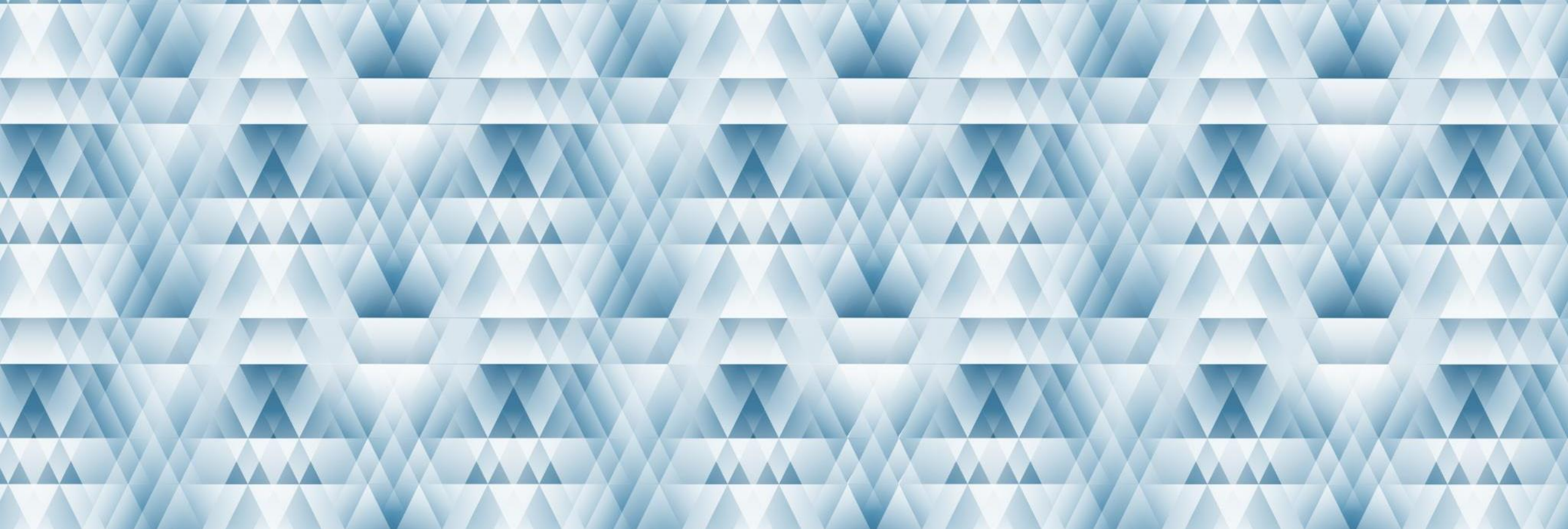


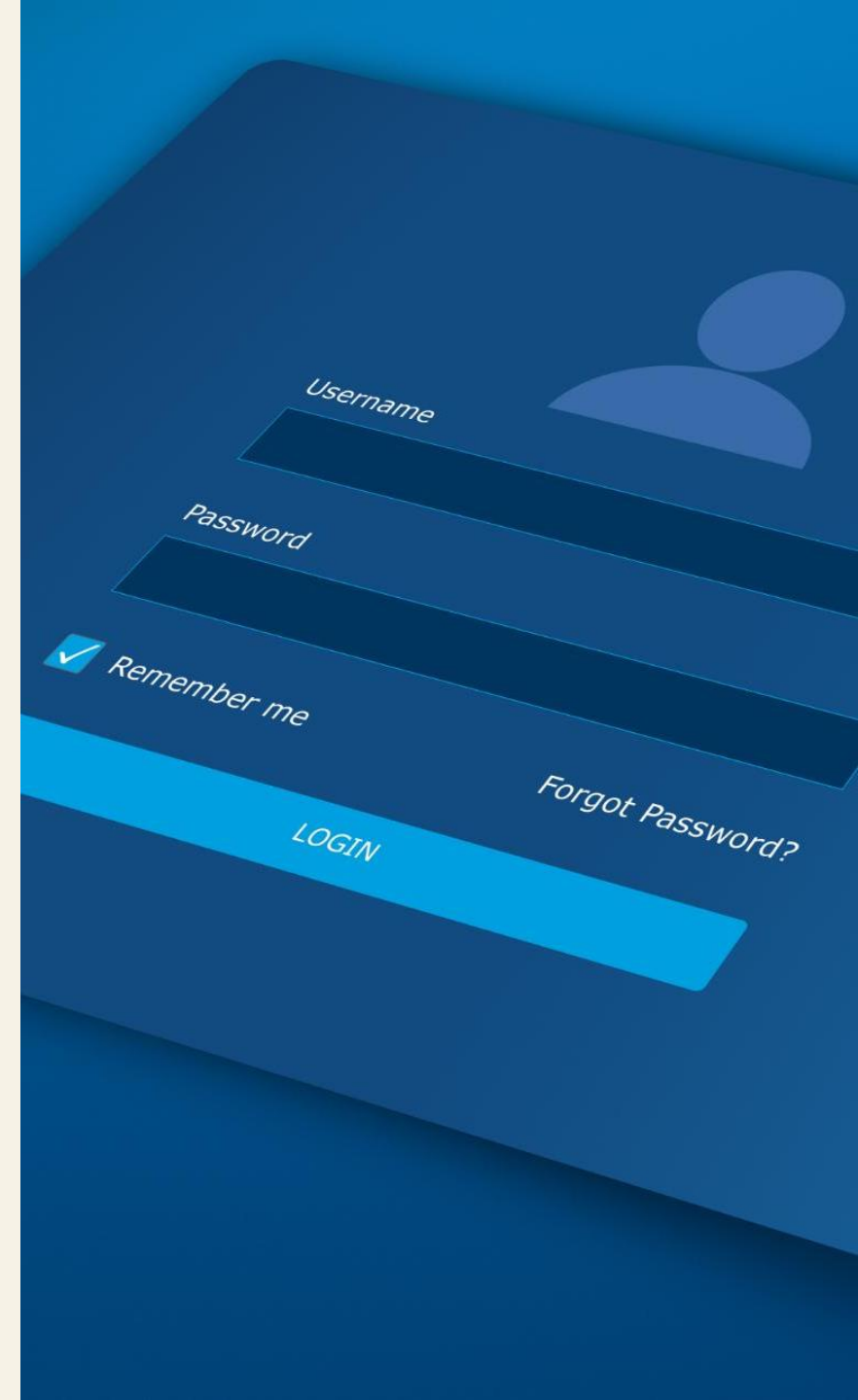


# VISION TO DECISION: AN OCULAR CASE STUDY ON ESTIMANDS

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# AGENDA

- ❑ Introduction to case study
- ❑ Basics of Estimand Framework
- ❑ ICE and Data handling strategies
- ❑ Impact on trial design, Conduct and Analysis datasets



# USE CASE: ABNORMAL EYE STUDY

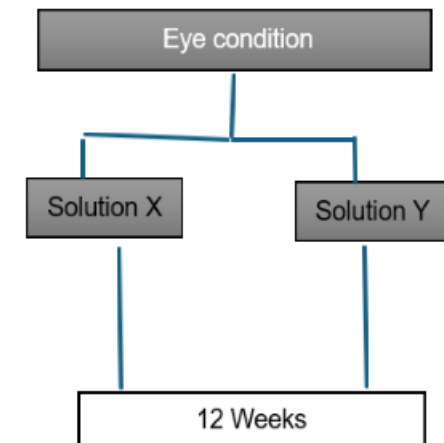
## Objective

To compare a 12-week course of a new Solution X against marketed Solution Y in routine practice for subjects having eye related issue.

**Endpoints:** IOP at the end of week 12

**What we want to find out:** Difference in the Solution X and Solution Y at end of Week 12.

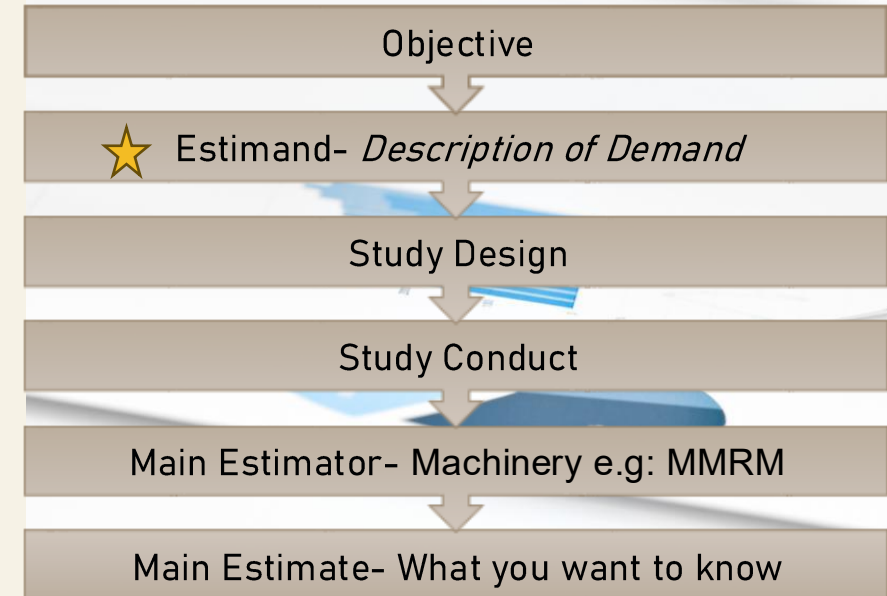
Is this objective ambiguous? We know the usage of emergency medication will affect the results. Early discontinuation due to Adverse Events will also disrupt the interpretation.



# ESTIMAND FRAMEWORK

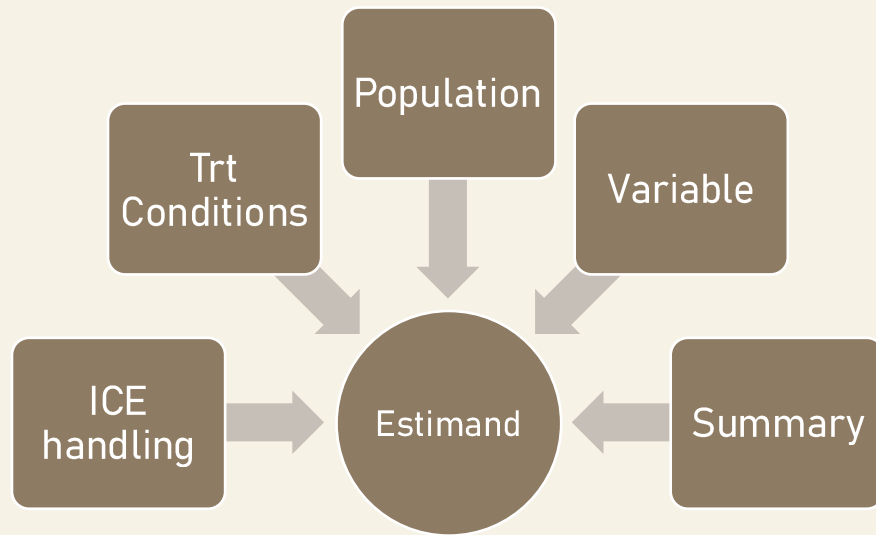
## ICH E9 estimand framework addresses key ambiguities

- Recognizes that treatment effects of interest are often not explicitly or precisely defined at the outset of a clinical trial.
- Limited transparency regarding how intercurrent events are addressed in the definition of the treatment effect.
- Traditional trial practice in which data collection and analysis methods implicitly determine the treatment effect being estimated.
- A shift towards explicitly defining the estimand of interest first, such that it directly informs and guides the data collection strategy and analytical approach.



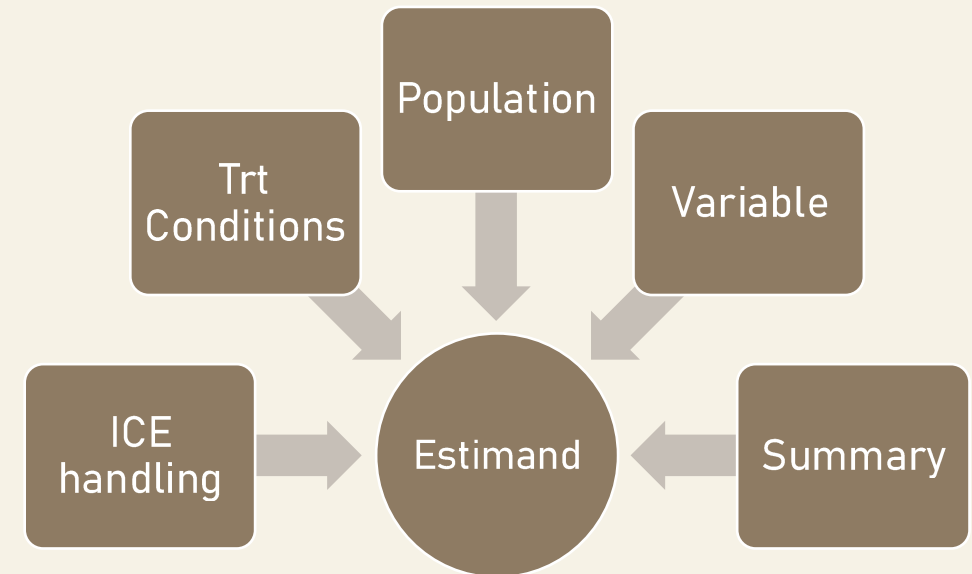
# ESTIMAND

- As Per ICH E9 (R1) the description of estimand includes 5 attributes.
- ICEs can be incorporated in treatment, population and/or variable attributes.



# ESTIMAND

- Treatment condition: TRT-A vs TRT-B or TRT-A+Med vs TRT-B+Med
- Population: Patients whom you want to know treatment effect for e.g: Met exclusion criteria, or meeting further criteria of baseline or patients adhere to treatment of different strata.
- Variable: Outcome variable/endpoint to be measured for each patient.
- Summary: How, at a population level, the variable of interest is compared across treatment groups (e.g., difference in means, odds ratio, or hazard ratio)
- ICE handling: Strategy chosen to ensure treatment effect is accurately estimated.



# PRIMARY ESTIMAND FOR STUDY

Estimand description: Use of emergency medication.

Handling Intercurrent events:

- Ideal: Use of emergency medication not necessary
- Treatment Policy: use of emergency medication is ignored and considered as treatment.
- Hypothetical: No emergency medication has been taken

Treatment:

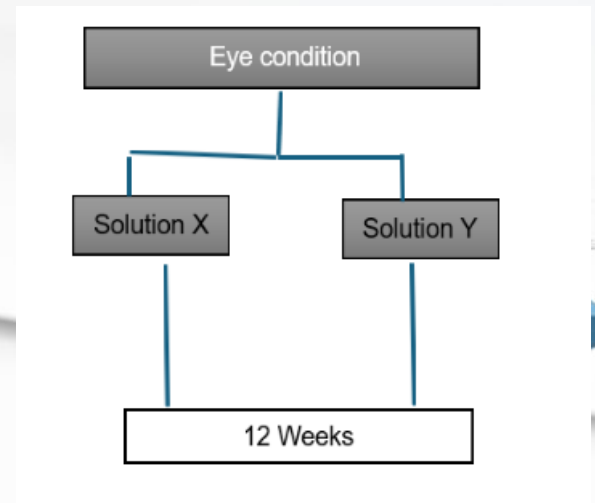
- Ideal: Experimental: Solution X, Control: Solution Y
- Treatment policy: Solution X + emergency medication, Solution Y + emergency medication
- Hypothetical: Experimental: Solution X, Control: Solution Y

Population: As defined by Inclusion/Exclusion Criteria

Variable: Change in Eye Condition from baseline to week 12

Population level difference: Mean difference

Individual attributes of the estimand change when the various strategies are used for the ICE 'use of emergency medication.



# PRIMARY ESTIMAND FOR STUDY

## Impact of estimand

- Trial design follows the specification of estimand.
- Trial conduct w.r.t. type, duration, discontinuation criteria, medication to be used or not, measurement of efficacy parameters.
- Data collection:
  - Collect data post treatment discontinuation as per treatment policy



# ANALYSIS DATASETS

## Creation of ADICE

- Each record represents one ICE event with its timing and assigned strategy.
- Use the flag suffixes to create appropriate variables e.g., EST01STP, EST02STP
- The values for these variables should be created as per specification and Protocol.
- While simultaneous ICE events are rare, they are possible.
- If two events overlap completely, the EST##STVariable should be populated only for the event with higher priority.



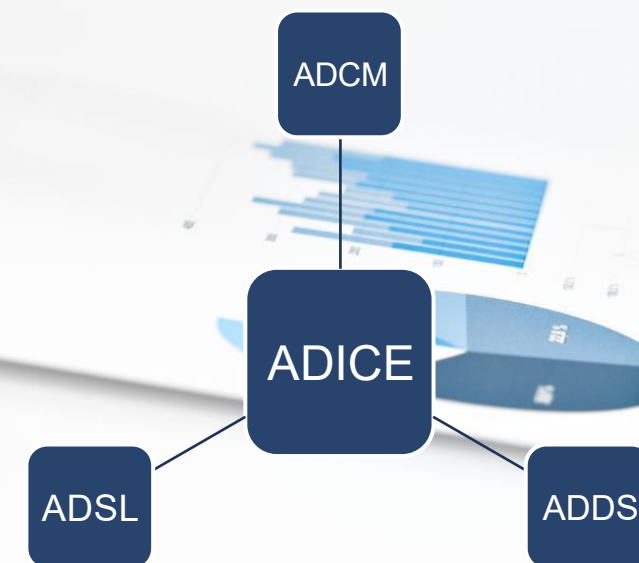
# ANALYSIS DATASETS

## Creation of ADICE (Cont.)

As per handling of ICE the data required are particularly from 3 datasets which are needed to create ADICE dataset.

- ADCM: The emergency medication are flagged in ADCM for each subject which are also ICE of interest.
- ADDS: The reason for discontinuation collected in disposition dataset becomes the source for ADICE too.
- ADSL: Subjects who are got NOT ASSIGNED to any treatment for any reason and has no post randomization data is ICE of interest.

| Analysis | ATERM        | ADECOD1                                                   | ASTDT     | AENDT     | EST01STP         | EST02STP         | EST03STP         |
|----------|--------------|-----------------------------------------------------------|-----------|-----------|------------------|------------------|------------------|
| 1        | AZITHROMYCIN | Use of emergency medication not expected to influence eye | 23-Jul-21 | 23-Jul-21 |                  |                  |                  |
| 2        | AZITHROMYCIN | Use of emergency medication not expected to influence eye | 23-Jul-21 | 23-Jul-21 | Treatment Policy | Treatment Policy | Treatment Policy |



# ANALYSIS DATASETS

## Creation of ADEFF

The dataset should be **squared** for all randomized subjects i.e., one record per subject, per parameter, per protocol-defined visit/measurement, regardless of whether data was observed.

*• carry over all EXT##STP variables (and EXT##STA if used) from ADICE.*

Example : Derivation logic for EST01STP

- set to the value of ADICE.EST01STP

Do the below derivations:

- Populate the strategy for the records where ADEFF.adt>=ADICE.astdt.
- For emergency medication ICEs, where ICE end date is not missing then populate values based on ADICE.AENDT that ADEFF.ADT is in between ADICE.ASTDT and ADICE.AENDT.
- If emergency medication has no end date, then flag for all visits after start date.



# ANALYSIS DATASETS

## Creation of ADEFF(Contd)

Similarly other estimand derivations are done in ADEFF. After the derivation these datapoint for each subject with impacted ICE strategies, we have to derive impact flags for ICE events per estimand.

E.g: ICE01S,ICE02S. These document data point affected by intercurrent event.

|   | A      | B           | C     | D           | E                          | F                | G                | H      | I | J |
|---|--------|-------------|-------|-------------|----------------------------|------------------|------------------|--------|---|---|
| 1 | SUBJID | ASTDT       | AENDT | ADT         | ADECOD1                    | EST01STP         | EST01STP         | ICE01S |   |   |
| 2 | XX1    |             |       | 13-May-2021 |                            |                  |                  |        |   |   |
| 3 | XX1    |             |       | 14-May-2021 |                            |                  |                  |        |   |   |
| 4 | XX1    |             |       | 15-May-2021 |                            |                  |                  |        |   |   |
| 5 | XX1    |             |       | 16-May-2021 |                            |                  |                  |        |   |   |
| 6 | XX1    |             |       | 17-May-2021 |                            |                  |                  |        |   |   |
| 7 | XX1    |             |       | 18-May-2021 |                            |                  |                  |        |   |   |
| 8 | XX1    | 19-May-2021 |       | 19-May-2021 | Emergency Medication taken | Treatment Policy | Treatment Policy | 1      |   |   |



# CONCLUSION

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Aligns objective, design, conduct analysis, inference.

Deduce trial objective into estimand during planning stage.

Consider ICE and strategies relevant for clinical context.

Based on define strategies create ADICE, ADEFF datasets.





THANK YOU.