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Estimands Framework
Through the Eye of a Statistical Programmer

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ABSTRACT

The gold standard that we follow for long is the ITT principle – where we are estimating the average effect of a subject being randomized to receive treatment vs control, irrespective of potential events that may have taken place - Once randomized, always analyzed! Whereas Estimand helps to structure discussions about relationship between patient journeys and the treatment effect of interest. It defines what is being estimated, why it matters (treatment effect), where it applies (target population), and how intercurrent events are addressed. Since the ICH E9(R1) addendum has brought estimands to forefront, necessitating its integration into the protocol, CRF, SAP and TFLS. Statistical programmers must interpret these documents carefully for accurate implementation of trial's intent into programming specifications, datasets and outputs. This presentation demonstrates the programmer's vital role in bridging clinical intent and statistical execution for accurate and traceable implementation of estimands from trial conduct to reporting through a case study.

INTRODUCTION

Imagine you're planning a road trip. You pick your destination, pack your bags, and set off. But along the way, things happen, you hit traffic, take detours, maybe even switch to a different route. Now, if someone asks, 'How was your trip?' What exactly do you tell them? The original plan? The actual journey? Or something in between?

Clinical trials are a lot like that road trip. Traditionally, we've used the ITT principle—Intention-To-Treat. It's like saying, "No matter what happens on the road, we'll still count you as if you were on the original route.' Even if you stopped halfway, switched cars, or took a completely different path, you're still considered part of that first route. Why? Because it keeps things fair and unbiased, which is crucial for the study's validity.

But here's the catch: clinical scenario is complex. Participants stop treatment, switch drugs, or develop new health conditions—these are called intercurrent events. And when we ignore these detours, the final picture can get blurry. Are we really measuring the treatment effect, or the effect of all those unexpected events?

That's where estimands come in. Think of them as your GPS. They don't just tell you the destination, they define the route & how to handle detours. They answer the question clearly: 'What exactly is the effect of the treatment?' by specifying who, what, when, and how to deal with those twists and turns. That's where the ICH has brought the estimands to fore front.

EMERGENCE OF ESTIMANDS

In clinical trials, sometimes participant stop treatment or have other events that affect results (these are **intercurrent events**). This makes it hard to clearly say what the treatment effect really is. **Estimands** were introduced to solve this problem. An **estimand** is a clear description of **what exactly we want to measure** about the treatment effect, and **how we handle those events**.

It gives a **precise framework** and **clarifies the research question** by specifying:

- **Who** is included (population)
- **What** outcome is measured
- **When** it is measured
- **How** to handle events like treatment discontinuation

So, instead of a vague question, we have a **clear, structured question** that changes the game for data analysis.

IMPACT ON STATISTICAL PROGRAMMING

This affects **how programmers work with data** because:

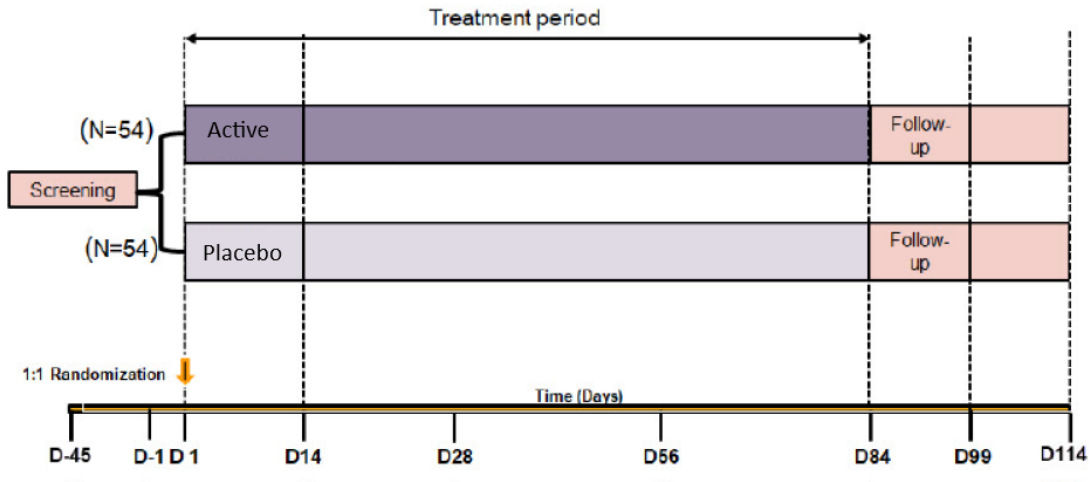
- **Data Handling Changes** Programmers need to know which data to include or exclude based on the estimand. For example, if the estimand says "ignore data after treatment discontinuation," programmers must cut off data after that point.
- **Analysis Strategies Change** Different estimands require different statistical methods. For example, one estimand might need imputation for missing data, while another might use censoring rules.
- **Programming Complexity Increases:** More logic, more complexity, but ultimately, more clarity. Because when the question is clear, the answer—and the analysis—becomes meaningful "Programmers must implement different datasets and algorithms for each estimand.

UNDERSTANDING ESTIMANDS WITH A CASE STUDY:

STUDY DESIGN

Title: A randomized, placebo-controlled study investigating the safety and efficacy of Drug A in patients with symptomatic knee osteoarthritis

Figure 1-1 Study design



ESTIMAND ATTRIBUTES-

Primary objective is to determine the efficacy of Active vs. Placebo in participants with knee Osteoarthritis for relieving pain.

Five key attributes:

- **Population of interest (**Who are we studying**):** refers to the population intend to be treated and reflected in clinical questions (not analysis population).Here in our case, patients with symptomatic knee osteoarthritis

- **Endpoint (**What outcome are we measuring**)**: Change from baseline in Osteoarthritis Outcome Score (KOOS) pain sub-scale at week 12

- **Treatment** (Which treatment or comparison): the randomized treatment (the investigational treatment Drug A or placebo)

- **Summary Measure (**How do we summarize the effect**)** : difference between treatment groups in mean change in KOOS pain sub-scale score from baseline to week 12

- **Intercurrent events** (How do we handle any unexpected events):
  - At least 1 missed dose within 48 hours prior to an assessment
  - At least 12 doses missed
  - Use of NSAID as rescue medication within 48 hours prior to an assessment
  - Unforeseen use of prohibited medication expected to have a sustained effect
  - Unforeseen use of prohibited medication expected to have a limited effect

IDENTIFICATION AND HANDELING OF INTERCURRENT EVENTS (ICEs)

When the estimand is defined, estimand attributes including the strategies selected for the identified will be linked to the clinical question of interest. Examples of types of clinical question of interest formulations (implying different ICE strategies) are presented below:

- Treatment effect under the assignment to either experimental treatment or placebo, regardless of ICE—**Treatment policy strategy**
- Treatment effect under a counterfactual scenario (e.g., as if patients would continue treatment as assigned or as if patients would not start other pharmacological treatments)—**Hypothetical strategy**
- Treatment effect on the likelihood of a patient experiencing a treatment response, where the response definition incorporates the ICE (e.g., patient with ICE is considered as non-responder)—**Composite Variable strategy**
- Treatment effect while treatment is being taken—**While on treatment strategy**
- Treatment effect in a stratum of patients who would/would not experience the ICE —**Principal Stratum strategy**.

CASE STUDY: HANDELING OF INTERCURRENT EVENTS

Intercurrent events		**Handling of event**
Missed treatment doses	At least 1 missed dose within 48 hours prior to an assessment	Hypothetical Strategy- Only assessment immediately following this ICE will be excluded
	At least 12 missed doses.	Hypothetical Strategy- all assessments following this ICE will be excluded
Rescue medication	Use of NSAID as rescue medication within 48 hours prior to an assessment .	Hypothetical Strategy- Only assessment immediately following this ICE will be excluded

Prohibited Medication	Use of prohibited medication expected to have a limited effect	Hypothetical Strategy- Only assessment immediately following this ICE will be excluded
	Use of prohibited medication expected to have a sustained effect	Hypothetical Strategy- all assessments following this ICE will be excluded

HANDELING OF INTERCURRENT EVENTS IN ADAMs:

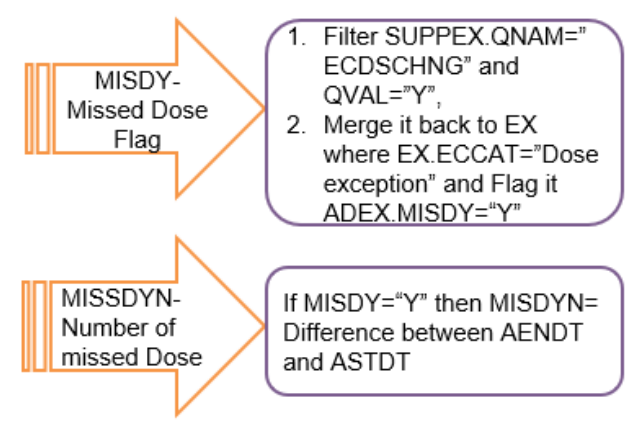
ADEX:

- ADEX: Challenges faced while identifying ICEs

  We don't have missing dose information collected on database.

- Solution: Discussed with DM, Stats and Trial Medical Expert (TME). Documented to consider missed days as missed dose

ADEX : Creating ICE Flags



SUBJID	ASTDT	AENDT	MISDY	MISDYN
110206	2024-06-19	2024-06-19	Y	7
300705	2024-02-16	2024-02-16	Y	25
800100	2022-09-02	2022-09-02	Y	7
800303	2022-08-07	2022-08-07	Y	23
800308	2023-11-27	2023-11-27	Y	11
801400	2024-09-05	2024-09-05	Y	5

Data shown here are for the illustrative purpose only.

ADCM:

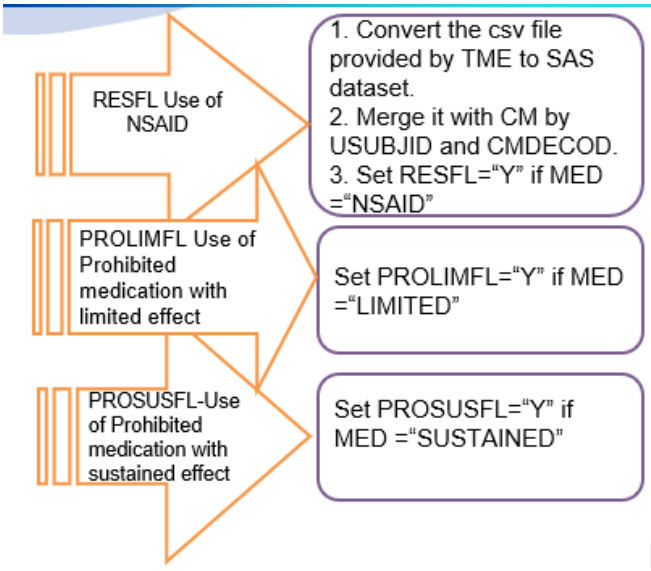
- ADCM: Challenges faced while identifying ICEs

We do have rescue medications category under CM domain however we do not know which CMDECOD is considered as NSAIDs. What are prohibited medications and further how to segregate with limited and sustained impact

- Solution:

After discussions with DM, Statistics, and the Trial Medical Expert (TME), the team decided to seek confirmation from the TME regarding the identification of NSAIDs and prohibited medications with limited or sustained effects. Consequently, we needed to consult the TME for every data snapshot until the database lock.

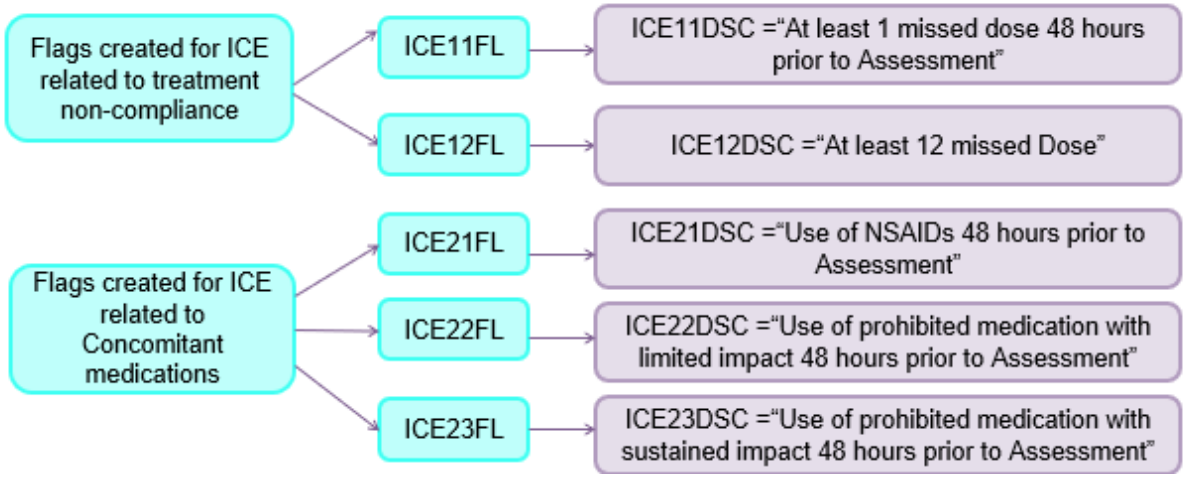
ADCM: Creating ICE Flags



SUBJID	CMDECOD	PROLIMFL	RESFL	PROSUSFL
100100	PARACETAMOL	Y	Y	
300705	DICLOFENAC			
800100	KETOROLAC		Y	
800303	CHONDROITIN SULFATE			Y
800308	CLONAZEPAM	Y		
801400	GLUCOSAMNE			Y

Data shown here are for the illustrative purpose only.

ADQS: Creating ICE Flags



STATISTICAL ANALYSIS

- **Primary Estimand Analysis:** The change from baseline in KOOS pain subscale will be analyzed using a MMRM. The model will include baseline, treatment, time point, baseline * time points and treatment *time points as fixed effects. A two-sided 95% confidence interval for the treatment effect at week 12 will be reported

- **Supplementary Analysis**: The change from baseline in KOOS pain subscale will be analyzed using same analysis as primary estimand with all ICEs handled as per treatment policy strategy (I.e. all data will be included as collected)

RECORD SELECTION FOR PRIMARY AND SECONDARY ESTIMANDS:

DATASET	ESTIMAND	RECORD SELECTION CRITERIA
ADQS	For Primary Analysis	Where PARAMCD="KOOS144" and ANL01FL="Y" and (ICE11FL ne "Y" and ICE12FL ne "Y" and ICE21FL ne "Y" and ICE22FL ne "Y" and ICE23FL ne "Y")
	For Supplementary Analysis	Where PARAMCD="KOOS144" and ANL01FL="Y"

ANL01FL flags the non-missing post baseline records

STATSTICAL ANALYSIS SAS CODE & REPORT FOR PRIMARY ESTIMAND:

```
proc mixed data= qs1;
class trtan avisitn USUBJID ;
model chg = base trtan avisitn base*avisitn trtan*avisitn /s alpha=0.05 ddfm=KR;
repeated avisitn / subject=USUBJID type=UN ;
estimate "week 2" trtan 1 -1  trtan*avisitn   1 0 0 0  -1 0 0 0/ cl alpha=0.05;
estimate "week 4" trtan 1 -1  trtan*avisitn   0 1 0 0  0 -1 0 0/ cl alpha=0.05  ;
estimate "week 8" trtan 1 -1  trtan*avisitn   0 0 1 0  0 0 -1 0/ cl alpha=0.05 ;
estimate "week 12" trtan 1 -1  trtan*avisitn   0 0 0 1  0 0 0 -1  / cl alpha=0.05 ;
lsmeans trtan*avisitn / pdiff cl alpha=0.05 ;
run;
```

Table A
Primary estimand: Model based analysis of change from baseline in KOOS pain score
Full analysis set

Test vs Ref.	No. of participants contributing to analysis			Adjusted least square means (SE)		Comparison of adjusted least square mean: Test vs Ref			
(Comparison)	Test	Ref.	Week	Test	Ref.	Diff (Test-Ref.)	SE	95% CI	1-sided p-value
Active (N=58) vs Placebo (N=57)	47	39	2	12.8 (1.78)	9.9 (1.92)	2.9095	2.6206	(-4.3, 6.1)	0.4647
	45	42	4	16.8 (1.92)	11.4 (1.98)	5.4588	2.7611	(-2, 8.9)	0.3066
	44	43	8	18 (2.47)	13.3 (2.51)	4.6784	3.5236	(-1.3, 12.7)	0.1552
	45	41	12	25.7 (2.52)	18.7 (2.61)	7.9806	3.6408	(-2.2, 12.2)	0.0672

Report shown here is for illustrative purpose only.

REPORTS SPECIFIC TO ICEs

There may be few reports expected specific to ICEs and its handling which may or may not be used for CSR reporting. However, it helps to understand the participant journey and accordingly Clinical trial team may decide to perform further exploratory analysis. Some of them are –

- Frequency of participants with ICEs
- Frequency of ICEs
- Frequency of participants with ICEs for primary estimand by visit
- Graphical representation of participant journey using swimmer plot

EXAMPLE OF REPORTs SUMMARISING ICEs –

- Frequency of participants with intercurrent events

Table 14.2-5.1 (Page 1 of 1)
Frequency of participants with intercurrent events
Safety analysis set

Intercurrent event	Active N=58 n (%)	Placebo N=57 n (%)	Total N=115 n (%)
Number of participants with any intercurrent event	10(17.2)	18(31.6)	28(24.3)
At least one missed dose 48 hours prior to an assessment	6 (10.3)	10(17.5)	16(13.9)
At least 12 missed doses	1 (1.7)	2 (3.5)	3 (2.6)
Use of NSAIDs 48 hours prior to an assessment	7 (12.0)	10(17.5)	17(14.8)
Use of prohibited medication with limited impact 48 hours prior to an assessment	6 (10.3)	10(17.5)	16(13.9)
Use of prohibited medication with sustained impact	10(17.2)	18(31.6)	28(24.3)

A participant may experience the same intercurrent event more than once during the trial and will be counted only one time for that intercurrent event.
Intercurrent events were handled as specified in the statistical analysis plan in section 1.4.
N=Total number of patients in the treatment arm.

- Frequency of intercurrent events:

Table 14.2-5.2 (Page 1 of 1)
Frequency of intercurrent events
Safety analysis set

Intercurrent event	Active M= 20 n (%)	Placebo M=45 n (%)	Total M=65 n (%)
At least one missed dose 48 hours prior to an assessment	6 (30.0)	15 (33.3)	21 (32.3)
At least 12 missed doses	1 (5.0)	2 (4.4)	3 (4.6)
Use of NSAIDs 48 hours prior to an assessment	4 (20.0)	16 (35.6)	20 (30.8)
Use of prohibited medication with limited impact 48 hours prior to an assessment	6 (30.0)	10 (22.2)	16 (24.6)
Use of prohibited medication with sustained impact	3 (15.0)	2 (4.4)	5 (7.7)

A participant may experience the same intercurrent event more than once during the trial and will be counted for all its occurrences.
Intercurrent events were handled as specified in the statistical analysis plan in sections 1.4.
M=Total number of intercurrent events in the treatment arm. Percentages are calculated as n/m.

CONCLUSION:

This paper demonstrates the role of statistical programmers for successful implementation of Estimands framework in clinical trials with a case study that highlights key points to focus for accurate and traceable execution throughout the lifecycle of a clinical trial.

KEY TAKEAWAYs FOR ROLE OF STATISTICAL PROGRAMMER.

- **Understand Study Design and Estimands Early:** Estimands define exactly what question you're answering. If you understand these early, you avoid surprises later.
- **Validate CRFs for ICE-Related Data: If** the CRFs don't capture these properly, your analysis will be incomplete. So, we should check early that the forms have the right fields to record these events.
- **Interpret SAP Thoroughly:** The Statistical Analysis Plan (SAP) provides detailed instructions on how estimands will be implemented in analysis. Thorough interpretation avoids misalignment between programming logic and statistical intent.
- **Create/Review of TFL Shells:** Creating TFL shells early ensures everyone agrees on what will be presented and how. It avoids last-minute surprises and helps programmers plan the logic and datasets as needed.

- **Collaborate Across Teams:** Continuous communication between data management, statisticians, and programmers and other stakeholders is essential during conduct. Proactive collaboration prevents delays and ensures consistency across teams.

- **Clear Documentation is crucial:** We all know how crucial Clear documentation if. It ensures traceability and consistency across teams and facilitates audits and regulatory review.

- **Robust programming is the key:** It is important that programming must handle real-world data complexities. Robust programming ensures accurate analyses even when data is complex.

REFERENCES

1. Implementation of ICH E9 (R1) Estimands Framework using Data Standards Implementation+of+Estimands+Using+Data+Standards+-+White+Paper.pdf

2. ICH E9(R1) Expert Working Group E9(R1) Training Material - PDF_0.pdf (ich.org) E9(R1) Training Material - PDF_0.pdf

3. Estimands implementation using data standards 2024_CDISC-Session 7B ADaM_DAVISTER COCHINAIRE_Estimands.pdf

4. ICH E9 (R1)

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