



PP06: Implementation of the ICH E9(R1) Estimands Framework Using Data Standards

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Get Involved



About Estimands

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

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

Examples:



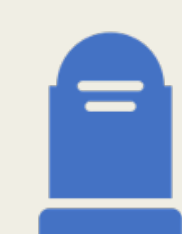
Treatment Discontinuation



Rescue Medication



Treatment Switch



Death

Estimand = A precise description of the treatment effect reflecting the clinical question posed by the trial objective



Population-level Summary Measure



Endpoint



Target Population



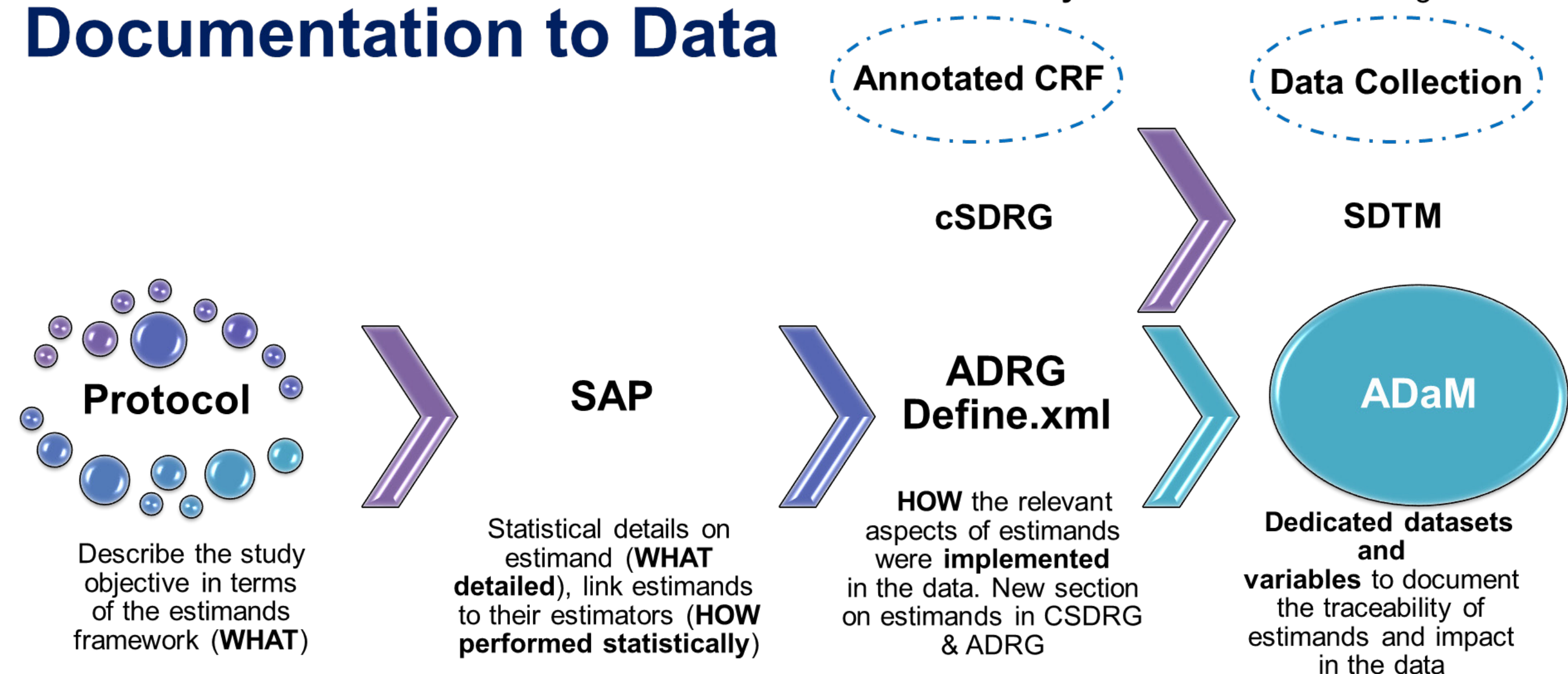
Treatment Conditions



Strategies for Intercurrent Events

Documentation to Data

Get sufficiently detailed answers during collection



Data Collection & Tabulation

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.DSDECDG DS.DSTERM	- DEATH - ADVERSE EVENT. List the adverse event ID: _____ - PREGNANCY - LOSS 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 - GEOLOGICAL LOGISTICAL RESTRICTIONS - OPERATIONAL ERROR - BLIND BROKEN - LOST TO FOLLOW-UP
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Row	STUDYID	DOMAIN	USUBJID	OSTERM	DSDECDG	DSDECDG	EPOCH	DSSTDT
1	ABC456	DS	456101	LOST TO FOLLOW-UP	DISPOSITION EVENT	DISPOSITION EVENT	TREATMENT	2003-09-21
2	ABC456	DS	456103	RELOCATION	LOGISTICAL PROBLEM	LOGISTICAL PROBLEM	TREATMENT	2003-10-15



Accuracy



Granularity

Intercurrent Events – Concomitant Medication

Suggested CRF for Concomitant Medication

SDTM Mapping CM & SUPPCM Domain

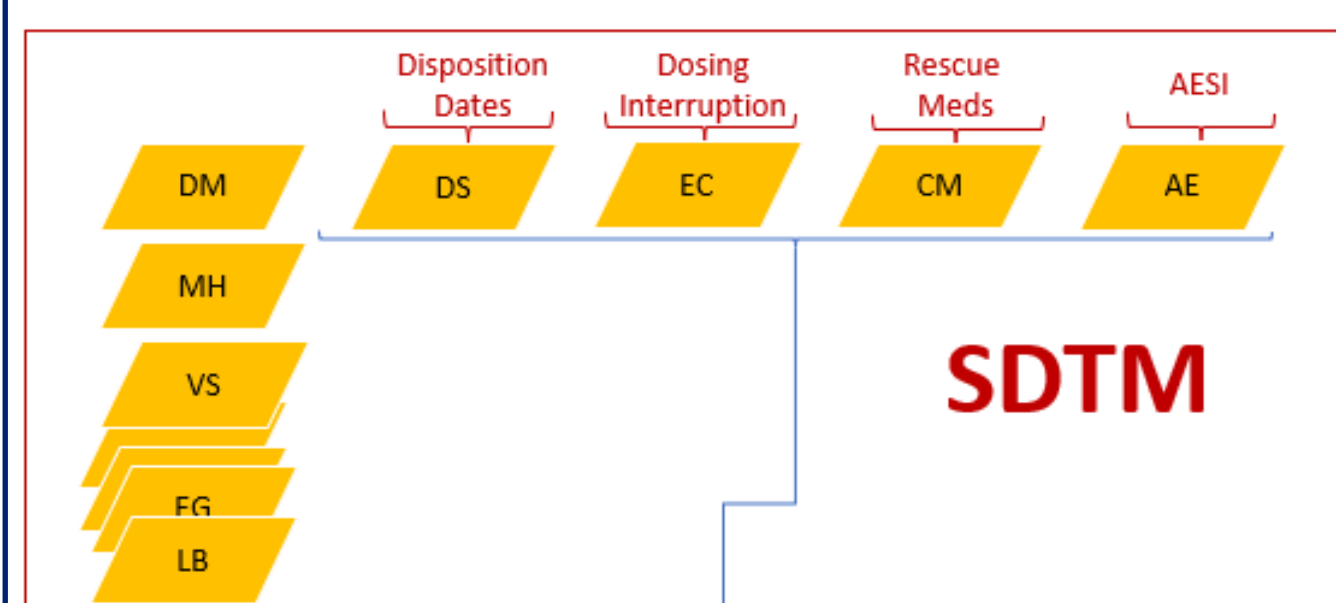
Indicate if the subject took any concomitant medication/treatment.	Were any concomitant medications taken? ☐ Yes ☐ No
Record only one treatment per line. Provide full trade name of the medication/treatment.	What was the medication? CM.CMTT
Record specific indication the medication was taken.	For what indication was the medication taken? CM.CMINDC
Record specific reason the medication was taken.	For what reason was the medication taken? SUPPCM.QVAL = "CM.CMTT" and SUPPCM.QLABEL = "Reason"
Start Date CM.CMSTDT	☐ Yes
Is the medication ongoing? CM.CMENDC	☐ Yes
End Date CM.CMENDT	

Row	STUDYID	DOMAIN	USUBJID	CMSEQ	CMTRT	CMINDC	CMSTDT	CMENDT	CMENDT
1	ABC456	CM	456101	1	METHYLPHENIDOLONE	ADVERSE EVENT	2003-07-21	2003-08-15	2003-09-01
2	ABC456	CM	456103	2	SPRIVAX				

Row	STUDYID	DOMAIN	USUBJID	CMSEQ	CMTRT	CMINDC	CMSTDT	CMENDT	CMENDT
1	ABC456	CM	456101	CMSEQ	1	ADAE	Specified related AE	NEUROPATHIC PAIN	
2	ABC456	CM	456103	CMSEQ	2	ADAE	Reason	PROPHYLAXIS FOR COVID-19	

Enhancing CRF standards to improve the accuracy and specificity of data collection for intercurrent events is necessary

Data Analysis



ADaM

Depending on the definition of the estimand, subjects and/or certain data points may be included or excluded from data point sets (increased granularity).

To allow full traceability of intercurrent events a new ADaM OCCDS domain ADICE is proposed

- 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.)
- Extra suffixes **[D] Dom.**, **[V] Var.**, **[F] flag**, **[N] FI**, **N**

USUBJID	ASEQ	UTERM	ATERM	ADECDy	ACATy	ASTDT	AENDT	SRCDOM	SRCSEQ

USUBJID	[...]	FASFL	SAFFL	PSyFL

USUBJID	PARAMCD	AVISIT	[...]	AVAIL	[...]	IC[Cy][Ezz][*]	[*]

Conclusions

Collection of Data

- Accurate and granular data collection of intercurrent events is critical
- Sponsor should assess study designs

Codelists & NSV

- Recommendations for adding new terms to existing codelist or new codelist
- Proposals for submission to CDASH/ NSV Registry

SDTM

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

cSDRG

- Subsection for Intercurrent Events
- Defining the collection of intercurrent events and their SDTM domains mapping

New ADaM Dataset (ADICE)

- Consistent documentation of all intercurrent events across all estimands
- Facilitates traceability and supports harmonized workflows

New ADaM Variables

- BDS/OCCDS/ADaM Other: Flexible building blocks for variables (IC[Cy][Ezz][*]) to identify data points impacted by intercurrent events

ADRG

- Describes how the estimand(s)/estimator(s) are implemented in the data