



Estimands in ADaM: Overcoming Challenges of Multiple Estimands and Intercurrent Events

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Meet the Speakers

Dennis Kusian

Title: Senior Statistical Programmer

Organization: Metronomia Clinical Research GmbH

Dennis has a degree in Statistics and is working as a statistical programmer for more than 7 years.

In his role at Metronomia Clinical Research GmbH he is responsible for ADaM and TLF programming, as well as creating standard templates, with a special focus on efficacy analyses.

Dr. Marius Klotz

Title: Statistical Programmer

Organization: Metronomia Clinical Research GmbH

With a PhD in biology and several years of research experience Marius has been involved in designing, analyzing and publishing scientific studies. During that time he developed a thorough understanding of applied statistics, programming and their challenges. Since joining Metronomia Clinical Research GmbH about a year ago, his focus has shifted to statistical programming.



Disclaimer and Disclosures

- The views and opinions expressed in this presentation are those of the authors and do not necessarily reflect the official policy or position of CDISC.
- The authors have no real or apparent conflicts of interest to report.



What are Estimands & Intercurrent Events?

What are Estimands & Intercurrent Events (ICEs)?

The ICH E9 R1 Addendum introducing the **Estimand Framework** took effect in 2020.

Estimand





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Estimand



Agenda

- 1. Motivation: Challenges in Clinical Studies
- 2. Estimands of Example Study
- 3. ICEs in ADaM ADICE
- 4. ICEs in other ADaMs ADEFF
- 5. How to Select Records for Different Estimands?
- 6. Imputation of Missing Data

Motivation: Challenges in Clinical Studies

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Two Studies conducted at Metronomia in which Estimand Framework had been used.

Challenges

Primary endpoints are **Diary Scores** collected **Daily** plus various additional secondary endpoints

+ Up to ~10 Intercurrent Events (ICEs)

+ Supplementary estimands with different ICE Handling Strategies

+ Hierarchical Multiple Imputation based on ICEs

Where to start?





Overview of Primary Estimand

Treatment	Active versus Placebo										
Population	Subjects with certain disease as described in protocol										
Endpoint	Total Score (one value per week)										
	 The following intercurrent events (ICEs) were identified: (1) Treatment non-compliance (2) Prohibited medication with low expected impact 										
ICEs	 (3) Prohibited medication with high expected impact (4) Discontinuation of treatment (probably caused by treatment) (5) Discontinuation of treatment (unlikely caused by treatment) 										
Population level summary	Difference in mean score between active and placebo group										





Overview of Primary Estimand

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Population level summary	Difference in mean score between active and placebo group										



Overview of ICE Handling Strategies in Primary Estimand

ICE	Strategy
Treatment non-compliance	Hypothetical Strategy with Missing at Random (MAR) assumption
	→ Set values to missing and impute using Multiple Imputation (MI)
Prohibited medication with low	Treatment policy
expected impact	→ Use all values as collected
Prohibited medication with high	Hypothetical Strategy with MAR assumption
expected impact	→ Set values to missing and impute using Multiple Imputation (MI)
Discontinuation of treatment	Hypothetical Strategy with Missing Not at Random (MNAR) assumption
(probably caused by treatment)	→ Set values to missing and impute by Jump to reference (J2R) strategy
Discontinuation of treatment	Treatment policy
(unlikely caused by treatment)	→ Use all values as collected

Order of implementation:

Hypothetical strategy (J2R) > Hypothetical strategy (MI) > Treatment policy strategy





Primary Estimand - Example

Planned schedule









Primary Estimand - Example Subject ABC002





ICE Handling Strategies in Supplementary Estimand 1 vs. Primary Estimand

We assume that all prohibited medication had an impact on the score.

ICE	Strategy Primary Estimand vs. Supplementary Estimand 1								
Prohibited medication with low expected impact	Treatment policy (Values as collected)	(Multiple imputation)							





ICE Handling Strategies in Supplementary Estimand 2 vs. Primary Estimand

We assumed treatment non-compliance had no influence on collected values.

ICE	Strategy Primary Estimand vs. Supplementary Estimand 2									
Treatment non-compliance	Hypothetical Strategy (Multiple Imputation)	Treatment Policy (Values as collected)								

Values after discontinuation probably caused by treatment are missing at random.

ICE	Strategy Primary Estimand vs. Supplementary Estimand 2								
Discontinuation of treatment probably caused by treatment	Hypothetical Strategy (Jump to Reference)	Hypothetical Strategy (Multiple imputation)							



ICEs in ADaM – ADICE

ICEs in ADaM – ADICE

Set up of ADICE (Structure OTHER) – Subset of variables presented

Variable	Label	Variable	Label
USUBJID	Unique Subject Identifier	EST01STR	Estimand 01 handling strategy
ASEQ	Analysis Sequence Number	EST02STR	Estimand 02 handling strategy
ACAT1	Analysis Category 1	EST03STR	Estimand 03 handling strategy
ACAT2	Analysis Category 2		
ATERM	Analysis Term		
ASTDT	Analysis Start Date		
AENDT	Analysis End Date		



ICEs in ADaM – ADICE

Set up of ADICE (Structure OTHER)

USUBJID	ASEQ	ACAT1	ACAT2	ATERM	ASTDT	AENDT	EST01STR	EST02STR	EST03STR
ABC001	1	Prohibited medication	Prohibited medication with low expected impact	Prohibited medication xxx	2015-01-05	2015-01-30	Treatment Policy	Hypothetical (MAR)	Treatment Policy
	-								-
ABC002	1	Prohibited medication	Prohibited medication with high expected impact	Prohibited medication xxx	2015-02-14	2015-03-14	Hypothetical (MAR)	Hypothetical (MAR)	Hypothetical (MAR)
ABC002	2	Discontinuation of treatment	Discontinuation of treatment (probably caused by treatment)	Discontinuation of treatment due to lack of efficacy	2015-02-28		Hypothetical (J2R)	Hypothetical (J2R)	Hypothetical (MAR)
					_				
ABC003	1	Treatment non- compliance	Treatment non-compliance with expected impact	Missed several treatments	2015-03-14		Hypothetical (MAR)	Hypothetical (MAR)	Treatment Policy
ABC003	2	Discontinuation of treatment	Discontinuation of treatment (unlikely caused by treatment)	Discontinuation of treatment due to adverse event	2015-03-28		Treatment Policy	Treatment Policy	Treatment Policy
ABC004	1	Discontinuation of treatment	Discontinuation of treatment (probably caused by treatment)	Discontinuation of treatment due to lack of efficacy	2015-04-14		Hypothetical (J2R)	Hypothetical (J2R)	Hypothetical (MAR)
ABC004	2	Prohibited medication	Prohibited medication with high expected impact	Prohibited medication xxx	2015-04-28	2015-05-14	Hypothetical (MAR)	Hypothetical (MAR)	Hypothetical (MAR)
ABC005	1	Prohibited medication	Prohibited medication with low expected impact	Prohibited medication xxx which has only impact while taken	2015-05-15	2015-05-25	Treatment Policy	Hypothetical (MAR)	Treatment Policy

Learning:

Think about the numbering of your estimands early, for example

- Start with 01 for the primary estimand and use 02, 03 etc. for the supplementary estimands related to the primary estimand.
- Start with 11 for the first secondary estimand and use 12, 13 etc. for the supplementary estimands related to this secondary estimand.
- Consider using the 2nd digit consistently for similar approaches, e.g. the same variation of ICE strategy.

Strategies for Primary Estimand Strategies for Supplementary Estimands



ICEs in other ADaMs - ADEFF

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ADEFF: Efficacy Analysis Dataset - Subset of variables presented

Variable	Label	Variable	Label
USUBJID	Unique Subject Identifier	ICESEQ01	Impacting ICE seq. Num. for Est. 01
PARAM	Parameter	ICESEQ02	Impacting ICE seq. Num. for Est. 02
AVISIT	Analysis Visit	ICESEQ03	Impacting ICE seq. Num. for Est. 03
ADT	Analysis Date	EST01RFL	Estimand 01 Record-Level Flag
AVAL	Analysis Value	EST02RFL	Estimand 02 Record-Level Flag
DTYPE	Derivation Type	EST03RFL	Estimand 03 Record-Level Flag



ICEs in other ADaMs - ADEFF

ADEFF: Efficacy Analysis Dataset Example subject ABC001 Dataset Structure – All Estimands

USUBJID	PARAM	AVISIT	ADT	AVAL	DTYPE	ICESEQ01	ICESEQ02	ICESEQ03	EST01RFL	EST02RFL	EST03RFL
ABC001	Total Score	Baseline	2015-01-01	5					Y	Y	Y
ABC001	Total Score	Week 1	2015-01-08	9		1		1	Y		Y
ABC001	Total Score	Week 1	2015-01-08		MI-MAR		1			Y	
ABC001	Total Score	Week 2	2015-01-15	3		1		1	Y		Y
ABC001	Total Score	Week 2	2015-01-15		MI-MAR		1			Y	
ABC001	Total Score	Week 3	2015-01-22	12		1		1	Y		Y
ABC001	Total Score	Week 3	2015-01-22		MI-MAR		1			Y	
ABC001	Total Score	Week 4	2015-01-29			1		1	Y		Y
ABC001	Total Score	Week 4	2015-01-29		MI-MAR		1			Y	

ICEs affecting Primary Estimand ICEs affecting Supplementary Estimands RecordsRecordsused forused for analysisanalysis ofofPrimarySupplementaryEstimandEstimands



ADEFF: Efficacy Analysis Dataset Example subject ABC001 Primary Estimand

USUBJID	PARAM	AVISIT	ADT	AVAL	DTYPE	ICESEQ01	ICESEQ02	ICESEQ03	EST01RFL	EST02RFL	EST03RFL
ABC001	Total Score	Baseline	2015-01-01	5					Y	Y	Y
ABC001	Total Score	Week 1	2015-01-08	9		1		1	Y		Y
ABC001	Total Score	Week 1	2015-01-08		MI-MAR		1			Y	
ABC001	Total Score	Week 2	2015-01-15	3		1		1	Y		Y
ABC001	Total Score	Week 2	2015-01-15		MI-MAR		1			Y	
ABC001	Total Score	Week 3	2015-01-22	12		1		1	Y		Y
ABC001	Total Score	Week 3	2015-01-22		MI-MAR		1			Y	
ABC001	Total Score	Week 4	2015-01-29			1		1	Y		Y
ABC001	Total Score	Week 4	2015-01-29		MI-MAR		1			Y	
Values i will be ii Imputat	missing at mputed via ion	random a Multipl	e			ICEs affecting Primary Estimand	I		Recor used f analys Prima Estima	ds for sis of ry and	

Resulting dataset for primary estimand: ADEFFM01 stored, but considered as "Analysis Dataset", not ADaM



ADEFF: Efficacy Analysis Dataset Example subject ABC001 Supplementary Estimand 1

USUBJID	PARAM	AVISIT	ADT	AVAL	DTYPE	ICESEQ01	ICESEQ02	ICESEQ03	EST01RFL	EST02RFL	EST03RFL
ABC001	Total Score	Baseline	2015-01-01	5					Y	Y	Y
ABC001	Total Score	Week 1	2015-01-08	9		1		1	Y		Y
ABC001	Total Score	Week 1	2015-01-08	1	MI-MAR		1			Y	
ABC001	Total Score	Week 2	2015-01-15	3		1		1	Y		Y
ABC001	Total Score	Week 2	2015-01-15		MI-MAR		1			Y	
ABC001	Total Score	Week 3	2015-01-22	12		1		1	Y		Y
ABC001	Total Score	Week 3	2015-01-22		MI-MAR		1			Y	
ABC001	Total Score	Week 4	2015-01-29			1		1	Y		Y
ABC001	Total Score	Week 4	2015-01-29	-	MI-MAR		1			Y	
Values ı will be iı Imputat	missing at mputed via ion	random a Multipl	e				ICEs affecting Supplem Estimano	entary d 1		Records used for a of Suppleme Estimand	nalysis entary 1

Resulting dataset for supplementary estimand 1: ADEFFM02 stored, but considered as "Analysis Dataset", not ADaM



ADEFF: Efficacy Analysis Dataset Example subject ABC001 Supplementary Estimand 2

USUBJID	PARAM	AVISIT	ADT	AVAL	DTYPE	ICESEQ01	ICESEQ02	ICESEQ03	EST01RFL	EST02RFL	EST03RFL
ABC001	Total Score	Baseline	2015-01-01	5					Y	Y	Y
ABC001	Total Score	Week 1	2015-01-08	9		1		1	Y		Y
ABC001	Total Score	Week 1	2015-01-08		MI-MAR		1			Y	
ABC001	Total Score	Week 2	2015-01-15	3		1		1	Y		Y
ABC001	Total Score	Week 2	2015-01-15		MI-MAR		1			Y	
ABC001	Total Score	Week 3	2015-01-22	12		1		1	Y		Y
ABC001	Total Score	Week 3	2015-01-22		MI-MAR		1			Y	
ABC001	Total Score	Week 4	2015-01-29			1		1	Y		Y
ABC001	Total Score	Week 4	2915-01-29		MI-MAR		1			Y	
Values will be i Imputat	e	ICEs affecting Primary Estimand			ICEs affecting Supplementary Estimand 2		Records I used for u analysis of o Primary S Estimand		Records used for analysi of Supplementary Estimand 2		

Resulting dataset for supplementary estimand 2: ADEFFM03 stored, but considered as "Analysis Dataset", not ADaM



ADEFF: Efficacy Analysis Dataset Example subject ABC002 Primary Estimand

USUBJID	PARAM	AVISIT	ADT	AVAL	DTYPE	ICESEQ01	ICESEQ02	ICESEQ03	EST01RFL	EST02RFL	EST03RFL
ABC002	Total Score	Baseline	2015-02-01	9					Y	Y	Y
ABC002	Total Score	Week 1	2015-02-08	9					Y	Y	Y
ABC002	Total Score	Week 2	2015-02-15	8							
ABC002	Total Score	Week 2	2015-02-15		MI-MAR	1	1	1	Y	Y	Y
ABC002	Total Score	Week 3	2015-02-22								
ABC002	Total Score	Week 3	2015-02-22		MI-MAR	1	1	1	Y	Y	Y
ABC002	Total Score	Week 4	2015-02-01	7							
ABC002	Total Score	Week 4	2015-03-01		MI-MAR			1			Y
ABC002	Total Score	Week 4	2015-03-01	1	J2R-MNAR	2	2		Y	Y	
Values missing at random will be imputed via Multiple Imputation Values missing not at random (after J2R-ICE) will be imputed via J2R						CEs affecting Primary Estimand	I		Record used f analys Prima Estima	ds for sis of ry and	

Resulting dataset for primary estimand: ADEFFM01 stored, but considered as "Analysis Dataset", not ADaM



Imputation of Missing Data





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Imputation of Missing Data





Conclusion

- Estimands and ICEs will become a major aspect in future clinical trials, posing new challenges
- Handling observations affected by ICEs and their programmatic implementation needs thorough planning
- ADICE dataset and variables linking ICEs from ADICE to records in other ADaM datasets as central tool





Thank You!





Discussion