



Estimands Framework Through the Eye of a Statistical Programmer

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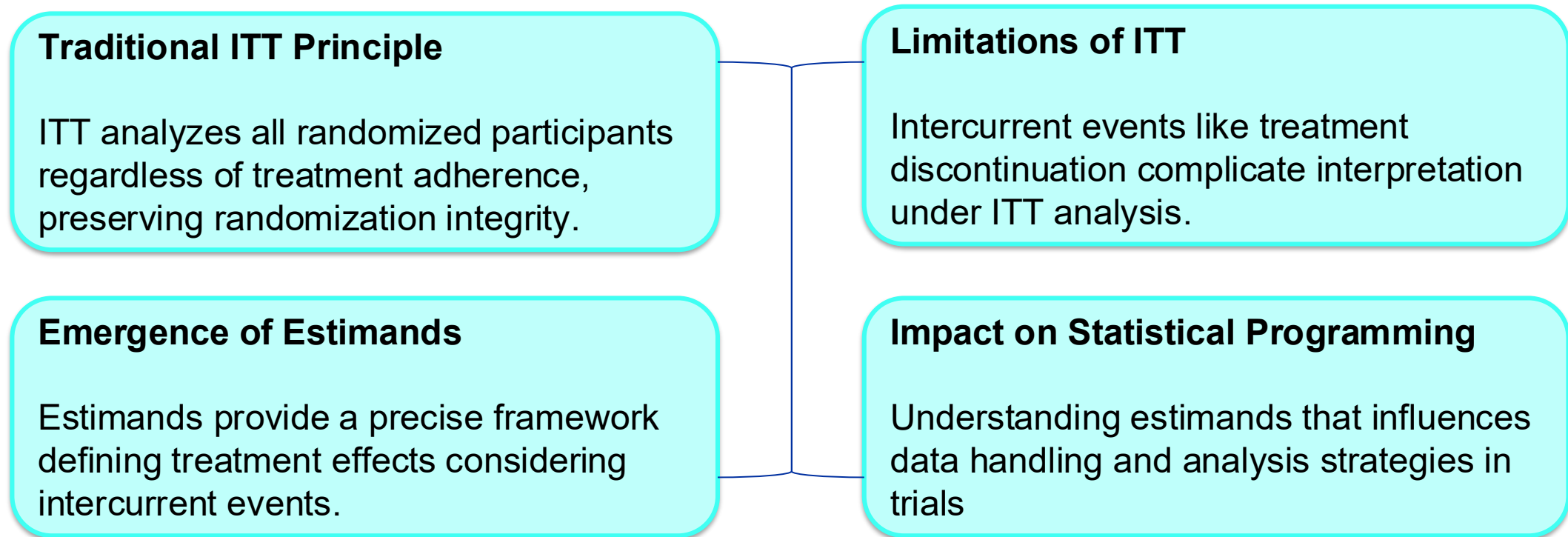


Agenda

- Introduction
- Estimands Attributes
- ICEs and their strategies
 - Treatment Non-Compliance
 - Concomitant Medications
- ADaMs for handling ICEs
- Estimands Framework: Statistical Programmers Role
- Analysis Reporting
- Reports specific to Intercurrent Events
- Key Takeaways

Introduction

Traditional Intend to Treat (ITT) Principle and Emergence of Estimands



Estimands Attributes

Population of interest

Patients with symptomatic knee osteoarthritis

Treatment

Active versus Placebo

Endpoint

Change from baseline in Osteoarthritis Outcome Score (KOOS) pain sub-scale at week 12

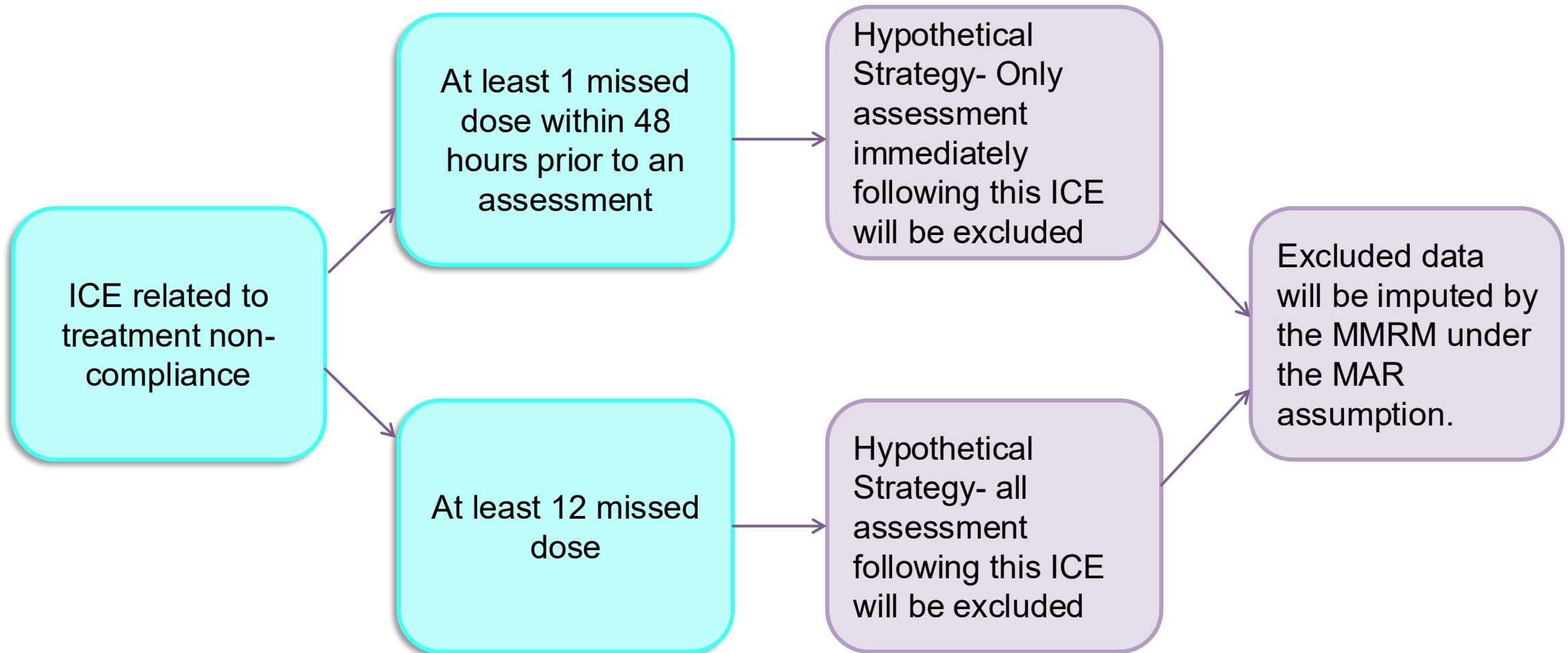
Summary Measure

Difference between treatment groups in mean change in KOOS pain sub-scale score from baseline to week 12

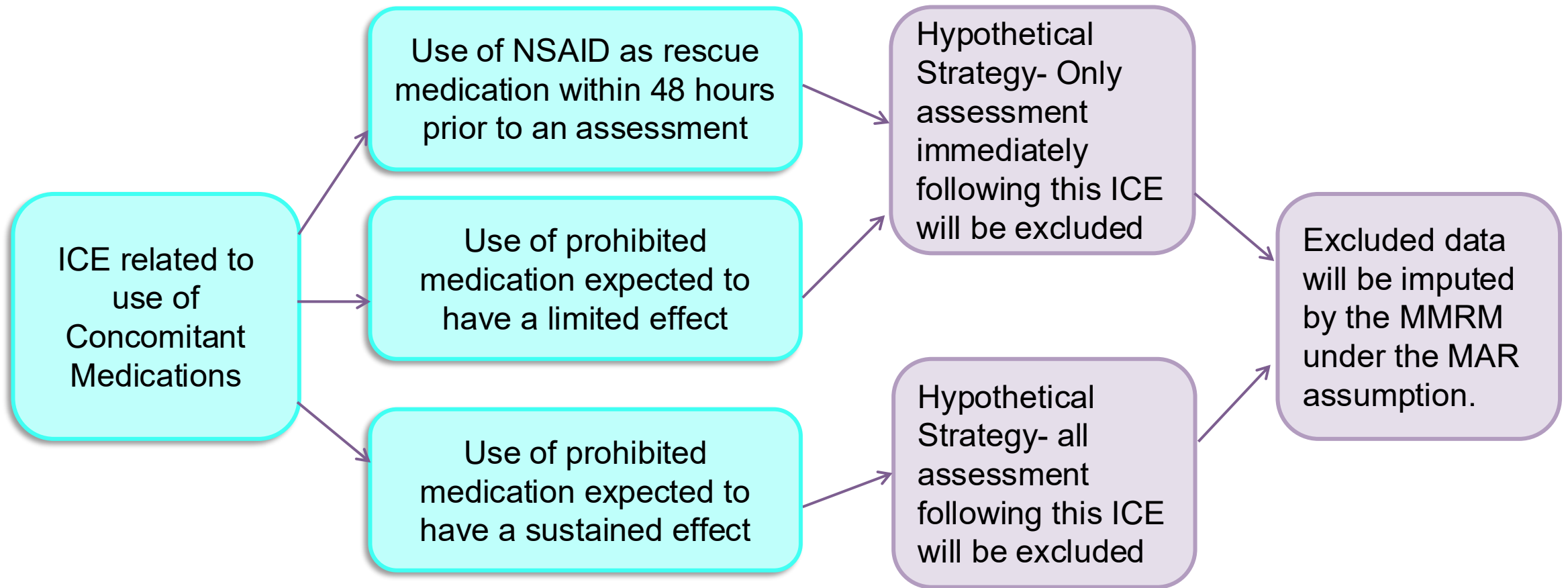
Intercurrent events (ICEs)

At least 1 missed dose within 48 hours prior to an assessment
At least 12 dose 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

ICEs and their strategies : Treatment Non-Compliance



ICEs and their strategies : Concomitant Medications



ADEX : Challenges faced while identifying ICEs



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



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

ADEX : Creating ICE Flags

MISDY-
Missed Dose
Flag

1. Filter SUPPEX.QNAM="ECDSCHNG" and QVAL="Y",
2. Merge it back to EX where EX.ECCAT="Dose exception" and Flag it ADEX.MISDY="Y"

MISSDYN-
Number of
missed Dose

If MISDY="Y" then MISSDYN=
Difference between AENDT
and ASTDT

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 : 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



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

RESFL Use of
NSAID

1. Convert the csv file provided by TME to SAS dataset.
2. Merge it with CM by USUBJID and CMDECOD.
3. Set RESFL="Y" if MED="NSAID"

PROLIMFL Use of
Prohibited
medication with
limited effect

Set PROLIMFL="Y" if MED
="LIMITED"

PROSUSFL-Use
of Prohibited
medication with
sustained effect

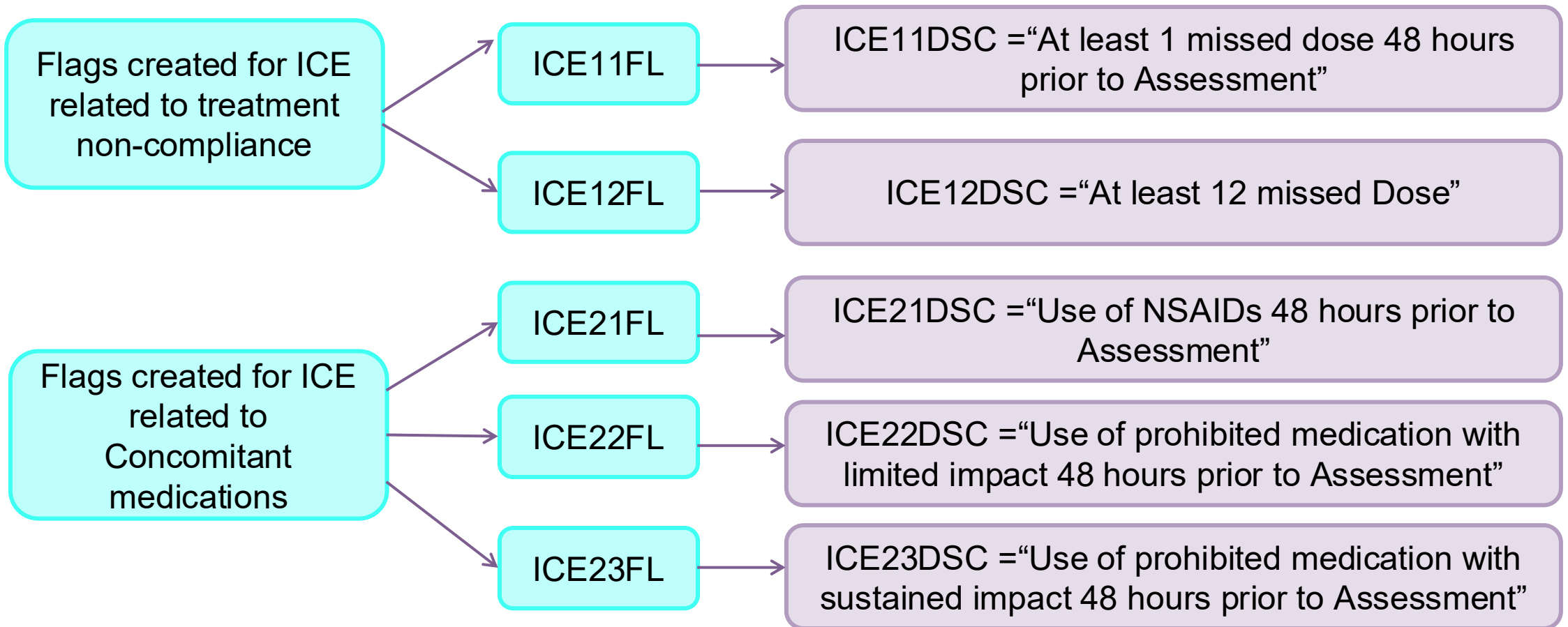
Set PROSUSFL="Y" if
MED ="SUSTAINED"

SUBJID	CMDECOD	PROLI MFL	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.

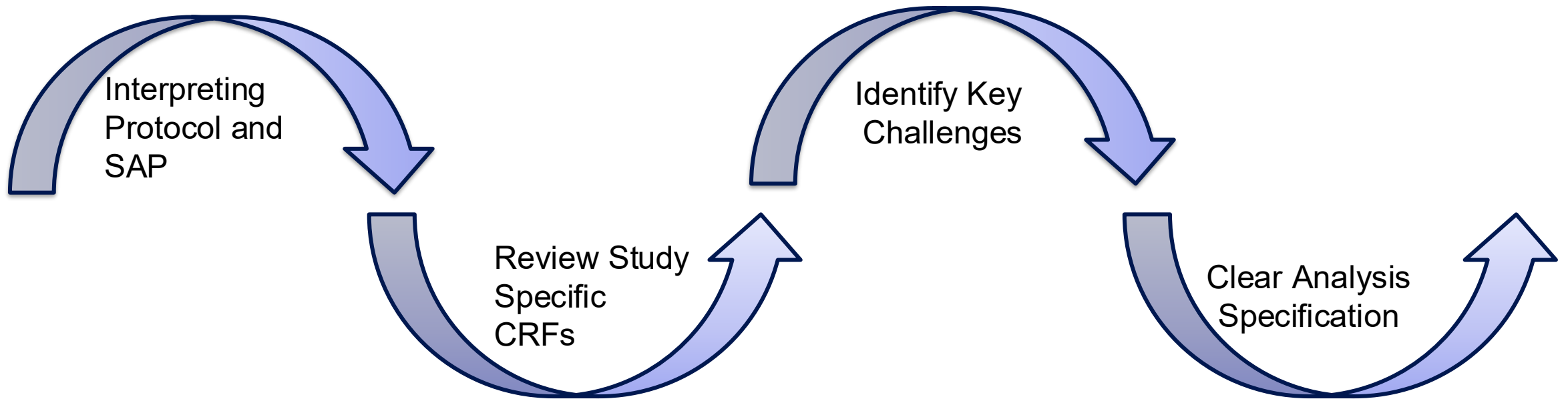
ADQS : Creating ICE Flags

Data Flow: Source Data QS → SDTM.QS, ADaM.ADEX , ADaM.ADCM → ADQS



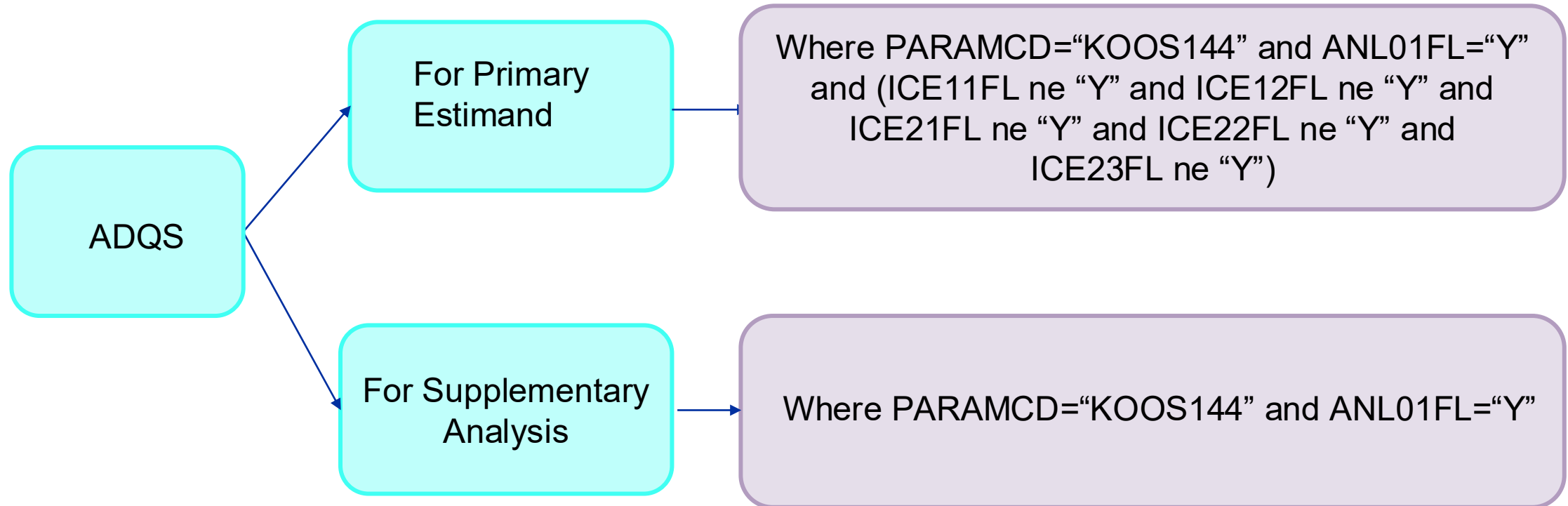
Estimands Framework: Statistical Programmers Role

It is important to proceed sequentially for embedding Estimands into Clinical Trial Lifecycle



Analysis Reporting

Record Selection for Primary estimand and supplementary Analysis



ANL01FL flags the non missing post baseline records

Reports specific to ICEs

- 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

Reports : Summarizing the ICEs

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

	Active N=58 n (%)	Placebo N=57 n (%)	Total N=115 n (%)
Intercurrent event			
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)

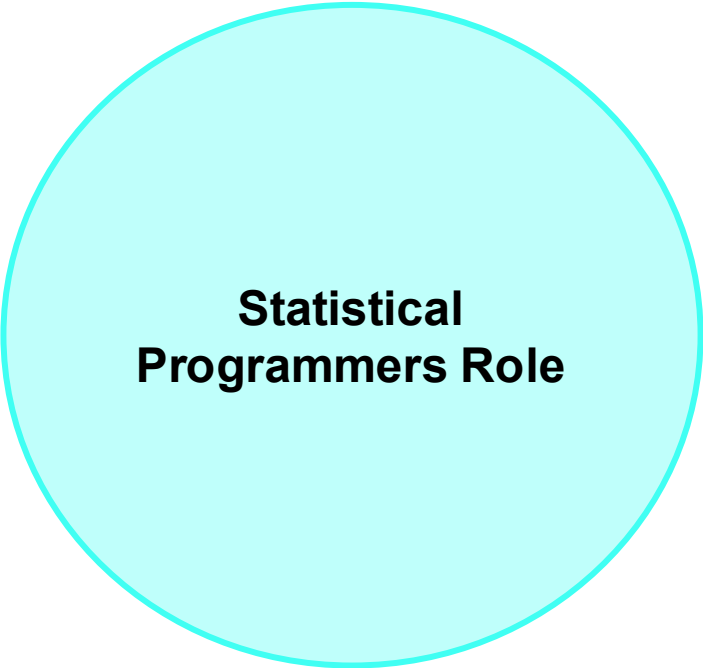
A participant may experience the same intercurrent event more than once during the trial and will be counted only one time for that intercurrent event.
Intercurrent events were handled as specified in the statistical analysis plan in section 1.4.
N=Total number of patients in the treatment arm.

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

	Active M= 20 n (%)	Placebo M=45 n (%)	Total M=65 n (%)
Intercurrent event			
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.

Key Takeaways

A large, light blue circle with a teal border, containing the text "Statistical Programmers Role".

Statistical Programmers Role

1 Understand Study Design and Estimands Early

2 Validate CRFs for ICE-Related Data

3 Interpret SAP Thoroughly

4 Create/review TFL Shell

5 Collaborate Across Teams

6 Clear Documentation is crucial

7 Robust programming is the key

Thank You !!!