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

PHUSE NJ Single Day Event 2023

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Disclaimers

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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 initial internal recommendations are subject to change upon completion of the PHUSE project.

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.

Agenda

- Introduction
- Data Collection & Tabulation
- Data Analysis
- Conclusion & Next Steps

Introduction

Introduction

ICH E9(R1)

- Addendum on Estimands and Sensitivity Analysis in Clinical Trials to the Guideline on Statistical Principles for Clinical Trials
- 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
- Additional guidance for the implementation of the estimands framework in the data flow is necessary

PHUSE Project

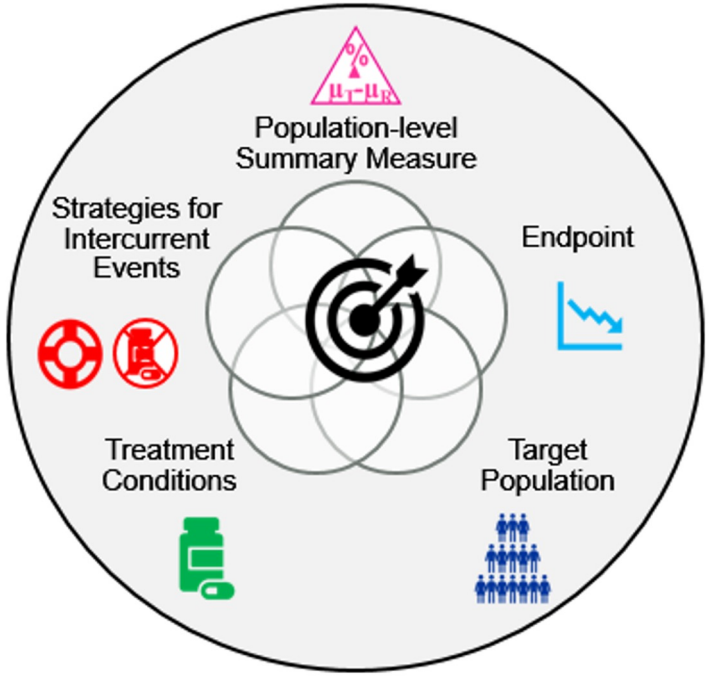
- Developing a White Paper to provide recommendations and best practices to implement the estimands framework in data standards
- Collaboration with CDISC

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 attributes:



*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

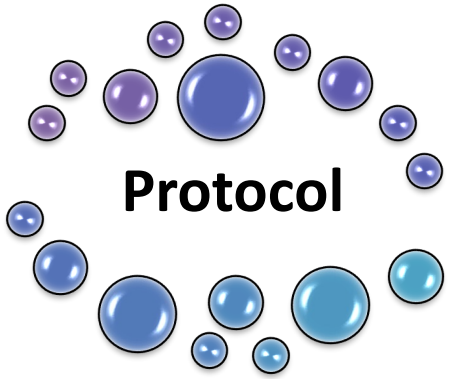
Get **sufficiently detailed answers** during collection

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

Commonly Observed Intercurrent Events

Direct Consequences of Treatment

- Treatment Discontinuation
- Treatment Interruption
- Infusion Interruption
- Dose Adjustment
- Treatment Delay

Additional / Alternative Treatment

- Concomitant Medication
- Concomitant Procedure
- Subsequent Cancer Surgery*
- Subsequent Radiotherapy*

*oncology

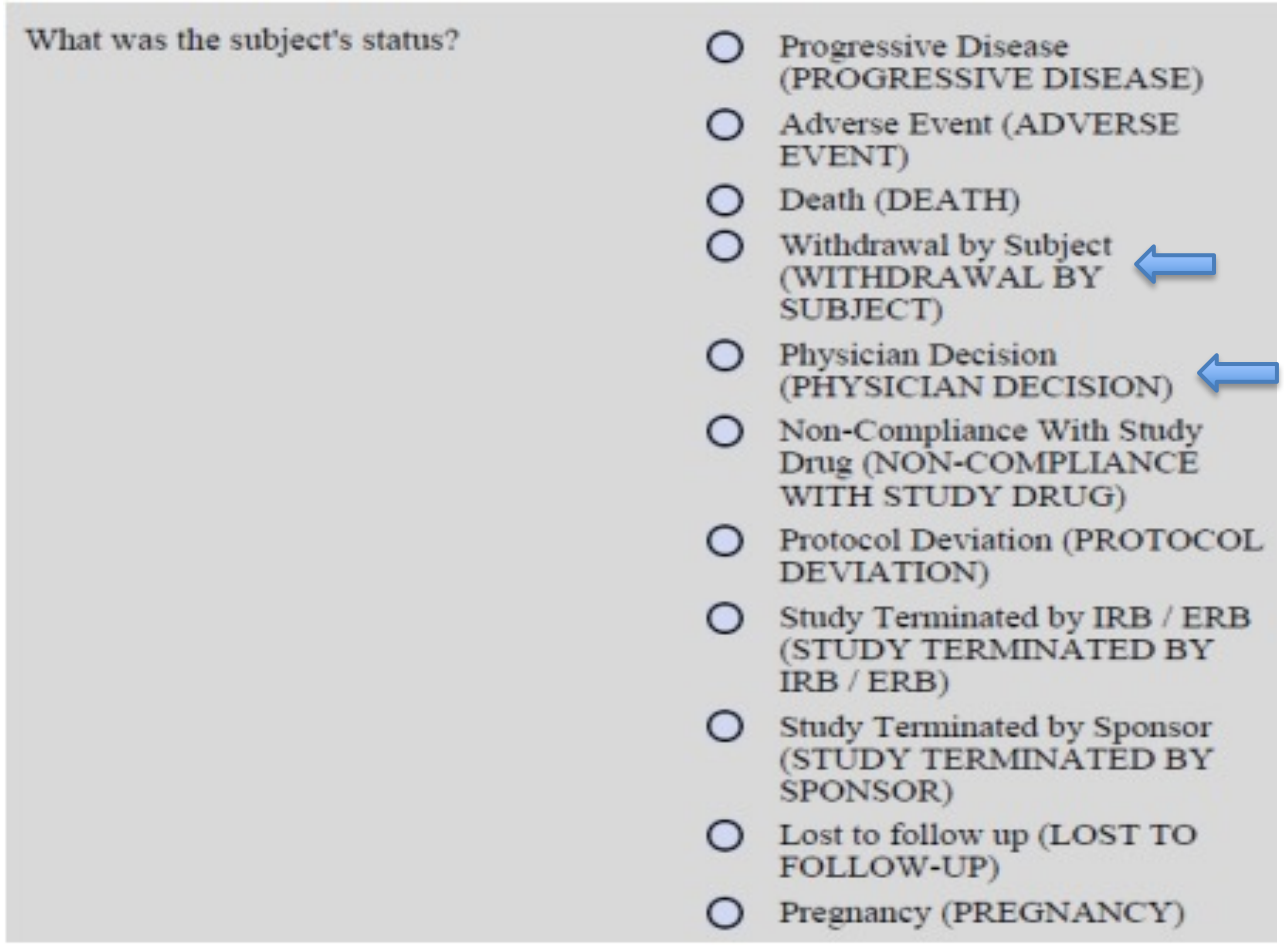
Need for Data Collection Enhancements

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

- Granular data collection of the reasons, e.g., for treatment discontinuations

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

Current Data Collection Practices



Example Case Report Form
Treatment Discontinuation

- Ambiguous data collection leads to inaccurate data analyses and reporting

Intercurrent Events – Treatment Discontinuation

Suggested CRF for Treatment Discontinuation

SDTM Mapping DS Domain

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**

Row	STUDYID	DOMAIN	USUBJID	DSTERM	DSDECOD	DSCAT	EPOCH	DSSTDTC
1	ABC456	DS	456[illegible]	LOST TO FOLLOW-UP	LOST TO FOLLOW-UP	DISPOSITION EVENT	TREATMENT	2003-09-21
2	ABC456	DS	456[illegible]	RELOCATION	LOGISTICAL PROBLEM	DISPOSITION EVENT	TREATMENT	2003-10-15

Intercurrent Events – Concomitant Medication

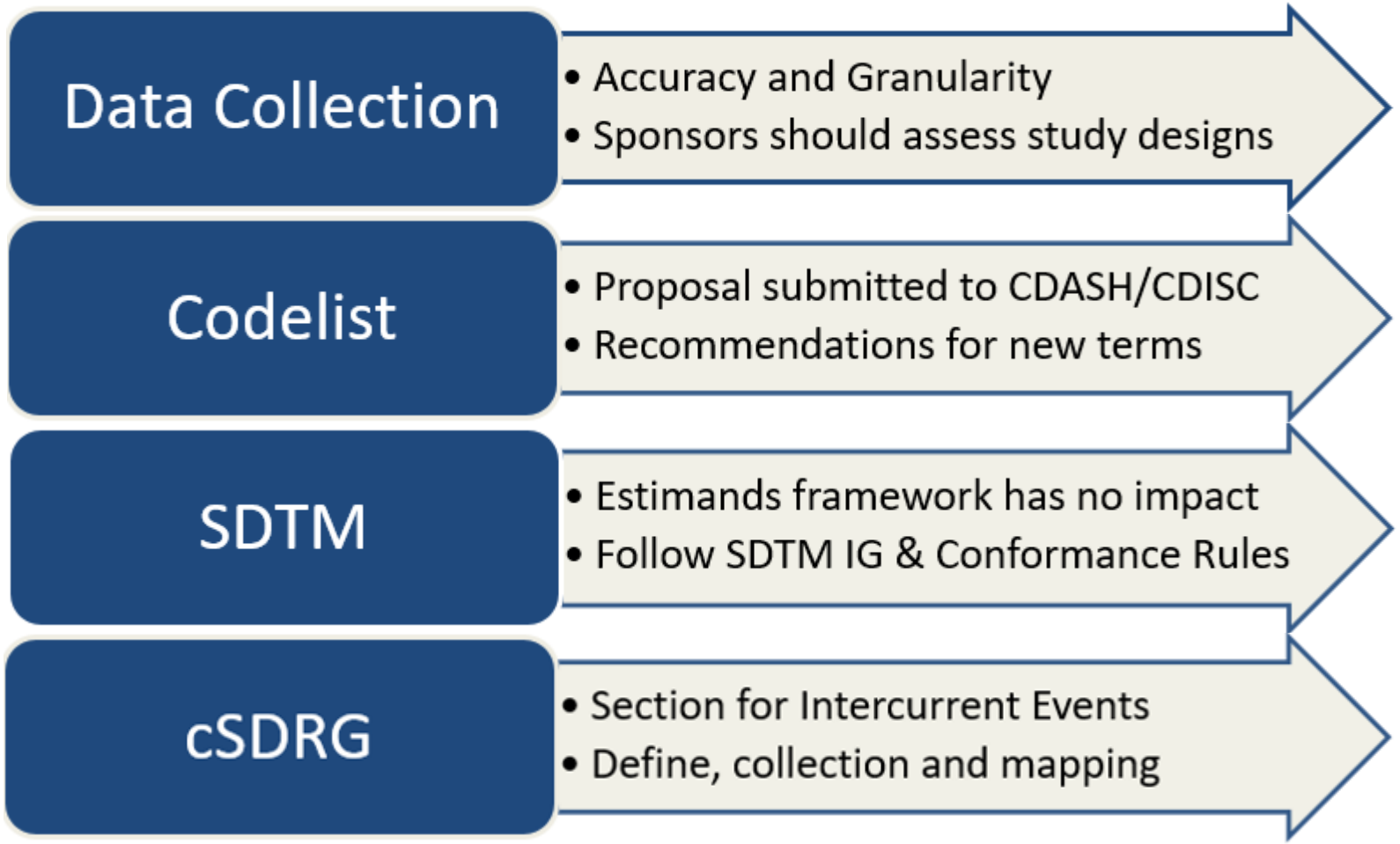
Suggested CRF for Concomitant Medication

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

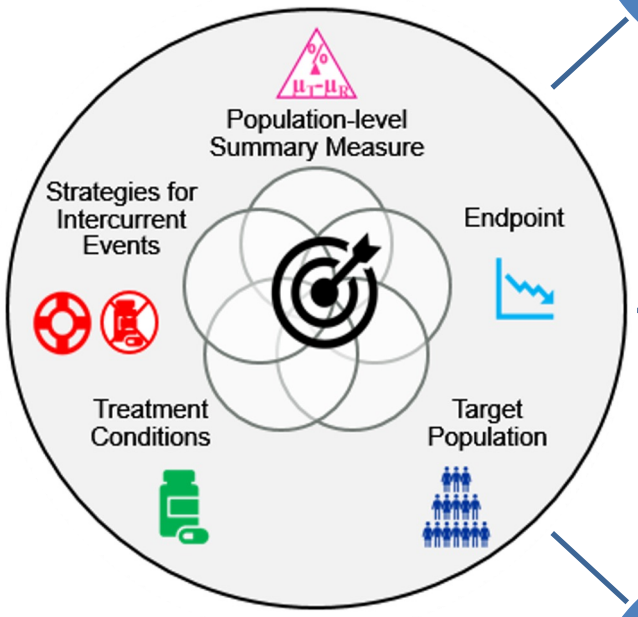
Row	STUDYID	DOMAIN	USUBJID	CMTRT	CMINDC	CMSTDTC	CMENRF	CMENDTC
1	ABC456	CM	456101	ASPIRIN	PROPHYLAXIS FOR INFECTION	2003-07-21	ONGOING	
2	ABC456	CM	456103	ANTACIDS	RESCUE THERAPY	2003-08-15		2003-09-01

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

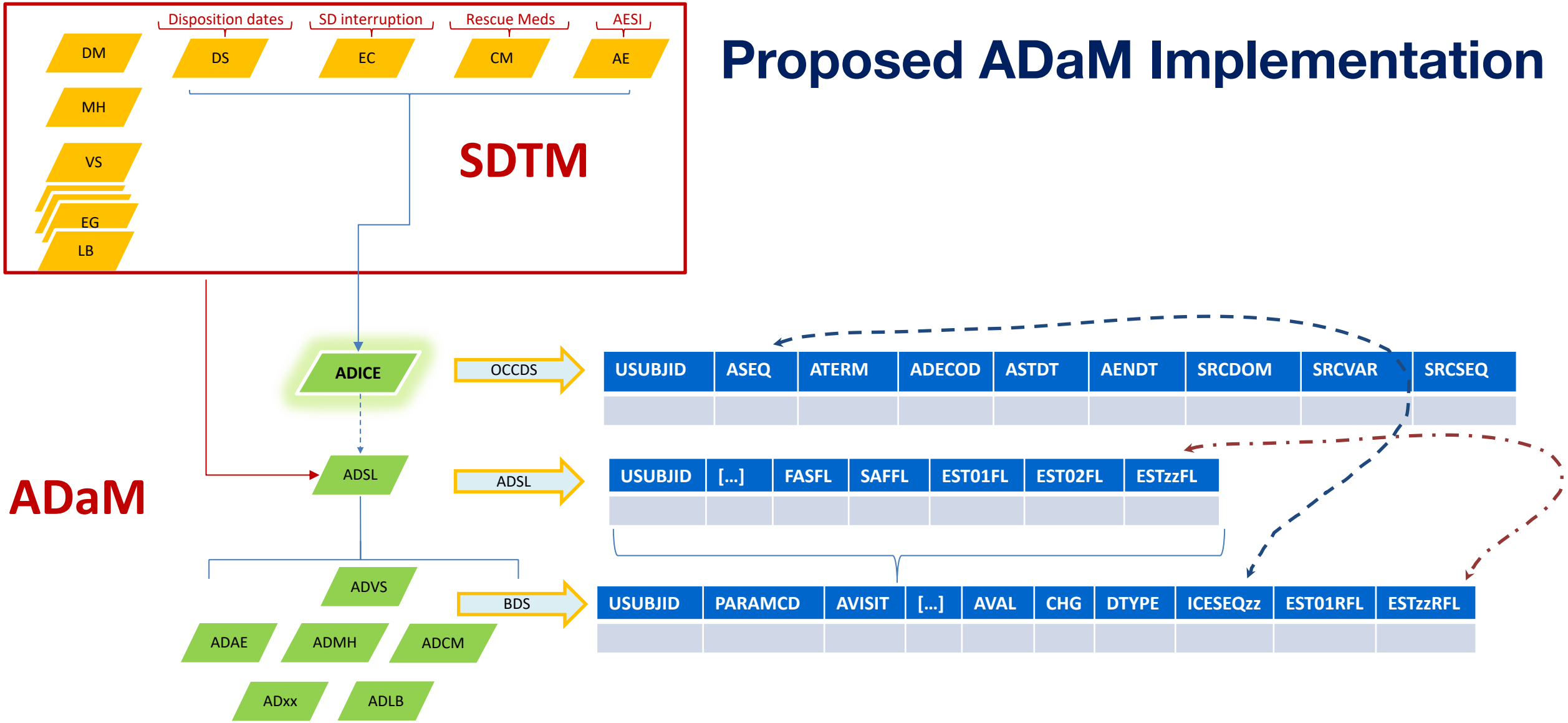
Traceability

- 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	ADECOD	ASTDT(M)	AENDT(M)	SRCDOM	SRCVAR	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

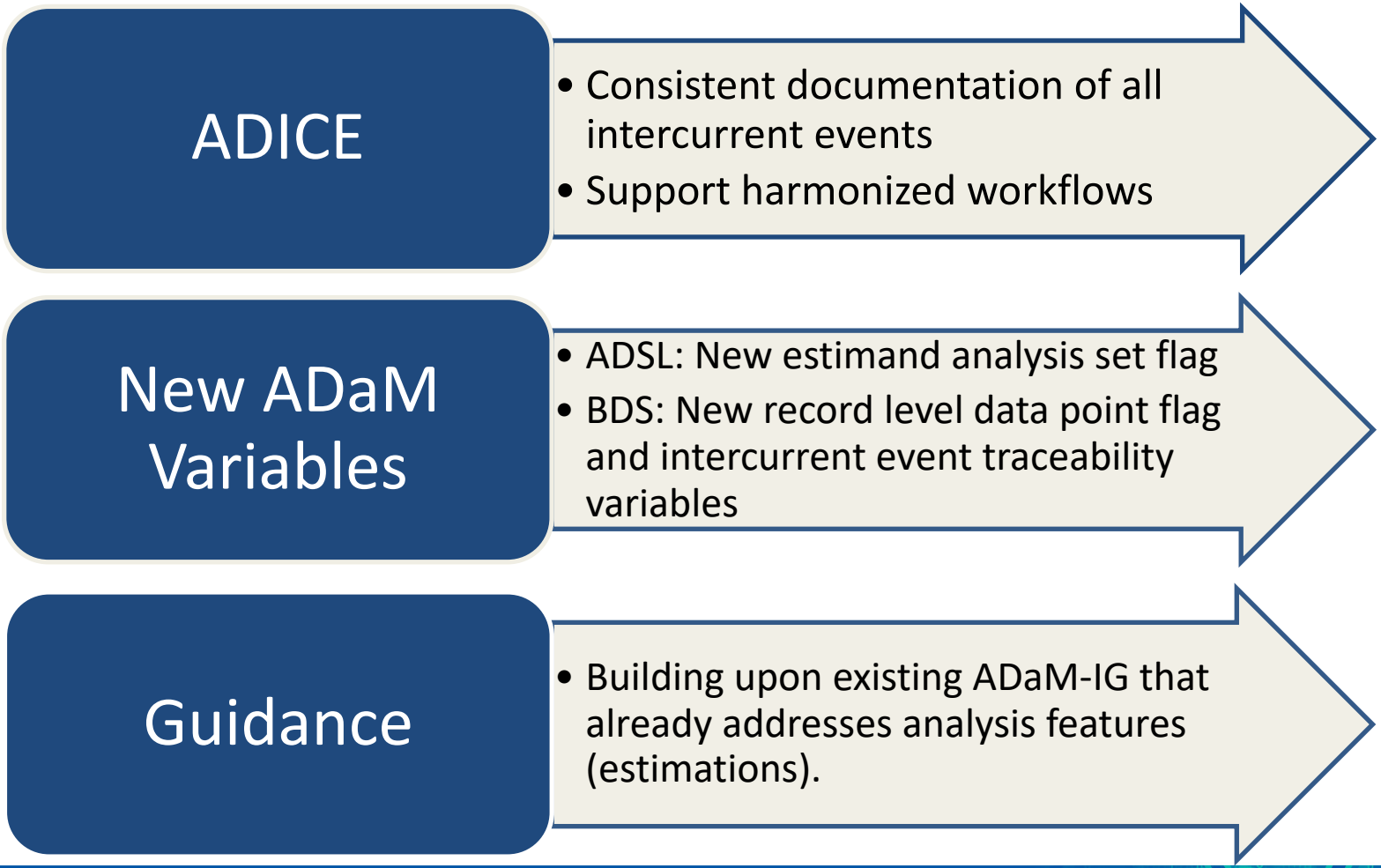
  - **ESTzzFL**: Subjects considered in all estimand zz estimations

- 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

Data Analysis - Summary



Conclusion & Next Steps

Conclusion

Cross-functional interaction critical

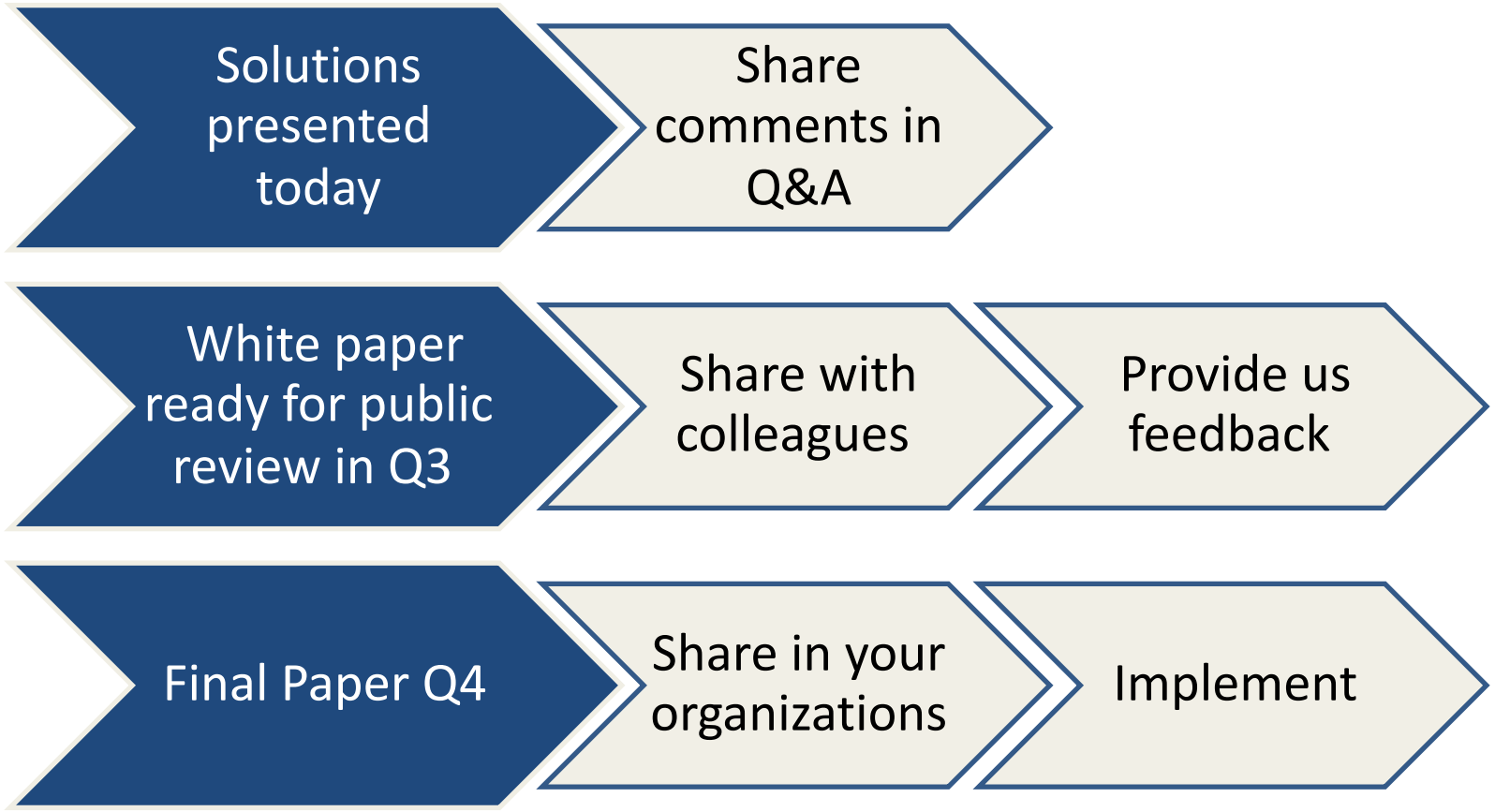
Impacts protocol, data collection and data analysis

Different implementation approaches may be appropriate

Need to update/extend existing data standards

Consistent implementation of estimands is beneficial

How Can You Help?



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

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Back Up Slides

SAP Overview for Proposed Toy (Example) Study

- **Therapeutic Area:** Cardiovascular diseases
- **Disease:** Hypertension (HTN)
- **Study Design:** 24-week placebo-controlled study, parallel groups, repeated measures
- **Population:** Adults suffering from hypertension {as defined by [insert name/procedure] diagnosis and severity cut-offs at baseline]}
- **Study Endpoints:** Systolic Blood Pressure (SBP), assessed as 2 different estimands based on Intercurrent events relevant and prespecified in the estimands
- **I/E criteria:** The target population of interest is "Adults suffering from hypertension" {as defined by [ESH/ESC] diagnosis and severity cut-offs at baseline] systolic blood pressure (SBP) ≥ 140 mmHg and/or a diastolic blood pressure (DBP) ≥ 90 mmHg}
- **Treatment (Estimand Attribute):** Experimental treatment (toyexamplimab) or control (placebo)
- **Intercurrent Events:**

1. Rescue medication (RM) intake at any time point (due to any reason) and in any dose.
2. Treatment discontinuation (TD) at any time point (permanently/intermittently and due to any reason).

Variable	Population level summary	Strategies for addressing intercurrent events
***Estimand 1*:** What is the treatment effect on SBP in adults suffering from hypertension after 24 weeks (Visit 6) of treatment administered as the only medication to treat hypertension compared to no treatment being taken, *regardless of any intercurrent events?*		
systolic blood pressure (SBP)	The difference in mean SBP between the experimental and control arm at 24 weeks (Visit 6) (pre-planned timepoint) after initiating treatment.	Treatment policy is the strategy for addressing the two relevant intercurrent events (RM and TD). Clinical outcomes are used regardless of these two intercurrent events of interest being experienced by trial participants. **ADaM flags: ADVS: EST01RFL**
***Estimand 2*:** What is the treatment effect on SBP in adults suffering from hypertension after 24 weeks (Visit 6) of treatment administered as the only medication to treat hypertension compared to no treatment being taken, *if no patient needed rescue medication and no patients stopped the treatment?*		
systolic blood pressure (SBP)	The difference in mean SBP between the experimental and control arm at 24 weeks (Visit 6) (pre-planned timepoint) after initiating treatment.	Hypothetical strategy is the strategy for addressing the two relevant intercurrent events (RM and TD). A hypothetical scenario is envisaged where participants would not need rescue medication and where all participants were to take treatment as specified in the protocol. **ADaM flags: ADVS: ICESEQ02; EST02RFL**

Intercurrent Events Datasets (ADICE)

USUBJID	ASEQ	ATERM	ADECOD	ASTDT	AENDT	SRCDOM	SRCVAR	SRCSEQ
1001	1	Aspirin	Rescue Medication	07Feb2022	14Feb2022	CM	CMTERM	1
1002	1	LACK OF EFFICACY	Withdrawal	22May2022	22May2022	DS	DSTERM	5
1002	2	Aspirin	Rescue Medication	24Apr2022	30Apr2022	CM	CMTERM	1
1002	3	Hypertension	Hypertension (SMQ 20000147)	4/24/2022	29Apr2022	AE	AEDECOD	1
1003	1	PATIENT DISCONTINUED STUDY TREATMENT DUE TO COVID19	Withdrawal	17Mar2022	17Mar2022	DS	DSTERM	6
1003	2	Treatment discontinued due to COVID19	Treatment discontinued	17Mar2022	17Mar2022	EC	ECREAS	4
1004	1	PATIENT DISCONTINUED STUDY TREATMENT DUE TO COVID19	Withdrawal	22May2022	22May2022	DS	DSTERM	7
1004	2	Treatment discontinued due to COVID19	Treatment discontinued	22May2022	22May2022	EC	ECREAS	6
1005	1	PATIENT DISCONTINUED STUDY TREATMENT DUE TO COVID19	Withdrawal	17May2022	17May2022	DS	DSTERM	8
1005	2	Treatment discontinued due to COVID19	Treatment discontinued	18May2022	18May2022	EC	ECREAS	5

ADSL

USUBJID	TRT01P	FASFL	SAFFL	EST01FL	EST02FL	EST03FL
1001	DRUG X	Y	Y	Y	Y	Y
1002	DRUG X	Y	Y	Y	Y	N
1003	DRUG X	Y	Y	Y	Y	Y
1004	DRUG X	Y	Y	Y	Y	Y
1005	DRUG X	Y	Y	Y	Y	Y
1006	DRUG X	Y	Y	Y	Y	Y
1007	DRUG X	Y	Y	Y	Y	Y
1008	DRUG X	Y	Y	Y	Y	Y
1009	DRUG X	Y	Y	Y	Y	Y
1010	DRUG X	Y	Y	Y	Y	Y
1011	DRUG X	Y	Y	Y	Y	Y
1012	DRUG X	Y	Y	Y	Y	Y
1013	DRUG X	Y	Y	Y	Y	Y
1014	DRUG X	Y	Y	Y	Y	Y
1015	DRUG X	Y	Y	Y	Y	Y
1016	DRUG X	Y	Y	Y	Y	Y

ADVS – Subjects 1001 and 1002

	USUBJID	FASFL	SAFFL	EST01FL	EST02FL	EST03FL	PARAM	VISIT	AVISIT	ADT	AVAL	CHG	ABLFL	DTYPE	ICESEQ02	*ICESEQ03*		EST01RFL	EST02RFL	EST03RFL	ANL01FL
RM at week 5 completed the study	1001	Y	Y	Y	Y	Y	Systolic BP (mmHg)	**week0**	**BL**	**02Jan2022**	**120**		Y					Y	Y	Y	Y
	1001	Y	Y	Y	Y	Y	Systolic BP (mmHg)	week4	V1	30Jan2022	138	18						Y	Y	Y	
	1001	Y	Y	Y	Y	Y	Systolic BP (mmHg)	week8	V2	27Feb2022	131	11			1			Y		Y	
	1001	Y	Y	Y	Y	Y	Systolic BP (mmHg)	week12	V3	27Mar2022	122	2			1			Y		Y	
	1001	Y	Y	Y	Y	Y	Systolic BP (mmHg)	week16	V4	24Apr2022	122	2			1			Y		Y	
	1001	Y	Y	Y	Y	Y	Systolic BP (mmHg)	week20	V5	22May2022	136	16			1			Y		Y	
	1001	Y	Y	Y	Y	Y	Systolic BP (mmHg)	week24	V6	19Jun2022	121	1			1			Y		Y	Y
	1001	Y	Y	Y	Y	Y	Systolic BP (mmHg)		V2	27Feb2022	138	18		LOCF					Y		
	1001	Y	Y	Y	Y	Y	Systolic BP (mmHg)		V3	27Mar2022	138	18		LOCF					Y		
	1001	Y	Y	Y	Y	Y	Systolic BP (mmHg)		V4	24Apr2022	138	18		LOCF					Y		
	1001	Y	Y	Y	Y	Y	Systolic BP (mmHg)		V5	22May2022	138	18		LOCF					Y		
	1001	Y	Y	Y	Y	Y	Systolic BP (mmHg)		V6	19Jun2022	138	18		LOCF					Y		
RM LoE at week 15, study withdrawal at w19	1002	Y	Y	Y	Y	N	Systolic BP (mmHg)	**week0**	**BL**	**08Jan2022**	**120**					3		Y	Y		Y
	1002	Y	Y	Y	Y	N	Systolic BP (mmHg)	week4	V1	05Feb2022	130	10				3		Y	Y		
	1002	Y	Y	Y	Y	N	Systolic BP (mmHg)	week8	V2	05Mar2022	127	7				3		Y	Y		
	1002	Y	Y	Y	Y	N	Systolic BP (mmHg)	week12	V3	02Apr2022	129	9				3		Y	Y		
	1002	Y	Y	Y	Y	N	Systolic BP (mmHg)	week16	V4	30Apr2022	126	6			2	3		Y			Y
	1002	Y	Y	Y	Y	N	Systolic BP (mmHg)	week20	V5											Y	
	1002	Y	Y	Y	Y	N	Systolic BP (mmHg)	week24	V6											Y	
	1002	Y	Y	Y	Y	N	Systolic BP (mmHg)		V4	30Apr2022	129	9		LOCF					Y		

ADVS – Subject 1003

	USUBJID	FASFL	SAFFL	EST01FL	EST02FL	EST03FL	PARAM	VISIT	AVISIT	ADT	AVAL	CHG	ABLFL	DTYPE	ICESEQ02	*ICESEQ03*		EST01RFL	EST02RFL	EST03RFL	ANL01FL
TD related to COVID-19 at week 9, completed the visit via remote visit, completed the study	1003	Y	Y	Y	Y	Y	Systolic BP (mmHg)	**week0**	**BL**	**12Jan2022**								Y	Y	Y	Y
	1003	Y	Y	Y	Y	Y	Systolic BP (mmHg)	week4	V1	09Feb2022	131	11						Y	Y	Y	
	1003	Y	Y	Y	Y	Y	Systolic BP (mmHg)	week8	V2	09Mar2022	125	5						Y	Y	Y	
	1003	Y	Y	Y	Y	Y	Systolic BP (mmHg)	week12	V3	06Apr2022	139	19			2			Y		Y	
	1003	Y	Y	Y	Y	Y	Systolic BP (mmHg)	week16	V4	04May2022	126	6			2			Y		Y	
	1003	Y	Y	Y	Y	Y	Systolic BP (mmHg)	week20	V5	01Jun2022	137	17			2			Y		Y	
	1003	Y	Y	Y	Y	Y	Systolic BP (mmHg)	week24	V6	29Jun2022	139	19			2			Y		Y	Y
	1003	Y	Y	Y	Y	Y	Systolic BP (mmHg)		V3	06Apr2022	125	5		LOCF					Y		
	1003	Y	Y	Y	Y	Y	Systolic BP (mmHg)		V4	04May2022	125	5		LOCF					Y		
	1003	Y	Y	Y	Y	Y	Systolic BP (mmHg)		V5	01Jun2022	125	5		LOCF					Y		
	1003	Y	Y	Y	Y	Y	Systolic BP (mmHg)		V6	29Jun2022	125	5		LOCF					Y		

ADVS – Subject 1004

	USUBJID	FASFL	SAFFL	EST01FL	EST02FL	EST03FL	PARAM	VISIT	AVISIT	ADT	AVAL	CHG	ABLFL	DTYPE	ICESEQ02	*ICESEQ03*		EST01RFL	EST02RFL	EST03RFL	ANL01FL
TD related to COVID-19, Study withdrawal related to COVID-19 (patient calls)	1004	Y	Y	Y	Y	Y	Systolic BP (mmHg)	week0	BL	02Jan2022	120							Y	Y	Y	Y
	1004	Y	Y	Y	Y	Y	Systolic BP (mmHg)	week5	V1	30Jan2022	139	19						Y	Y	Y	
	1004	Y	Y	Y	Y	Y	Systolic BP (mmHg)	week8	V2	27Feb2022	129	9						Y	Y	Y	
	1004	Y	Y	Y	Y	Y	Systolic BP (mmHg)	week12	V3	27Mar2022	131	11						Y	Y	Y	
	1004	Y	Y	Y	Y	Y	Systolic BP (mmHg)	week16	V4	24Apr2022	138	18						Y	Y	Y	
	1004	Y	Y	Y	Y	Y	Systolic BP (mmHg)	week20	V5	22May2022	139	19			2			Y		Y	Y
	1004	Y	Y	Y	Y	Y	Systolic BP (mmHg)	week24	V6	19Jun2022										Y	
	1004	Y	Y	Y	Y	Y	Systolic BP (mmHg)		V5	22May2022	138	18		LOCF					Y		

ADVS – Subject 1005

	USUBJID	FASFL	SAFFL	EST01FL	EST02FL	EST03FL	PARAM	VISIT	AVISIT	ADT	AVAL	CHG	ABLFL	DTYPE	ICESEQ02	*ICESEQ03*		EST01RFL	EST02RFL	EST03RFL	ANL01FL
TD related to COVID-19, patient had a remote visit, patient completed the study	1005	Y	Y	Y	Y	Y	Systolic BP (mmHg)	**week0**	**BL**	**26Jan2022**								Y	Y	Y	Y
	1005	Y	Y	Y	Y	Y	Systolic BP (mmHg)	week4	V1	23Feb2022	134	14						Y	Y	Y	
	1005	Y	Y	Y	Y	Y	Systolic BP (mmHg)	week8	V2	23Mar2022	139	19						Y	Y	Y	
	1005	Y	Y	Y	Y	Y	Systolic BP (mmHg)	week12	V3	20Apr2022	136	16						Y	Y	Y	
	1005	Y	Y	Y	Y	Y	Systolic BP (mmHg)	week16	V4	18May2022	129	9			1			Y		Y	
	1005	Y	Y	Y	Y	Y	Systolic BP (mmHg)	week20	V5	15Jun2022	121	1			1			Y		Y	
	1005	Y	Y	Y	Y	Y	Systolic BP (mmHg)	week24	V6	13Jul2022	121	1			1			Y		Y	Y
	1005	Y	Y	Y	Y	Y	Systolic BP (mmHg)		V4	18May2022	136	16		LOCF					Y		
	1005	Y	Y	Y	Y	Y	Systolic BP (mmHg)		V5	15Jun2022	136	16		LOCF					Y		
	1005	Y	Y	Y	Y	Y	Systolic BP (mmHg)		V6	13Jul2022	136	16		LOCF					Y		