current Data Collection Practices

What was the subject's status?

- ○ Progressive Disease (PROGRESSIVE DISEASE)
- ○ Adverse Event (ADVERSE EVENT)
- ○ Death (DEATH)
- ○ Withdrawal by Subject (WITHDRAWAL BY SUBJECT)
- ○ Physician Decision (PHYSICIAN DECISION)
- ○ Non-Compliance With Study Drug (NON-COMPLIANCE WITH STUDY DRUG)
- ○ Protocol Deviation (PROTOCOL DEVIATION)
- ○ Study Terminated by IRB / ERB (STUDY TERMINATED BY IRB / ERB)
- ○ Study Terminated by Sponsor (STUDY TERMINATED BY SPONSOR)
- ○ Lost to follow up (LOST TO FOLLOW-UP)
- ○ Pregnancy (PREGNANCY)

Need for Data Collection Enhancements

- Accurate collection of intercurrent events is critical in defining estimands and constructing the estimators

- Granular data collection of the reasons for treatment discontinuations

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

Commonly Observed Intercurrent Events

Intercurrent Events – Treatment Discontinuation

Suggested CRF for Treatment Discontinuation

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	○ DEATH ○ ADVERSE EVENT. List the adverse event ID: _____ ○ PREGNANCY ○ LACK OF EFFICACY ○ SUFFICIENT EFFICACY PROTOCOL DEVIATIONS ○ DID NOT MEET STUDY ELIGIBILITY CRITERIA AT ENROLLMENT ○ TOOK PROTOCOL PROHIBITED CONCOMITANT MEDS ○ NONCOMPLIANCE TO STUDY PROCEDURES ○ NON-COMPLIANCE WITH STUDY DRUG 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

SDTM Mapping DS Domain

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

Intercurrent Events – Concomitant Medication

Suggested CRF for Concomitant Medication

Indicate if the subject took any concomitant medication/treatment.	Were any concomitant medications taken? Not submitted	o Yes o 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	o ADVERSE EVENT. LINK TO ADVERSE EVENT: _____ o MEDICAL HISTORY. LINK TO MEDICAL HISTORY: _____ o CLINICAL EVENT. LINK TO CLINICAL EVENT: _____ o PROPHYLAXIS FOR ANTIVIRAL o PROPHYLAXIS FOR ANTIFUNGAL o PROPHYLAXIS FOR INFECTION o PROPHYLAXIS FOR INFUSION REACTION o THROMBOPROPHYLAXIS o PROPHYLAXIS FOR TUMOR LYSIS SYNDROME o PROPHYLAXIS FOR COVID-19 o VACCINATIONS o REQUIRED CONCOMITANT MEDICATION FOR THE STUDY o <STUDY INDICATION> o RESCUE THERAPY o BRIDGING THERAPY o NON-THERAPEUTIC USE o SUPPORTIVE CARE o DIETARY SUPPLEMENT
	Start Date CM.CMSTDTC	
	Is the medication ongoing? CM.CMENRF or CMENRTPT	o Yes
	End date CM.CMENDTC	

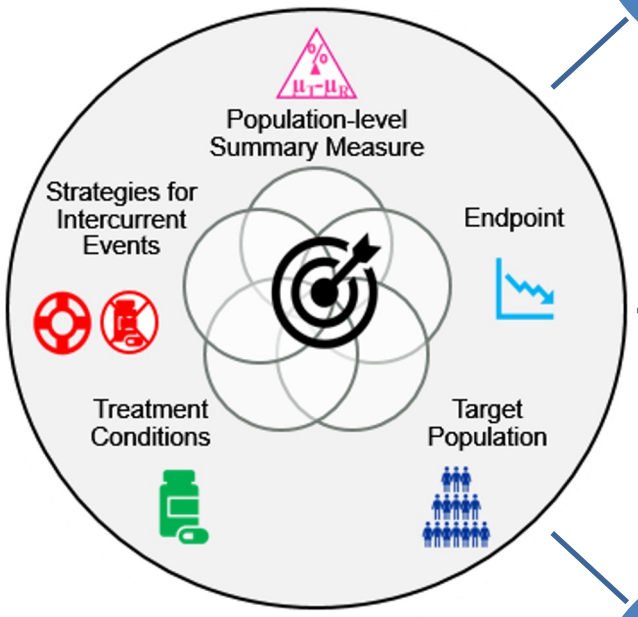
SDTM Mapping CM Domain

Row	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

Data Collection & Tabulation - Summary


Data
Analysis

Estimands Impact on Analysis



Analysis

- Mapping intercurrent events
- Identifying subjects and data points for estimand-based analyses
- Enhanced ADaM dataset guidance is needed

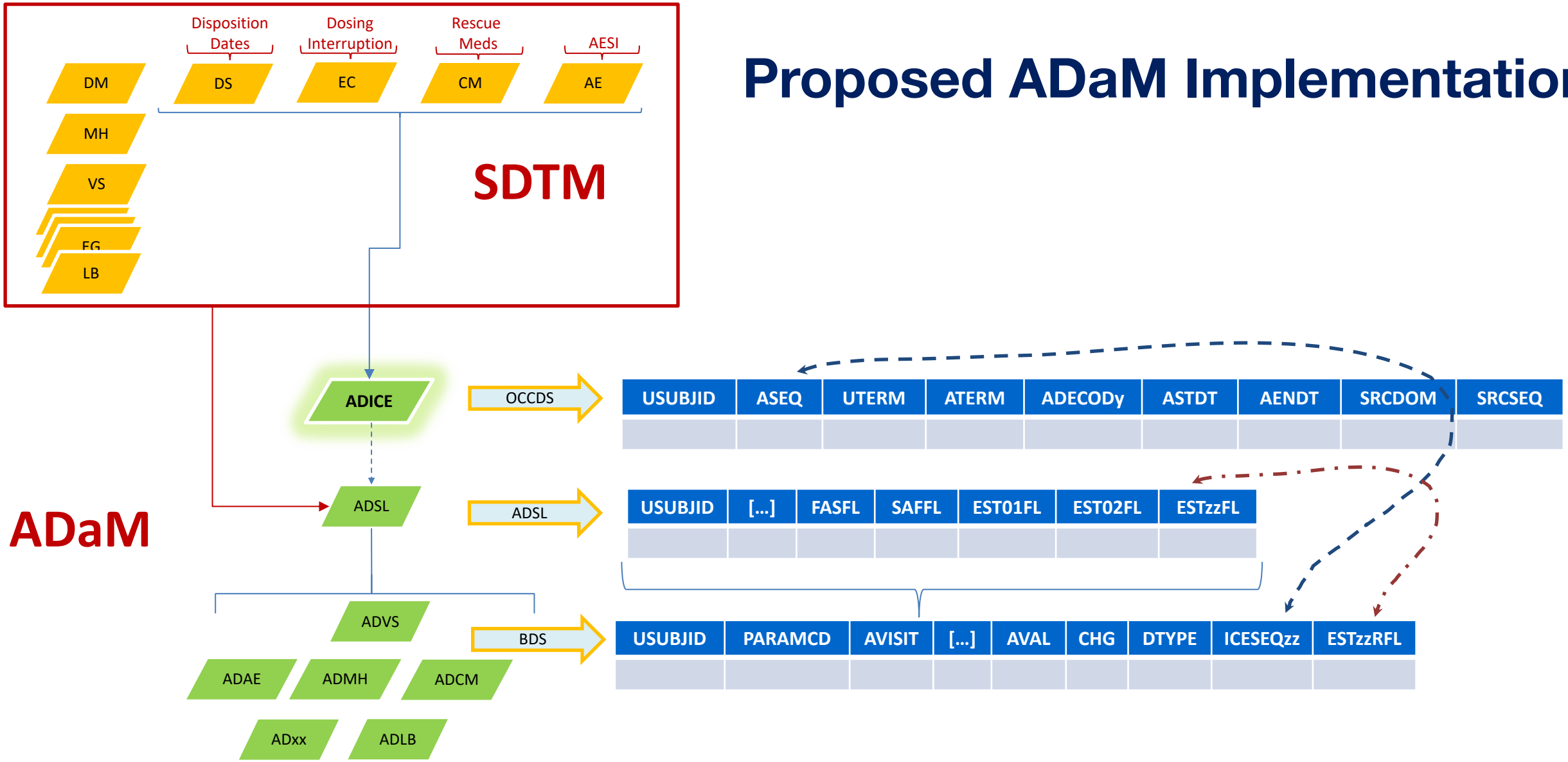
Traceability

- Documentation
- Estimands description and implementation

Flexible Solutions

- Based on user needs
- Proposed examples will be offered in white paper

Proposed ADaM Implementation



NEW Intercurrent Events Dataset (ADICE)

- Documents intercurrent events across all estimands
- Facilitates traceability and inclusion of intercurrent events into other datasets
- OCCDS structure (one record per intercurrent event)
- This is an ***optional*** and supportive dataset to consolidate all intercurrent events in one place

USUBJID	ASEQ	ATERM	ADECODy	ASTDT(M)	AENDT(M)	SRCDOM	SRCSEQ

- Optional columns per estimand:
  - **ESTzzSTR**: Strategy (e.g., treatment policy) for handling the intercurrent event for estimand zz
  - **ESzzGRID**: Group multiple intercurrent events affecting a datapoint for estimand zz

NEW ADaM Dataset Variables

- ADSL (Subject-Level)

USUBJID	[…]	FASFL	SAFFL	EST01FL	EST02FL	ESTzzFL

  - **ESTzzFL**: Subjects considered in all estimand zz estimations

- BDS (Basic Data Structure)

USUBJID	PARAMCD	AVISIT	[…]	AVAL	CHG	DTYPE	ICESEQzz	EST01RFL	EST02RFL	ESTzzRFL

  - **ESTzzRFL**: Record-level datapoints considered in all estimand zz estimations
  - **ICESEQzz**: Links the intercurrent event(s) impacting the datapoint for estimand zz
    - Point to **ASEQ** of the single intercurrent event affecting the datapoint
    - Point to **ESzzGRID** of the multiple intercurrent events affecting the datapoint (advanced)
    - Note: if ADICE is not implemented: **ICEDOMzz** and **ICEVARzz** link to SDTM source
  - Similar for OCCDS and ADaM OTHER structures

Example – Major Depressive Disorder (MDD)

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

Example - Subject Journeys

Subject ID	BASELINE / 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 x any			
ABC002	R/TI		TD (xAE/LoE)	SO x any						
ABC003	R/TI				SO x any			TD (xAE/LoE)		
ABC004	R/TI									

Outcome collected

No intercurrent event, all outcomes collected

'New' outcome data following hypothetical strategy for addressing the intercurrent event

R/TI= Randomisation/Treatment initiation

Intercurrent Event of interest:

TD (xAE/LoE): Treatment discontinuation due to adverse event or lack of efficacy

SO x any: Start of other pharmaceutical treatment for any reason

Example - ADICE

USUBJID	ASEQ	ATERM	ADECOD1	*ACAT1*	ASTDT	AENDT	EST01STR	EST03STR	SRCDOM	SRCSEQ
ABC001	1	DULOXETINE	Starting other pharmacological treatments	Starting other pharmacological treatments	10APR2022		Hypothetical		CM	1
ABC002	1	ADVERSE EVENT	Treatment discontinuation due to adverse events	Treatment discontinuation	30MAR2022		Treatment Policy	Composite	DS	3
ABC002	2	FLUOXETINE	Starting other pharmacological treatments	Starting other pharmacological treatments	03APR2022		Treatment Policy		CM	1
ABC003	1	LORAZEPAM	Starting other pharmacological treatments	Starting other pharmacological treatments	06APR2022	20APR2022	Treatment Policy		CM	1
ABC003	2	LACK OF EFFICACY	Treatment discontinuation due to lack of efficacy	Treatment discontinuation	27APR2022		Treatment Policy	Composite	DS	3

Example - ADHDRS

USUBJID	PARAMCD	ADT	AVISIT	AVAL	BASE	CHG	ICESEQ01	ICESEQ03	ANL01FL	EST01RF	EST03RFL
ABC001	HDRS	16MAR2022	BASELINE	25	25				Y	Y	Y
ABC001	HDRS	23MAR2022	WEEK 1	26	25	1			Y	Y	Y
ABC001	HDRS	30MAR2022	WEEK 2	24	25	-1			Y	Y	Y
ABC001	HDRS	06JUN2022	WEEK 3	23	25	-2			Y	Y	Y
ABC001	HDRS	13APR2022	WEEK 4	19	25	-6			Y	Y	Y
ABC001	HDRS	20APR2022	WEEK 5	18	25	-7	1		Y		Y
ABC001	HDRS	27APR2022	WEEK 6	23	25	-2			Y		Y
ABC001	HDRS	04MAY2022	WEEK 7	21	25	-4			Y		Y
ABC001	HDRS	25MAY2022	WEEK 8	16	25	-9			Y		Y
ABC002	HDRS	16MAR2022	BASELINE	31	31				Y	Y	Y
ABC002	HDRS	23MAR2022	WEEK 1	31	31	0			Y	Y	Y
ABC002	HDRS	30MAR2022	WEEK 2	30	31	-1	1	1	Y	Y	
ABC002	HDRS	03APR2022	WEEK 2 UNSCHEDULED	16	31	-15	2			Y	
ABC002	HDRS	06JUN2022	WEEK 3	30	31	-1			Y	Y	
ABC002	HDRS	13APR2022	WEEK 4	32	31	1			Y	Y	
ABC002	HDRS	20APR2022	WEEK 5	30	31	-1			Y	Y	
ABC002	HDRS	27APR2022	WEEK 6	34	31	3			Y	Y	
ABC002	HDRS	04MAY2022	WEEK 7	29	31	-2			Y	Y	

Data Analysis - Summary

Conclusion & Next Steps

Conclusion

Cross-functional interaction is critical

Impacts protocol, data collection and data analysis

Different implementation approaches may be appropriate

Need to update/extend existing data standards

Consistent implementation of estimands is beneficial

How Can You Help?

White paper now available for public review

Share with colleagues

Provide us feedback

Final Paper due Q1 24

Share in your organizations

Implement

Contact Information

Email: workinggroups@phuse.global

PHUSE Advance Hub:
https://advance.phuse.global/display/WEL/Implementation+of+Estimands+%28ICH+E9+%28R1%29%29+using+Data+Standards

The premier community for people working in the biometric area

Contact Channels
UK +44 1843 609600
USA +1 609 514 5105
office@phuse.eu
phuse.eu

Social Media
@phusetwitta
/phusebook
/phusetube
/company/phuse