Implementation of ICH E9(R1) Estimands Framework using Data Standards - Example Document

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Contents

Revision History

Version	Date	Summary
1.0	2025-05-06	Initial Version

Appendix

The illustrated example aims to demonstrate how to translate the estimands described in the protocol and SAP into data collection and creation of SDTM and ADaM datasets based on the ICH E9(R1) estimands framework. The two estimands presented in this paper are inspired from Polverejan et al. They were modified from the original version to reflect a relevant mix of intercurrent events that allow some degree of complexity in participant trajectories in conjunction with strategies for addressing intercurrent events.

Key points to note in the example are:

1. Estimands used for illustration are referred to as Estimand 1 (E1) and Estimand 2 (E2).
2. The two illustrated estimands (E1 and E2) are used to show how to implement the recommendations in the white paper. Additional complexities may be present with different estimands. However, the same principles should be applied.
3. We focus on the implementation of the estimands framework into data standards, and not on clinical or estimation relevance. We consider all datapoints are collected for all clinical outcomes and intercurrent events (no intermittent missing data, no study withdrawals, no terminal events/deaths).
4. The example should not be interpreted as a recommendation for a particular study design, endpoint, estimand definition or intercurrent events.

1. Protocol/SAP

The tabular view used below was proposed by Polverejan et al. We are following a similar presentation with some adjustments (i.e. removing information related to the statistical methodology for the primary and sensitivity analysis) to help us focus on the estimand attributes, especially on the translation of the strategies used for the intercurrent events of interest into the derivation of analysis datasets that will be ultimately supplied to an estimator for the purpose of the analysis. For the purpose of this paper, the choice of estimators (including missing data handling) is not of interest.

For this illustration of the estimands framework implementation in data standards, we hypothesised a few possible study participant journeys, as sketched in Figure 1. A summary is provided for each participant, which describes their behaviour during the study with respect to intercurrent events occurrence.

Summary of selected participant journeys in the hypothesised trial used for the illustrative example:

Figure 1: Selected participant journeys

Subject ID	Week 0 (Baseline)	Week 1	Week 2	Unsch week 2.1	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8 (Follow-up)
ABC001	R/TI			---			SO			
ABC002	R/TI		TD	SO						
ABC003	R/TI			---	SO			TD		
ABC004	R/TI			---			TD		SO	
ABC005	R/TI			---		TD				

Legend

R/TI	Randomisation/Treatment initiation
	Starting other pharmaceutical treatment for MDD for any reason [SO x any]
	Treatment discontinuation due to Adverse Event/Lack of Efficacy [TD AE/LoE]
	Treatment discontinuation due to a geopolitical logistical restriction [TD Log]
	Outcome collected
---	Outcome not collected

The study design is as follow:

– Trial from Week 0 to Week 8. Visits are scheduled at the end of each week. At the "Week x" visit, the participant is assessed retrospectively on Week x (reflecting the effect of treatments administered up to the end of Week x-1) and then receives a new treatment dose, which will be evaluated at the end of Week x+1. Treatments are administered from Week 0 through to Week 7, with assessments conducted from Week 0 (baseline) to Week 8. If treatment is discontinued in Week x, no dose is given at the visit, and its effects will appear in subsequent assessments. Concomitant medications reported at Week x are prescribed during that

week visit and their effects will be evaluated from Week x+1 onwards.

Patient journeys:

- Participant ABC001: received the full study treatment for MDD and, in addition, at Week 5 visit, the participant was prescribed another treatment for MDD, taken until the end of the trial. The participant completed the study with all outcomes collected.
- Participant ABC002: received the study treatment for MDD until Week 1 visit and experienced a treatment discontinuation due to geopolitical logistical restrictions at the Week 2 visit, and at an unscheduled visit between Weeks 2 and 3, the participant was prescribed treatment for MDD until the end of the trial. The participant completed the study with all outcomes collected.
- Participant ABC003: received the study treatment for MDD up to the Week 5 visit, then the participant experienced a treatment discontinuation due to geopolitical logistical restrictions at the Week 6 visit. The participant was prescribed another treatment for MDD at the Week 3 visit, taken until the end of the trial. (From the Week 3 visit to the week 5 visit, that treatment was administered in parallel to the study treatment.) The participant completed the study with all outcomes collected.
- Participant ABC004: received study treatment for MDD up to the Week 4 visit and experienced a treatment discontinuation due to adverse event at the week 5 visit. The participant started receiving another treatment for MDD at the Week 7 visit. The participant completed the study with all outcomes collected.
- Participant ABC005: received study treatment for MDD up to the Week 3 visit, then had a treatment discontinuation due to Lack of Efficacy at the week 4 visit. The participant completed the study with all outcomes collected.

1.1 Estimand 1 (E1)

The table below presents how the clinical question of interest and corresponding estimand translate into specifications for data collection and analysis sets.

Document	Descriptor	Description
Protocol & SAP	Question of interest	What is the treatment effect of being assigned monotherapy drug X versus placebo on change from baseline to Week 8 in the total score of the 17-item version of the Hamilton Depression Rating Scale (HDRS) in patients with MDD, regardless of the use of other pharmaceutical treatments for MDD, regardless of treatment discontinuation due to AE/LoE, and if patients did not discontinue treatment due to geopolitical logistical restrictions (e.g. site closure due to the geopolitical logistical restrictions)?
Protocol & SAP	Attributes	1. **Treatment condition of interest vs Alternative treatment condition:** Assignment to monotherapy drug X vs placebo, at the selected dose and frequency of administration, regardless of "Starting other pharmacological treatments for MDD (for any reason)" and regardless of "Treatment discontinuation due to AE/LoE", and if patients did not discontinue treatment due to geopolitical logistical restrictions (e.g. in a geopolitical logistical restriction-free world). 2. **Population:** Patients with a diagnosis of MDD in a current major depressive episode with at least moderate symptom severity. 3. **Variable:** Change from baseline to Week 8 in the total score of HDRS. 4. **Population-level summary:** Difference in means. 5. **Intercurrent events and corresponding strategies: As described in the treatment** conditions of interest, each intercurrent event of interest will be addressed as follows: • Starting other pharmacological treatments for MDD (for any reason) will be addressed by the treatment policy strategy. • Treatment discontinuation due to AE/LoE will be addressed by the treatment policy strategy. • Treatment discontinuation due to geopolitical logistical restrictions will be addressed by a hypothetical strategy. For simplicity, other intercurrent events (such as treatment discontinuations due to any other reasons) are not included in the estimand definition.

Protocol & SAP	Implementation of strategies for addressing intercurrent events	• In this example, we assume that participants can only discontinue due to a single reason. Therefore, no conflict will exist between the intercurrent events of treatment discontinuation due to geopolitical restrictions and treatment discontinuation due to lack of efficacy or adverse event. If there are several reasons for the treatment discontinuation of a participant, the site should select the most relevant reason for data entering in the CRF. • In addition, treatment policy strategy is used if "Starting other pharmacological treatments for MDD" occurs prior to "Treatment discontinuation due to geopolitical logistical restrictions". The occurrence of "Starting other pharmacological treatments for MDD" prior to "Treatment discontinuation due to geopolitical logistical restrictions", at any timepoint, is considered irrelevant for the treatment effect of interest. Hypothetical strategy is used for addressing "Treatment discontinuation due to geopolitical logistical restrictions". This strategy takes priority once it occurs, regardless of the occurrence of "Starting other pharmacologic treatments for MDD". Data collected after "Treatment discontinuation due to geopolitical logistical restrictions" is not of interest (even if collected) and is excluded from analysis. An alternative scenario is envisaged where these study participants would have had clinical outcomes/trajectories according to this alternative scenario.
Protocol & SAP	Key implementation elements needed to address this estimand	Efficacy data after "SO x any reason" and "Treatment discontinuation due to AE/LoE" are directly relevant to this estimand and efforts should be made to collect them. Efficacy data after "Treatment discontinuation due to geopolitical logistical restrictions" is not relevant to this estimand, but study protocols should plan to collect the information because the data may be relevant to a different or supplementary estimand. The date of occurrence of each intercurrent event should be clearly documented in eCRF.
SAP	Estimand and Estimator Aligned Analysis Set	• Values of the outcome measure collected from baseline to Week 8 in all randomised participants who receive at least one dose of study treatment during the treatment phase, including the values collected after "Treatment discontinuation due to AE/LoE" and also values collected after "SO x any reason" when this is the only intercurrent event that occurs or if it occurs prior to "TD x geopolitical logistical restrictions". • If "TD x geopolitical logistical restrictions" AND "SO x any reason" occur on the same study participant, at the same time, or at different timepoints, the application of the hypothetical strategy for "TD x geopolitical logistical restrictions" takes priority after this ICE. Please see Figure 3 for the visualisation of the dataset derivation.
SAP	Data not used	Values of the outcome measure collected after the intercurrent event of treatment discontinuation due to geopolitical logistical restrictions, addressed by a hypothetical strategy.
Following the data collection, clinical outcomes and intercurrent events, the pre-specified strategies for addressing intercurrent events are implemented at data level (patient/outcome data at certain visit). This implementation of strategies is the basis for the ADaM dataset derivation.		

Figure 2: Selected study participant journeys for estimand 1 (after implementing intercurrent events data handling strategies)

Subject ID	Week 0 (Baseline)	Week 1	Week 2	Unsch week 2.1	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8 (Follow-up)
ABC001	R/TI			---			SO			
ABC002	R/TI		TD	X SO	X	X	X	X	X	X
ABC003	R/TI			---	SO			TD	X	X
ABC004	R/TI			---			TD		SO	
ABC005	R/TI			---		TD				

R/TI	Randomisation/Treatment initiation
	Starting other pharmaceutical treatment for MDD for any reason [SO x any]
	Treatment discontinuation due to Adverse Event/Lack of Efficacy [TD AE/LoE]
	Treatment discontinuation due to a geopolitical logistical restriction [TD Log]
	Outcome collected
X	Original outcome not used/replaced
---	Outcome not collected

Following this data collected, clinical outcomes and intercurrent events, the pre-specified strategies for addressing intercurrent events are implemented at data level (patient/outcome data at certain visit). This implementation of strategies is the basis for the dataset derivation. Following this step, the resulting dataset is supplied to the estimators.

Figure 3: Side-by-side view of study participant journeys with data as collected versus data for analysis considering the intercurrent events occurrences and data handling strategies for Estimand 1

Data as collected

Subject ID	Week 0 (Baseline)	Week 1	Week 2	Unsch week 2.1	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8 (Follow-up)
ABC001	R/TI			---			SO			
ABC002	R/TI		TD	SO						
ABC003	R/TI			---	SO			TD		
ABC004	R/TI			---			TD		SO	
ABC005	R/TI			---		TD				

Data for analysis after considering intercurrent events and data handling strategies

Subject ID	Week 0 (Baseline)	Week 1	Week 2	Unsch week 2.1	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8 (Follow-up)
ABC001	R/TI			---			SO			
ABC002	R/TI		TD	X SO	X	X	X	X	X	X
ABC003	R/TI			---	SO			TD	X	X
ABC004	R/TI			---			TD		SO	
ABC005	R/TI			---		TD				

Legend

R/TI	Randomisation/Treatment initiation
	Starting other pharmaceutical treatment for MDD for any reason [SO x any]
	Treatment discontinuation due to Adverse Event/Lack of Efficacy [TD AE/LoE]
	Treatment discontinuation due to a geopolitical logistical restriction [TD Log]
	Outcome collected
X	Original outcome not used/replaced
---	Outcome not collected

1.2 Estimand 2

The table below presents how the clinical question of interest and corresponding estimand translate into specifications for data collection and analysis sets.

Document	Descriptor	Description
Protocol & SAP	Question of interest	For a patient with MDD for whom acute drug monotherapy would be indicated, what would be the expected effect of prescribing drug X on the likelihood of experiencing a treatment response at Week 8 if the patient did not discontinue treatment due to geopolitical logistical restrictions (e.g. site closure due to the geopolitical logistical restrictions)? Treatment response requires a substantial improvement of symptoms without starting a different MDD treatment, and with no premature treatment discontinuation due to adverse event or lack of efficacy.
Protocol & SAP	Attributes	1. **Treatment condition of interest vs Alternative treatment condition:** Assignment to drug X vs placebo, at the selected dose and frequency of administration as if patients would not discontinue treatment due to geopolitical logistical restrictions (e.g. in a geopolitical logistical restriction-free world). 2. **Population:** Patients with a diagnosis of MDD in a current major depressive episode with at least moderate symptom severity. 3. **Variable:** Binary responder variable, where a responder is defined as a participant who has at least 50% reduction from baseline to Week 8 in the HDRS total score and does not discontinue treatment early due to AE/LoE or start other pharmacological treatment for MDD by Week 8. 4. **Population-level summary:** Difference in responder proportions vs placebo. 5. **Intercurrent events and corresponding strategies:** • Treatment discontinuation due to geopolitical logistical restriction is handled with the hypothetical strategy. • Treatment discontinuation due to AE/LoE is handled with composite variable strategy. • Start of other pharmacological treatment for MDD is handled with composite variable strategy. For simplicity, other intercurrent events (such as treatment discontinuations due to other reasons) are not included in the estimand definition.

Protocol & SAP	Implementation of strategies for addressing intercurrent events	• In this example, we assume that participants can only discontinue due to a single reason. Therefore, no conflict will exist between the intercurrent events of treatment discontinuation due to geopolitical restrictions and treatment discontinuation due to lack of efficacy or adverse event. If there are several reasons for the treatment discontinuation of a participant, the site should select the most relevant reason for data entering in the CRF. • If a participant discontinues treatment due to geopolitical logistical restrictions after the participant has already started other pharmacological treatment for MDD, the composite strategy will be applied at the time of "SO x any". • If "TD due to geopolitical logistical restrictions" is the only intercurrent event for a participant or if it occurs prior to "SO x any", then the hypothetical strategy will be used. An appropriate imputation method should be used for the assessment of achieving at least 50% reduction from baseline to Week 8 in the HDRS total score. Since imputation methods are not in scope for this example, this topic is not discussed.
Protocol & SAP	Key implementation elements needed to address this estimand	The date of occurrence of each intercurrent event should be clearly documented in eCRF.
SAP	Estimand and Estimator aligned analysis set	Values of the outcome measure collected from baseline to Week 8 in all randomised participants. Please see Figure 5 for the visualisation of the dataset derivation.
SAP	Data not used	Values of the outcome measure collected after the ICE of TD due to AE/LoE, values after TD due to geopolitical logistical restrictions, and values after the start of other pharmacological treatment for MDD.
Following the collected data, clinical outcomes and intercurrent events, the pre-specified strategies for addressing intercurrent events are implemented at data level (patient/outcome data at certain visit). This implementation of strategies is the basis for the ADaM dataset derivation.		

Figure 4: Selected Study Participant Journeys for Estimand 2 (After Implementing Intercurrent Events Data Handling Strategies)

Data as collected										
Subject ID	**Week 0 (Baseline)**	**Week 1**	**Week 2**	**Unsch week 2.1**	**Week 3**	**Week 4**	**Week 5**	**Week 6**	**Week 7**	**Week 8 (Follow-up)**
ABC001	R/TI			---			SO			
ABC002	R/TI		TD	SO						
ABC003	R/TI			---	SO			TD		
ABC004	R/TI			---			TD		SO	
ABC005	R/TI			---		TD				

Legend

R/TI	Randomisation/Treatment initiation
	Starting other pharmaceutical treatment for MDD for any reason [SO x any]
	Treatment discontinuation due to Adverse Event/Lack of Efficacy [TD AE/LoE]
	Treatment discontinuation due to a geopolitical logistical restriction [TD Log]
	Outcome collected
	Original outcome not used/replaced
	Composite outcome
---	Outcome not collected

Following these data collected, clinical outcomes and intercurrent events, the pre-specified strategies for addressing intercurrent events are implemented at data level (patient/outcome data at certain visit). This implementation of strategies is the basis for the dataset derivation. Following this step, the resulting dataset is supplied to the estimators.

Figure 5: Side-by-side view of study participant journeys with data for Estimand 2 as collected versus used for analysis considering the intercurrent events occurrences and their data handling strategies

Data as collected										
Subject ID	Week 0 (Baseline)	Week 1	Week 2	Unsch week 2.1	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8 (Follow-up)
ABC001	R/TI			---			SO			
ABC002	R/TI		TD	SO						
ABC003	R/TI			---	SO			TD		
ABC004	R/TI			---			TD		SO	
ABC005	R/TI			---		TD				

Data for analysis after considering intercurrent events and data handling strategies										
Subject ID	Week 0 (Baseline)	Week 1	Week 2	Unsch week 2.1	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8 (Follow-up)
ABC001	R/TI			---			SO			
ABC002	R/TI		TD	SO						
ABC003	R/TI			---	SO			TD		
ABC004	R/TI			---			TD		SO	
ABC005	R/TI			---		TD				

Legend

R/TI	Randomisation/Treatment initiation
	Starting other pharmaceutical treatment for MDD for any reason [SO x any]
	Treatment discontinuation due to Adverse Event/Lack of Efficacy [TD AE/LoE]
	Treatment discontinuation due to a geopolitical logistical restriction [TD Log]
	Outcome collected
	Original outcome not used/replaced
	Composite outcome
---	Outcome not collected

2. Data Collection/Tabulation

2.1 CRF

The following CRFs contain the information about the intercurrent events identified in the patient journeys. For brevity, we have displayed only partial sections of the CRF here.

Please consider populating complete CRF pages in real-time clinical studies as well as other required CRF pages according to your study design.

The disposition CRF for participants ABC002, ABC003, ABC004 and ABC005 captures the intercurrent events, treatment discontinuation due to adverse event, lack of efficacy, or geopolitical logistical restrictions.

What was the subject's status? **DS.DSDECOD** **DS.DSTERM**	• **.....** • **ADVERSE EVENT. LINK TO ADVERSE EVENT:** • **LACK OF EFFICACY** • **LOGISTICAL PROBLEM** o ..... o GEOPOLITICAL LOGISTICAL RESTRICTIONS o .....

The adverse event CRF for patient ABC004 captures the details of the intercurrent event – 'Suicidal Thoughts' – the timing, and whether the intercurrent event is currently ongoing.

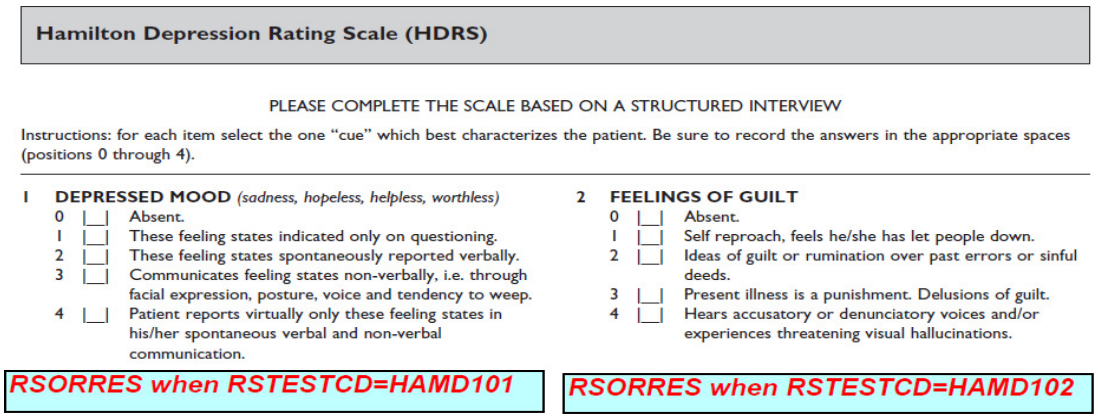
Were any adverse events experienced? **Not submitted**	• Yes • No
AE number **AE.AESPID**	1

What is the adverse event term? **AE.AETERM**	SUICIDAL THOUGHTS
Start date **AE.AESTDTC**	4/20/2022
Is the adverse event ongoing? **AE.AEENRF or AEENRTPT**	• Yes
End date **AE.AEENDTC**	

The concomitant medication CRF for participants ABC001, ABC002, ABC003 and ABC004 captures the intercurrent events, additional/alternative treatments for MDD, the timing, and whether the treatment is currently ongoing.

Were any concomitant medications taken? **Not submitted**	• Yes • No
What was the medication? **CM.CMTRT**	Duloxetine Fluoxetine Lorazepam
For what reason was the medication taken? **SUPPCM.QVAL where SUPPCM.QNAM = "CMREAS" and SUPPCM.QLABEL = "Reason"**	• ..... • REQUIRED CONCOMITANT MEDICATION FOR THE STUDY • .....
Start date **CM.CMSTDTC**	
Is the medication ongoing? **CM.CMENRF or CMENRTPT**	• Yes
End date **CM.CMENDTC**	

The Hamilton Depression Rating Scale (HDRS) CRF, also known as Ham-D, is a 17-item depression rating questionnaire that captures the symptoms of depression experienced in the past week. A snapshot of the CRF is shown here, while a comprehensive MDD CDISC TAUG is available.



Hamilton Depression Rating Scale (HDRS)

PLEASE COMPLETE THE SCALE BASED ON A STRUCTURED INTERVIEW

Instructions: for each item select the one "cue" which best characterizes the patient. Be sure to record the answers in the appropriate spaces (positions 0 through 4).

1 **DEPRESSED MOOD** *(sadness, hopeless, helpless, worthless)*
0 |__| Absent.
1 |__| These feeling states indicated only on questioning.
2 |__| These feeling states spontaneously reported verbally.
3 |__| Communicates feeling states non-verbally, i.e. through facial expression, posture, voice and tendency to weep.
4 |__| Patient reports virtually only these feeling states in his/her spontaneous verbal and non-verbal communication.

2 **FEELINGS OF GUILT**
0 |__| Absent.
1 |__| Self reproach, feels he/she has let people down.
2 |__| Ideas of guilt or rumination over past errors or sinful deeds.
3 |__| Present illness is a punishment. Delusions of guilt.
4 |__| Hears accusatory or denunciatory voices and/or experiences threatening visual hallucinations.

RSORRES when RSTESTCD=HAMD101

RSORRES when RSTESTCD=HAMD102

2.2 SDTM

For illustration purposes, we have only displayed partial SDTM domains here.

Participant ABC004 experienced suicidal thoughts on 2022-04-20 and discontinued from treatment due to adverse event; participants ABC002 and ABC003 discontinued from treatment due to geopolitical logistical restrictions; participant ABC005 discontinued from treatment due to lack of efficacy.

ae.xpt

Row	DOMAIN	USUBJID	AESEQ	AETERM	AEDECOD	EPOCH	AESTDTC	AEENDTC	AEENRF
1	DS	ABC004	1	SUICIDAL THOUGHTS	Suicidal ideation	TREATMENT	2022-04-20		ONGOING

ds.xpt

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

relrec.xpt

Row	RDOMAIN	USUBJID	IDVAR	IDVARVAL	RELID
1	AE	ABC004	AESEQ	1	1

Participants ABC001 and ABC002 took rescue therapy, and ABC003 took required concomitant medication per protocol.

cm.xpt

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

suppcm.xpt

Row	RDOMAIN	USUBJID	IDVAR	IDVARVAL	QNAM	QLABEL	QVAL
1	CM	ABC001	CMSEQ	1	CMREAS	Reason	REQUIRED CONCOMITANT MEDICATION FOR THE STUDY
2	CM	ABC002	CMSEQ	1	CMREAS	Reason	REQUIRED CONCOMITANT MEDICATION FOR THE STUDY
3	CM	ABC003	CMSEQ	1	CMREAS	Reason	REQUIRED CONCOMITANT MEDICATION FOR THE STUDY
4	CM	ABC004	CMSEQ	1	CMREAS	Reason	REQUIRED CONCOMITANT MEDICATION FOR THE STUDY

rs.xpt

Row	DOMAIN	USUBJID	RSTESTCD	RSTEST	RSCAT	RSSTRESN	RSLOBXFL	RSEVAL	VISITNUM	RSEVLINT	RSDTC
1	RS	ABC001	HAMD101	HAMD1-Depressed Mood	HAMD 17	3	Y	INVESTIGATOR	1	-P1	2022-03-16
2	RS	ABC001	HAMD102	HAMD1-Feelings of Guilt	HAMD 17	2	Y	INVESTIGATOR	1	-P1W	2022-03-16
3	RS	ABC001	HAMD103	HAMD1-Suicide	HAMD 17	2	Y	INVESTIGATOR	1	-P1W	2022-03-16
4	RS	ABC001	HAMD104	HAMD1-Insomnia Early - Early Night	HAMD 17	1	Y	INVESTIGATOR	1	-P1W	2022-03-16

5	RS	ABC001	HAMD105	HAMD1-Insomnia Middle - Middle Night	HAMD 17	2	Y	INVESTIGATOR	1	-P1W	2022-03-16
6	RS	ABC001	HAMD106	HAMD1-Insomnia Early Hours - Morning	HAMD 17	0	Y	INVESTIGATOR	1	-P1W	2022-03-16
7	RS	ABC001	HAMD107	HAMD1-Work and Activities	HAMD 17	3	Y	INVESTIGATOR	1	-P1W	2022-03-16
8	..										
9	RS	ABC001	HAMD118	HAMD1-Total Score	HAMD 17	5	Y	INVESTIGATOR	1	-P1W	2022-03-16

2.3 cSDRG

Were any intercurrent events collected?

- Yes, intercurrent events were collected in this study.

Intercurrent Event collected in the study	In which CRF forms were details of intercurrent events collected?	In which SDTM domains (and variables) were intercurrent events mapped?
Treatment Discontinuation (Geopolitical Logistical Restrictions)	Trial Period Disposition (Treatment Discontinuation)	DS (DSTERM, DSDECOD, DSSTDTC)
Treatment Discontinuation (Adverse Event)	Trial Period Disposition (Treatment Discontinuation) Adverse Event	DS (DSTERM, DSDECOD, DSSTDTC) AE (AETERM, AEDECOD, AESTDTC, AEENDTC, AEENRF)
Treatment Discontinuation (Lack of Efficacy)	Trial Period Disposition (Treatment Discontinuation)	DS (DSTERM, DSDECOD, DSSTDTC)
Starting other pharmacological treatments for MDD	Concomitant Medication	CM (CMTRT, CMDECOD, CMSTDTC, CMENDTC, CMENRF) SUPPCM (QNAM, QVAL)

3. Data Analysis

3.1 ADaM

3.1.1 Intercurrent Events Dataset – ADICE

Dataset-Level Metadata

Dataset	Description	Class – Subclass	Structure	Purpose	Keys	Documentation	Location
ADICE	Intercurrent Events	OCCURRENCE DATA STRUCTURE - INTERCURRENT EVENTS	One record per subject per intercurrent event	Analysis	STUDYID, USUBJID, ATERM, ASTDT	Presents the consolidated lists of intercurrent events related to the different estimands and the prespecified strategy to handle them. Based on combining records from SDTM DS and CM. First record set presents the treatment discontinuations and comes from SDTM DS where DSCAT = "DISPOSITION EVENT" and EPOCH = "TREATMENT". Second record set presents the start of other medications for MDD and comes from SDTM CM where CMCAT = "ANTIDEPRESSANTS".	adice.xpt

Variable-Level Metadata

In this example, ATERM is used to hold the original text from SDTM (disposition term/drug name); ADECOD1 is used to hold the more granular coded value of ATERM, based on the SAP description of intercurrent events; ACAT1 is used to hold a higher-level categorisation of ADECOD1 relevant to the analyses; ASTDT and AENDT hold the start and end date of the intercurrent events; EST01STP and EST02STP hold the strategy associated with the intercurrent event for estimands 1 and 2, respectively, per SAP; EST01STA and EST02STA hold the actual strategy for estimand 1; finally, SRCDOM and SRCSEQ trace the records back to the source SDTM records.

Variable Name	Variable Label	Variable Type	Codelist/Controlled Terms	Source/Derivation/Comment
USUBJID	Unique Subject Identifier	text		DM.USUBJID
ASEQ	Analysis Sequence Number	integer		Unique number per record, per participant. Assigned sequentially to records within subject, sorted according to dataset sort keys.
ATERM	Analysis Term	text		See Value-Level Metadata below, split out by SRCDOM.
ASTDT	Analysis Start Date	integer		See Value-Level Metadata below, split out by SRCDOM.
AENDT	Analysis End Date	integer		If CMCAT = "ANTIDEPRESSANTS", then AENDT = CM. CMENDTC, converted to numeric SAS date; else blank.
ADECOD1	Analysis Dictionary-Derived Term 1	text	"Starting other pharmacological treatments", "Treatment discontinuation due to adverse events", "Treatment discontinuation due to lack of efficacy", "Treatment discontinuation due to geopolitical logistical restrictions"	See Value-Level Metadata below, split out by SRCDOM.
ACAT1	Analysis Category 1	text	"Starting other pharmacological treatments", "Treatment discontinuation due to AE/LoE", "Treatment discontinuation due to geopolitical logistical restrictions"	If ADECOD1 in ("Treatment discontinuation due to lack of efficacy", "Treatment discontinuation due to adverse events"), then ACAT1 = "Treatment discontinuation due to AE/LoE"; else ACAT1 = ADECOD1.
EST01STP	Estimand 01 Planned Handling Strategy	text	"HYPOTHETICAL", "TREATMENT POLICY"	Planned strategy for handling the datapoints impacted by the intercurrent events related to estimand 01 (i.e. as described in the SAP). If ACAT1 = "Treatment discontinuation due to geopolitical logistical restrictions", then "HYPOTHETICAL", else "TREATMENT POLICY".
EST01STA	Estimand 01 Actual Handling Strategy	text	"HYPOTHETICAL"	Actual strategy for handling the datapoints impacted by the intercurrent events related to estimand 01. The variable is based on EST01STP and considers in addition the sequence of intercurrent events relevant to estimand 01 and their priority rules. Per protocol, one reason for treatment discontinuation is reported. If treatment discontinuation occurs due to geopolitical logistical restrictions, it will lead to hypothetical strategy from the moment it occurs, regardless of presence of other intercurrent events (i.e. starting other medication). Treatment policy by definition does not impact on the data present (used as is); therefore, the only actual strategy is Hypothetical when treatment discontinuation for geopolitical logistical restrictions occurs.
EST02STP	Estimand 02 Planned Handling Strategy	text	"COMPOSITE", "HYPOTHETICAL"	Planned strategy for handling the datapoints impacted by the intercurrent events related to estimand 02, as described in the protocol. If ACAT1 = "Treatment discontinuation due to geopolitical logistical restrictions", then "HYPOTHETICAL", else "COMPOSITE".

EST02STA	Estimand 02 Actual Handling Strategy	text	"COMPOSITE", "HYPOTHETICAL"	Actual strategy for handling the datapoints impacted by the intercurrent events related to estimand 02. The variable is based on EST02STP and considers in addition the sequence of intercurrent events relevant to estimand 02 and their priority rules. Per protocol, if "Treatment discontinuation due to geopolitical logistical restrictions" appears as the first or only intercurrent event, its associated hypothetical strategy will appear for subsequent datapoints. In all other situations, the treatment policy associated with the other intercurrent event will apply and prevail (i.e. composite).
VISITNUM	Visit Number	float		Visit number where event occurs (ASTDT). That is VISITNUM from SV where SVSTDTC (as numeric date)<=ASDT<=SVENDTC (as numeric date). Note that SV is set up in such a way that start and end dates of different visits do not overlap.
VISIT	Visit Name	text		Label associated with VISITNUM (per SV domain).
SRCDOM	Source Data	text	"CM", "DS"	Populate with the domain name that is the source of the record ("CM" or "DS").
SRCSEQ	Source Sequence Number	integer		CM.CMSEQ, DS.DSSEQ Populate with the sequence number of the record in the source dataset.

Value-Level Metadata

Note: this example uses SRCDOM to group records from the same source and create value-level metadata for ATERM, ADECOD and ASTDT. For more complex scenarios, the source/derivation column for value-level metadata could reference a table in the ADRG for specific details.

Variable	Where	Type	Codelist/ Controlled Terms	Source/Derivation/Comment
ATERM	SRCDOM="DS"	text		DS.DSDECOD
ATERM	SRCDOM="CM"	text		CM.CMDECOD
ADECOD1	SRCDOM="DS"	text		If ATERM = "LOGISTICAL PROBLEM", then ADECOD1 = "Treatment discontinuation due to geopolitical logistical restrictions". If ATERM ="LACK OF EFFICACY", then ADECOD1 = "Treatment discontinuation due to lack of efficacy". If ATERM = "ADVERSE EVENT", then ADECOD1 = "Treatment discontinuation due to adverse events".
ADECOD1	SRCDOM="CM"	text		ADECOD1 = "Starting other pharmacological treatments"
ASTDT	SRCDOM="DS"	integer		ASTDT = DS. DSSTDTC, converted to numeric SAS date
ASTDT	SRCDOM="CM"	integer		ASTDT = CM. CMSTDTC, converted to numeric SAS date

Example Dataset

The sample ADICE dataset contains only a subset of variables needed for the analysis and is for illustration purposes only. Additional variables may need to be created to make the dataset submission ready. In this table, information is provided to highlight the source data used to create this analysis dataset.

Of interest in the example are the differences between the planned strategy variables (EST01STP, EST02STP) and actual strategy variables (EST01STA, EST02STA). Planned strategy variables simply report the strategy associated in the protocol with the intercurrent event for the estimand. Actual strategy variables consider strategy without actual impact (planned strategy) and order and precedence of strategies; e.g. for subject ABC002, EST02STA is blank for the second intercurrent event (ASEQ=2) because the first one is associated with a hypothetical strategy and has precedence per protocol-defined rule.

Row	USUBJID	ASEQ	ATERM	ADECOD1	ACAT1	VISIT	VISITNUM	ASTDT	AENDT	SRCDOM	SRCSEQ	EST01STP	EST01STA	EST02STP	EST02STA
1	ABC001	1	DULOXETINE	Starting other pharmacological treatments	Starting other pharmacological treatments	WEEK 5	6	2022-04-20		CM	1	TREATMENT POLICY		COMPOSITE	COMPOSITE
2	ABC002	1	LOGISTICAL PROBLEM	Treatment discontinuation due to geopolitical logistical restrictions	Treatment discontinuation due to geopolitical logistical restrictions	WEEK 2	3	2022-03-30		DS	3	HYPOTHETICAL	HYPOTHETICAL	HYPOTHETICAL	HYPOTHETICAL
3	ABC002	2	FLUOXETINE	Starting other pharmacological treatments	Starting other pharmacological treatments	UNSCHEDULED WEEK 2.1	3.1	2022-04-03		CM	1	TREATMENT POLICY		COMPOSITE	
4	ABC003	1	LORAZEPAM	Starting other pharmacological treatments	Starting other pharmacological treatments	WEEK 3	4	2022-04-06		CM	1	TREATMENT POLICY		COMPOSITE	COMPOSITE
5	ABC003	2	LOGISTICAL PROBLEM	Treatment discontinuation due to geopolitical logistical restrictions	Treatment discontinuation due to geopolitical logistical restrictions	WEEK 6	7	2022-04-27		DS	3	HYPOTHETICAL	HYPOTHETICAL	HYPOTHETICAL	
6	ABC004	1	ADVERSE EVENT	Treatment discontinuation due to adverse events	Treatment discontinuation due to AE/LoE	WEEK 5	6	2022-04-20		DS	3	TREATMENT POLICY		COMPOSITE	COMPOSITE
7	ABC004	2	FLUOXETINE	Starting other pharmacological treatments	Starting other pharmacological treatments	WEEK 7	8	2022-05-04		CM	1	TREATMENT POLICY		COMPOSITE	
8	ABC005	1	LACK OF EFFICACY	Treatment discontinuation due to lack of efficacy	Treatment discontinuation due to AE/LoE	WEEK 4	5	2022-04-13		DS	3	TREATMENT POLICY		COMPOSITE	COMPOSITE

3.1.2 ADSL

Considering our simple example, there is nothing specific to the estimands framework in the ADSL dataset and it will therefore not be further illustrated. More specifically, we are using only the usual analysis sets present in the ADaM IG and do not use the new principal stratum flags (PsyFL), hence there is nothing specific to illustrate in the ADSL dataset.

3.1.3 Analysis Dataset Supporting the Estimators – ADHDRS

Dataset-Level Metadata

Nothing specific to estimands to illustrate.

Variable-Level Metadata

Some noteworthy intercurrent events impact variables are illustrated in this example. This highlights the differences and possible usages of the different types of impact variables: Sequence Number (S) versus Flag (F), and impact by event type (ICCy*), by event type by estimand (ICCyEzz*), by estimand (ICEzz*). Details on derivations rules are provided in the variable-level metadata table below.

- **Impact of intercurrent events per intercurrent event type (ICC1S, ICC2S, ICC3S).** The three intercurrent event types are based on the modalities of the ACAT1 variable. In this trial, once an intercurrent event impacts on a datapoint, it affects all subsequent occurrence of the measure (no end to the effect). If more than one intercurrent event of the same type impacts on a datapoint, the first occurrence is the one documented. The sequential number of the intercurrent event in ADICDE (ASEQ) is documented in ICCyS. These variables are set across all estimands and are relevant to this study because the two estimands share the same intercurrent events.
- **Impact flag of intercurrent events per intercurrent event type, per estimand (ICC1E01F, ICC2E01F, ICC3E01F, ICC1E02F, ICC2E02F, ICC3E02F).** These flags identify datapoints impacted by an intercurrent event of the respective modality for a given estimand. These variables are based on ICC1S, ICC2S, ICC3S and consider the strategy associated with the impacting intercurrent event (in the respective ICCyS variable) for the estimand of interest (E01, E02, respectively). The flag is set to Y when the corresponding ICCyS variable is filled (there is an impacting event), and that event can have an impact on the datapoint usage (i.e. it is not treatment policy).
- **Impact flag of intercurrent events per estimand (ICE01S, ICE02S).** There is one variable per estimand which documents if a datapoint is impacted by an intercurrent event for that estimand, and, if so, which intercurrent event (fill with the appropriate ICCyS value). It considers potential impacts of intercurrent events, based on the ICCyEzzF flag variables, and priority rules for the estimand when multiple intercurrent events impact on a datapoint. Once it has been assessed that a datapoint is impacted, and by which intercurrent event type, the impact variable ICEzzS is filled with the ID of the impacting event (taken from the ICCyS variable corresponding to the priority impacting event).

Not illustrated:

– Only some of the impacting sequence number and flag variables have been illustrated in the examples. The non-illustrated variables follow the same principles and rules as the one presented in the examples and have been left out only for space consideration and readability.
– The impacting source domain and source variables (ICCDOM, ICCVAR, ICCEzzD, ICCEzzV, ICEzzD, ICEzzV) are not shown because in this example, there is only one intercurrent event dataset (ADICE) and the sequence variable is always the default ASEQ. It is expected that this will be the case in most study use cases.

Variable Name	Variable Label	Variable Type	Codelist/Controlled Terms	Source/Derivation/Comment
USUBJID	Unique Subject Identifier	text		RS.USUBJID
RSSEQ	Sequence Number	integer		RS.RSSEQ
PARAMCD	Parameter Code	text	PARHDRSC	RS.RSTESTCD
PARAM	Parameter	text	PARHDRSL	RS.RSTEST
AVAL	Analysis Value	integer		RS.RSSTRESN
ABLFL	Baseline Record Flag	text	Y	RS.RSLOBXFL
VISITNUM	Visit Number	float		RS.VISITNUM
VISIT	Visit Name	text		RS.VISIT
RSEVLINT	Evaluation Interval	text		RS.RSEVLINT
ASTDT	Analysis Start Date	integer		RS.RSDTC converted to SAS numerical date – 6 days
AENDT	Analysis End Date	integer		RS.RSDTC converted to SAS numerical date. RSDTC is considered the last day of the evaluation week.
ICC1S	Impacting ICE Cat. Val. 1 Seq. Num.	integer		By subject (USUBJID), in ADICE, consider the earliest (by ADICE.ASTDT) intercurrent event with ADICE.ACAT1 modality 1 ("Starting other pharmacological treatments"). Fill ICC1S with the sequence number of that event (ADICE. ASEQ) for all records with ASTDT >= ADICE.ASTDT.
ICC2S	Impacting ICE Cat. Val. 2 Seq. Num.	integer		Similar to ICC1S but considering event with ADICE.ACAT1 modality 2 ("Treatment discontinuation due to geopolitical logistical restrictions").
ICC3S	Impacting ICE Cat. Val. 3 Seq. Num.	integer		Similar to ICC1S but considering event with ADICE.ACAT1 modality 3 ("Treatment discontinuation due to AE/LoE").
ICC1E01F	Imp. ICE Cat. Val. 1 for Est. 01 Flag	text	Y	Based on ICC1S, considering the Estimand 1 data handling strategy for "Starting other pharmacological treatments" intercurrent events; that is, "Treatment policy". There are no data usage consequences on datapoints impacted by this event, therefore the flag stays blank.
ICC2E01F	Imp. ICE Cat. Val. 2 for Est. 01 Flag	text	Y	Based on ICC2S, considering the Estimand 1 data handling strategy for "Treatment discontinuation due to geopolitical logistical restrictions" intercurrent events, that is "Hypothetical". All records with ICC2S filled will be set to "Y", else stay blank.
ICC3E01F	Imp. ICE Cat. Val. 3 for Est. 01 Flag	text	Y	Based on ICC3S, considering the Estimand 1 data handling strategy for "Treatment discontinuation due to AE/LoE" intercurrent events, that is "Treatment policy". There are no data usage consequences on datapoints impacted by this event, therefore the flag stays blank.
ICC1E02F	Imp. ICE Cat. Val. 1 for Est. 02 Flag	text	Y	Based on ICC1S, considering the Estimand 2 data handling strategy for "Starting other pharmacological treatments" intercurrent events, that is "Composite". All records with ICC1S filled will be set to "Y", else stay blank.
ICC2E02F	Imp. ICE Cat. Val. 2 for Est. 02 Flag	text	Y	Based on ICC2S, considering the Estimand 2 data handling strategy for "Treatment discontinuation due to geopolitical logistical restrictions" intercurrent event that is "Hypothetical". All records with ICC2S filled will be set to "Y", else stay blank.
ICC3E02F	Imp. ICE Cat. Val. 3 for Est. 02 Flag	text	Y	Based on ICC3S, considering the Estimand 2 data handling strategy for "Treatment discontinuation due to AE/LoE" intercurrent events, that is "Composite". All records with ICC1S filled will be set to "Y", else stay blank.

Variable Name	Variable Label	Variable Type	Codelist/Controlled Terms	Source/Derivation/Comment
ICE02S	Impacting ICE for Est. 02* Seq. Num.	integer		Consolidated intercurrent events impact on the datapoint for estimand 2, as for estimand 1. This time based on ICC1E02F, ICC2E02F, ICC3E02F and ICC1S, ICC2S, ICC3S. Step 1: is the datapoint impacted by one or more intercurrent event? If yes, from which modality considering priority rules? - Priority rule, per subject (USUBJID): - 1) intercurrent event modality 2 has priority when it occurs first. For a given subject, considering the 3 flags – ICC1E02F, ICC2E02F, ICC3E02F – if the first record with a "Y" by chronological order (ASTDT) comes from ICC2E02F column, then for all records of the subject, ICE02S = ICC2S. o 2) In all other situations, the first event to occur by chronological order takes precedence. That is, the impacting event is the one from the first modality to have a "Y" in any of ICC1E02F, ICC2E02F, ICC3E02F for the subject. That modality will be named p. Then, for all records of the subject, ICC02S = ICCpS, where p is the index of the modality having precedence.

Value-Level Metadata

There is only one parameter (PARAMCD="HAMD118") in this simple example dataset, presenting the total score. Everything can be documented at the variable level and there has not been a need to use value-level metadata.

Example Dataset

For space reason, the ADHDRS dataset is presented in two parts here below – the first with the core analysis variables, the second with the intercurrent events variables.

Regarding the dataset construction, the core variables part of ADHRDS is built first from RS, per usual ADaM rules. Then the intercurrent events variables are added through look-up (merges/selections) with the ADICE dataset to identify datapoints impacted by intercurrent events.

Construction/derivation rules for the dataset per the variable metadata are described above.

Core Variables

Row	USUBJID	RSSEQ	PARAMCD	PARAM	AVAL	ABLFL	VISITNUM	VISIT	RSEVLINT	ASTDT	AENDT
1	ABC001	18	HAMD118	HAMD1-Total Score	25	Y	1	BASELINE / WEEK 0	-P1W	2022-03-10	2022-03-16
2	ABC001	36	HAMD118	HAMD1-Total Score	26		2	WEEK 1	-P1W	2022-03-17	2022-03-23
3	ABC001	54	HAMD118	HAMD1-Total Score	24		3	WEEK 2	-P1W	2022-03-24	2022-03-30
4	ABC001	72	HAMD118	HAMD1-Total Score	23		4	WEEK 3	-P1W	2022-03-31	2022-04-06
5	ABC001	90	HAMD118	HAMD1-Total Score	19		5	WEEK 4	-P1W	2022-04-07	2022-04-13
6	ABC001	108	HAMD118	HAMD1-Total Score	18		6	WEEK 5	-P1W	2022-04-14	2022-04-20
7	ABC001	126	HAMD118	HAMD1-Total Score	23		7	WEEK 6	-P1W	2022-04-21	2022-04-27
8	ABC001	144	HAMD118	HAMD1-Total Score	21		8	WEEK 7	-P1W	2022-04-28	2022-05-04
9	ABC001	162	HAMD118	HAMD1-Total Score	16		9	FOLLOW UP / WEEK 8	-P1W	2022-05-19	2022-05-25
10	ABC002	18	HAMD118	HAMD1-Total Score	31	Y	1	BASELINE / WEEK 0	-P1W	2022-03-10	2022-03-16
11	ABC002	36	HAMD118	HAMD1-Total Score	31		2	WEEK 1	-P1W	2022-03-17	2022-03-23
12	ABC002	54	HAMD118	HAMD1-Total Score	30		3	WEEK 2	-P1W	2022-03-24	2022-03-30
13	ABC002	72	HAMD118	HAMD1-Total Score	16		3.1	UNSCHEDULED WEEK 2.1	-P1W	2022-03-28	2022-04-03
14	ABC002	90	HAMD118	HAMD1-Total Score	30		4	WEEK 3	-P1W	2022-03-31	2022-04-06
15	ABC002	108	HAMD118	HAMD1-Total Score	32		5	WEEK 4	-P1W	2022-04-07	2022-04-13
16	ABC002	126	HAMD118	HAMD1-Total Score	30		6	WEEK 5	-P1W	2022-04-14	2022-04-20
17	ABC002	144	HAMD118	HAMD1-Total Score	34		7	WEEK 6	-P1W	2022-04-21	2022-04-27
18	ABC002	162	HAMD118	HAMD1-Total Score	29		8	WEEK 7	-P1W	2022-04-28	2022-05-04
19	ABC002	180	HAMD118	HAMD1-Total Score	28		9	FOLLOW UP / WEEK 8	-P1W	2022-05-19	2022-05-25
20	ABC003	18	HAMD118	HAMD1-Total Score	26	Y	1	BASELINE / WEEK 0	-P1W	2022-03-10	2022-03-16
21	ABC003	36	HAMD118	HAMD1-Total Score	21		2	WEEK 1	-P1W	2022-03-17	2022-03-23
22	ABC003	54	HAMD118	HAMD1-Total Score	19		3	WEEK 2	-P1W	2022-03-24	2022-03-30

Row	USUBJID	RSSEQ	PARAMCD	PARAM	AVAL	ABLFL	VISITNUM	VISIT	RSEVLINT	ASTDT	AENDT
23	ABC003	72	HAMD118	HAMD1-Total Score	16		4	WEEK 3	-P1W	2022-03-31	2022-04-06
24	ABC003	90	HAMD118	HAMD1-Total Score	19		5	WEEK 4	-P1W	2022-04-07	2022-04-13
25	ABC003	108	HAMD118	HAMD1-Total Score	15		6	WEEK 5	-P1W	2022-04-14	2022-04-20
26	ABC003	126	HAMD118	HAMD1-Total Score	21		7	WEEK 6	-P1W	2022-04-21	2022-04-27
27	ABC003	144	HAMD118	HAMD1-Total Score	18		8	WEEK 7	-P1W	2022-04-28	2022-05-04
28	ABC003	162	HAMD118	HAMD1-Total Score	16		9	FOLLOW UP / WEEK 8	-P1W	2022-05-19	2022-05-25
29	ABC004	18	HAMD118	HAMD1-Total Score	24	Y	1	BASELINE / WEEK 0	-P1W	2022-03-10	2022-03-16
30	ABC004	36	HAMD118	HAMD1-Total Score	25		2	WEEK 1	-P1W	2022-03-17	2022-03-23
31	ABC004	54	HAMD118	HAMD1-Total Score	14		3	WEEK 2	-P1W	2022-03-24	2022-03-30
32	ABC004	72	HAMD118	HAMD1-Total Score	18		4	WEEK 3	-P1W	2022-03-31	2022-04-06
33	ABC004	90	HAMD118	HAMD1-Total Score	22		5	WEEK 4	-P1W	2022-04-07	2022-04-13
34	ABC004	108	HAMD118	HAMD1-Total Score	18		6	WEEK 5	-P1W	2022-04-14	2022-04-20
35	ABC004	126	HAMD118	HAMD1-Total Score	24		7	WEEK 6	-P1W	2022-04-21	2022-04-27
36	ABC004	144	HAMD118	HAMD1-Total Score	24		8	WEEK 7	-P1W	2022-04-28	2022-05-04
37	ABC004	162	HAMD118	HAMD1-Total Score	17		9	FOLLOW UP / WEEK 8	-P1W	2022-05-19	2022-05-25
38	ABC005	18	HAMD118	HAMD1-Total Score	25	Y	1	BASELINE / WEEK 0	-P1W	2022-03-10	2022-03-16
39	ABC005	36	HAMD118	HAMD1-Total Score	26		2	WEEK 1	-P1W	2022-03-17	2022-03-23
40	ABC005	54	HAMD118	HAMD1-Total Score	24		3	WEEK 2	-P1W	2022-03-24	2022-03-30
41	ABC005	72	HAMD118	HAMD1-Total Score	23		4	WEEK 3	-P1W	2022-03-31	2022-04-06
42	ABC005	90	HAMD118	HAMD1-Total Score	19		5	WEEK 4	-P1W	2022-04-07	2022-04-13
43	ABC005	108	HAMD118	HAMD1-Total Score	18		6	WEEK 5	-P1W	2022-04-14	2022-04-20
44	ABC005	126	HAMD118	HAMD1-Total Score	23		7	WEEK 6	-P1W	2022-04-21	2022-04-27
45	ABC005	144	HAMD118	HAMD1-Total Score	21		8	WEEK 7	-P1W	2022-04-28	2022-05-04
46	ABC005	162	HAMD118	HAMD1-Total Score	16		9	FOLLOW UP / WEEK 8	-P1W	2022-05-19	2022-05-25

Intercurrent Event Variables

Row	USUBJID	VISITNUM	VISIT	ASTDT	ICC1S	ICC2S	ICC3S	ICC1E01F	ICC2E01F	ICC3E01F	ICC1E02F	ICC2E02F	ICC3E02F	ICE01S	ICE02S
1	ABC001	1	BASELINE / WEEK 0	2022-03-10											
2	ABC001	2	WEEK 1	2022-03-17											
3	ABC001	3	WEEK 2	2022-03-24											
4	ABC001	4	WEEK 3	2022-03-31											
5	ABC001	5	WEEK 4	2022-04-07											
6	ABC001	6	WEEK 5	2022-04-14											
7	ABC001	7	WEEK 6	2022-04-21	1						Y				1
8	ABC001	8	WEEK 7	2022-04-28	1						Y				1
9	ABC001	9	FOLLOW UP / WEEK 8	2022-05-19	1						Y				1
10	ABC002	1	BASELINE / WEEK 0	2022-03-10											
11	ABC002	2	WEEK 1	2022-03-17											
12	ABC002	3	WEEK 2	2022-03-24											
13	ABC002	3.1	UNSCHEDULED WEEK 2.1	2022-03-28		1			Y			Y		1	1
14	ABC002	4	WEEK 3	2022-03-31	2	1			Y		Y	Y		1	1
15	ABC002	5	WEEK 4	2022-04-07	2	1			Y		Y	Y		1	1
16	ABC002	6	WEEK 5	2022-04-14	2	1			Y		Y	Y		1	1
17	ABC002	7	WEEK 6	2022-04-21	2	1			Y		Y	Y		1	1
18	ABC002	8	WEEK 7	2022-04-28	2	1			Y		Y	Y		1	1
19	ABC002	9	FOLLOW UP / WEEK 8	2022-05-19	2	1			Y		Y	Y		1	1
20	ABC003	1	BASELINE / WEEK 0	2022-03-10											
21	ABC003	2	WEEK 1	2022-03-17											
22	ABC003	3	WEEK 2	2022-03-24											
23	ABC003	4	WEEK 3	2022-03-31											
24	ABC003	5	WEEK 4	2022-04-07	1						Y				1
25	ABC003	6	WEEK 5	2022-04-14	1						Y				1
26	ABC003	7	WEEK 6	2022-04-21	1						Y				1
27	ABC003	8	WEEK 7	2022-04-28	1	2			Y		Y	Y		2	1
28	ABC003	9	FOLLOW UP / WEEK 8	2022-05-19	1	2			Y		Y	Y		2	1

Row	USUBJID	VISITNUM	VISIT	ASTDT	ICC1S	ICC2S	ICC3S	ICC1E01F	ICC2E01F	ICC3E01F	ICC1E02F	ICC2E02F	ICC3E02F	ICE01S	ICE02S
29	ABC004	1	BASELINE / WEEK 0	2022-03-10											
30	ABC004	2	WEEK 1	2022-03-17											
31	ABC004	3	WEEK 2	2022-03-24											
32	ABC004	4	WEEK 3	2022-03-31											
33	ABC004	5	WEEK 4	2022-04-07											
34	ABC004	6	WEEK 5	2022-04-14											
35	ABC004	7	WEEK 6	2022-04-21			1						Y		1
36	ABC004	8	WEEK 7	2022-04-28			1						Y		1
37	ABC004	9	FOLLOW UP / WEEK 8	2022-05-19	2		1				Y		Y		1
38	ABC005	1	BASELINE / WEEK 0	2022-03-10											
39	ABC005	2	WEEK 1	2022-03-17											
40	ABC005	3	WEEK 2	2022-03-24											
41	ABC005	4	WEEK 3	2022-03-31											
42	ABC005	5	WEEK 4	2022-04-07											
43	ABC005	6	WEEK 5	2022-04-14			1						Y		1
44	ABC005	7	WEEK 6	2022-04-21			1						Y		1
45	ABC005	8	WEEK 7	2022-04-28			1						Y		1
46	ABC005	9	FOLLOW UP / WEEK 8	2022-05-19			1						Y		1

3.1.4 ADRG

In this example ADRG, estimand 1 is covered in detail; while estimand 2 is not illustrated for space reason. (There is nothing specific to illustrate with estimand 2 that is not already illustrated with estimand 1.)

Please note that the example ADRG below is purely illustrative, including the statistical methods description – the focus is not to describe or recommend any analysis method for the topic. It just illustrates that the statistical analysis method would be documented and how.

3. Analysis Considerations Related to Multiple Analysis Datasets

3.1 Estimands and Estimators

Estimand/ Estimator ID	Descriptor	Description
1: Estimand 01 (E1)	Protocol	Protocol reference: see section 3.
	SAP	SAP reference: see section 1.1.
	Analysis dataset	Dataset name: ADHDRS ICE impact variable(s): ICE01S/F (supportive: ICC1S, ICC2S, ICC3S, ICC1E01F, ICC2E01F, ICC3E01F, ICE01S) Treatment variable: TRT01P, TRT01PN Treatment modalities: Placebo (1), Drug X (2) Endpoint variable: CHG where PARAM = "HAMD1-Total Score" (PARAMCD="HAMD118") Timing variable: AVISIT (only scheduled visit are considered for the estimations) from "BASELINE / WEEK 0" to "FOLLOW UP/ WEEK 8" Covariable(s): BASE Additional dataset: none.
	Analysis records	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 1) Starting other pharmacological treatments 2) Treatment discontinuation due to geopolitical logistical restrictions 3) Treatment discontinuation due to AE/LoE Estimand strategy variable: EST01STP, EST01STA Strategies: 1) Starting other pharmacological treatments: Treatment policy 2) Treatment discontinuation due to geopolitical logistical restrictions: Hypothetical 3) Treatment discontinuation due to AE/LoE: Treatment policy Priorities: 1) Treatment discontinuation due to geopolitical logistical restrictions takes precedence from the moment it occurs.
1.1 Main estimator	Protocol	Protocol Reference: see section 9.3.2.2
	SAP	SAP reference: see section 1.1, 4.2.2.
	Analysis record set	Analysis records: ICE01F <> "Y" and ANL01FL = "Y" (impacted records are simply removed and not explicitly replaced due to using the MMRM method)
	Analysis description	Analysis method: Mixed Effects Repeated Measures Model (MMRM): CHG ~ BASE TRT01PN*AVISIT, with measure repeated on USIBJID over AVIST. Treatment effect estimated through Least Square Mean difference on TRT01PN*AVISIT Analysis details: please refer to SAP Table 8.2.1.1
	Results	Table: Please refer to CSR Table 8.2.1.1

3.2 Core Variables

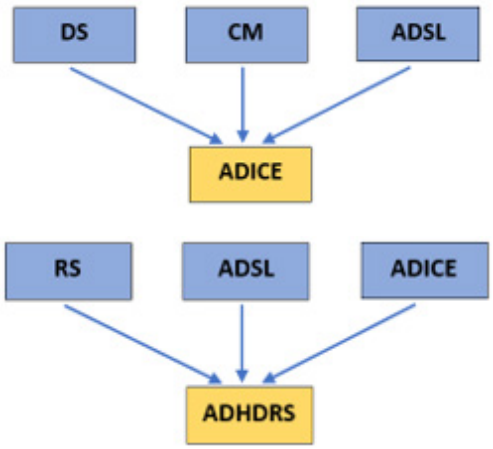
[There were no core variables specifically dedicated to estimand support in the ongoing example to use as illustration, like PSyFL. Therefore, the section is not filled in this example.]

3.6 Imputation/Derivation Methods

[No global imputation/derivation rules specific to estimands across multiple analysis datasets in this example study. Only ADHDRS is used. Therefore, all explanations will be presented in the 5.2.3 ADHDRS section.]

4. Analysis Data Creation and Processing Issues

4.1 Data Dependencies



5. Analysis Dataset Descriptions

5.1 Overview

• Were there any analysis datasets created to support the ICH (E9)R1 estimands framework? Yes

1. What dataset(s) are used for storing the intercurrent events? ADICE
2. What datasets and variables are used to support estimands analyses?
   – ADHDRS: ICC1S, ICC2S, ICC3S, ICC1E01S, ICC2E01F, ICC3E01F, ICC1E02F, ICC2E02F, ICC3E02F, ICE01S, ICE02S
3. Is there any additional information regarding implementation of the estimands framework? Please refer to section 3.1 for more details.

5.2 Analysis Datasets

Dataset Dataset Label	Class	Efficacy (E)/Safety (S)/Immunogenicity (I)	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	S/E				One observation per subject per intercurrent event
ADHDRS Hamilton Depression Rating Scale Analysis Dataset	BDS	E			X	One observation per subject, per parameter, per analysis visit
.....	.....					.....

5.2.1 ADSL – Participant-Level Analysis Dataset

The analysis set flag variables are defined in ADSL and copied together with the variables listed in section 3.2 into other analysis datasets as needed.

5.2.2 ADICE – Intercurrent Events Analysis Dataset

Structure:

The ADICE dataset contains one observation per subject per intercurrent event.

Source:

It is derived from DS for intercurrent events related to treatment discontinuation and from CM for intercurrent events related to start of other MDD-related treatments. This dataset consolidates all the intercurrent events information. It is built from two sources:

• First record set presents the treatment discontinuation. It comes from SDTM DS, where DSCAT = "DISPOSITION EVENT" and EPOCH = "TREATMENT". Records are identified by SRCDOM = "DS".

• Second record set presents the start of other medications for MDD. It comes from SDTM CM, where CMCAT = "ANTIDEPRESSANTS". Records are identified by SRCDOM = "CM".

Noteworthy Derivations/Variables:

- ADECOD1 contains the name of the four intercurrent events of interest, as specified in the protocol. It is mapped from ATERM that contains the source SDTM value.
- ACAT1: contains a grouping of ADECOD1 into the three categories of intercurrent events relevant to the analysis.
- EST01STP and EST02P hold the strategy associated with the intercurrent event, as described in the protocol, for estimands 1 and 2 respectively.
- EST01STA and EST02STA hold the actual strategy relevant for the intercurrent event for estimands 1 and 2, respectively, considering the priority rules of each estimand. It is set up based on EST01STP. See the Define-XML for derivations details.

Date Imputation Rules

There has not been imputation of intercurrent event(s) dates.

5.2.3 ADHDRS – Hamilton Depression Rating Scale Analysis Dataset

ADHDRS contains analysis data from the Hamilton Depression Rating Scale 17-item questionnaire, one of the primary efficacy endpoints.

Source:
It contains one record per subject per parameter (HAMD-17-item questionnaire) per visit. Source data can be traced back to the SDTM. RS domain using USUBJID and RSSEQ.

Noteworthy Derivations/Variables:

- Impact of intercurrent events per intercurrent event type (ICC1S, ICC2S, ICC3S). The three intercurrent event types are based on the modalities of the ACAT1 variable. In this trial, once an intercurrent event impacts on a datapoint, it affects all subsequent occurrence of the measure (no end to the effect). If more than one intercurrent event of the same type impacts on a datapoint, the first occurrence is the one documented. The sequential number of the intercurrent event in ADICDE (ASEQ) is documented in ICCyS. These variables are set across all estimands and are relevant to this study because the two estimands share the same intercurrent events.
- Impact flag of intercurrent events per intercurrent event type, per estimand (ICC1E01F, ICC2E01F, ICC3E01F, ICC1E02F, ICC2E02F, ICC3E02F). These flags identify datapoints impacted by an intercurrent event of the respective modality for a given estimand. These variables are based on ICC1S, ICC2S, ICC3S and consider the strategy associated with the impacting intercurrent event (in the respective ICCyS variable) for the estimand of interest (E01, E02, respectively). The flag is set to Y when the corresponding ICCyS variable is filled (there is an impacting event) and that event can have an impact on the datapoint usage (i.e. it is not treatment policy).
- Impact flag of intercurrent events per estimand (ICE01S, ICE02S). There is one variable per estimand that documents if a datapoint is impacted by an intercurrent event for that estimand and, if so, which intercurrent event (fill with the appropriate ICCyS value). It considers potential impacts of intercurrent events, based on the ICCyEzzF flag variables, and priority rules for the estimand when multiple intercurrent events impact on a datapoint. Once it has been assessed that a datapoint is impacted, and by which intercurrent event type, the impact variable ICEzzS is filled with the ID of the impacting event (taken from the ICCyS variable corresponding to the priority impacting event).

Date Imputation Rules
There has not been imputation of intercurrent event(s) dates.

References

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. (2023). *Ther Innov Regul Sci. 57*(5), 911–939.