Statistical and Pharmacometric Analysis Using Estimand Framework: A Case Study

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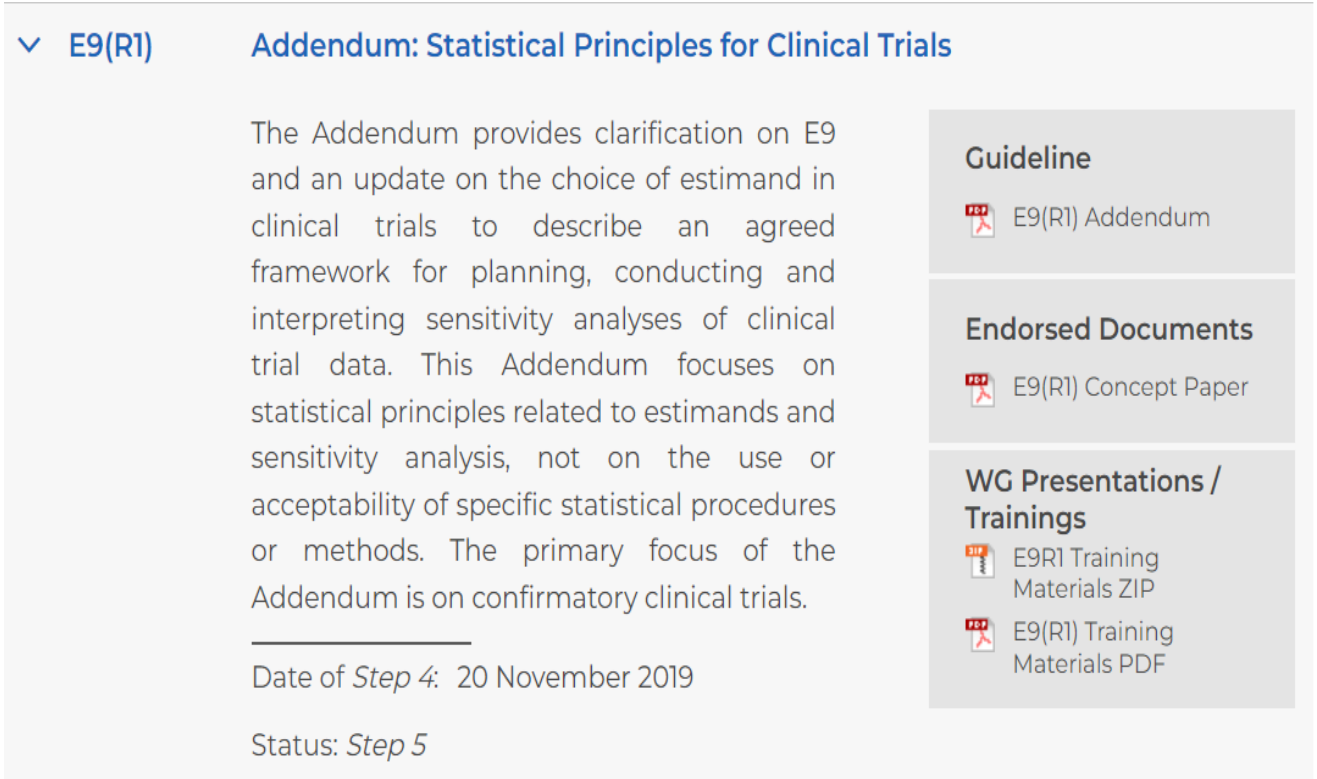
Outline

- Introduction of Estimands
- Case Study: a Ph2 study of nipocalimab in RA
  - Statistical analyses using the estimand framework
  - Impact of Dose Deviations (ICE) on PD Effect: PKPD Simulation Results
- Key Take Home Messages

ICH E9(R1) Addendum– Estimands in Clinical Trials

- Final ICH E9(R1) Addendum on “Estimands and Sensitivity Analysis in Clinical Trials” released in Nov 2019: https://database.ich.org/sites/default/files/E9_-R1_Step4_Guideline_2019_1203.pdf
- Increasing Pharmaregulatory interactions and requests seen on this topic



E9(R1) Addendum: Statistical Principles for Clinical Trials

The Addendum provides clarification on E9 and an update on the choice of estimand in clinical trials to describe an agreed framework for planning, conducting and interpreting sensitivity analyses of clinical trial data. This Addendum focuses on statistical principles related to estimands and sensitivity analysis, not on the use or acceptability of specific statistical procedures or methods. The primary focus of the Addendum is on confirmatory clinical trials.

Date of *Step 4*: 20 November 2019

Status: *Step 5*

Guideline

E9(R1) Addendum

Endorsed Documents

E9(R1) Concept Paper

WG Presentations / Trainings

E9R1 Training Materials ZIP

E9(R1) Training Materials PDF

Implementation status:

ANVISA, Brazil - In the process of implementation; Date: 1 December 2023;

COFEPRIS, Mexico - Not yet implemented;

EC, Europe - Implemented; Date: 30 July 2020; Reference: EMA/CHMP/ICH/436221/2017

FDA, United States - Implemented; Date: 11 May 2021; Reference: Posted on FDA, United States website

HSA, Singapore - Implemented; Date: 1 November 2019; Reference: HSA, Singapore webpage: Guidance documents for clinical trials

Health Canada, Canada - Implemented; Date: 21 July 2020; Reference: File #: 20-109237-45

MFDS, Republic of Korea - In the process of implementation; Date: 1 January 2022;

MHLW/PMDA, Japan - In the process of implementation;

MHRA, UK - Implemented; Date: 1 July 2020;

NMPA, China - Implemented; Date: 25 January 2022; Reference: NMPA, China Announcement No. 16 (2021)

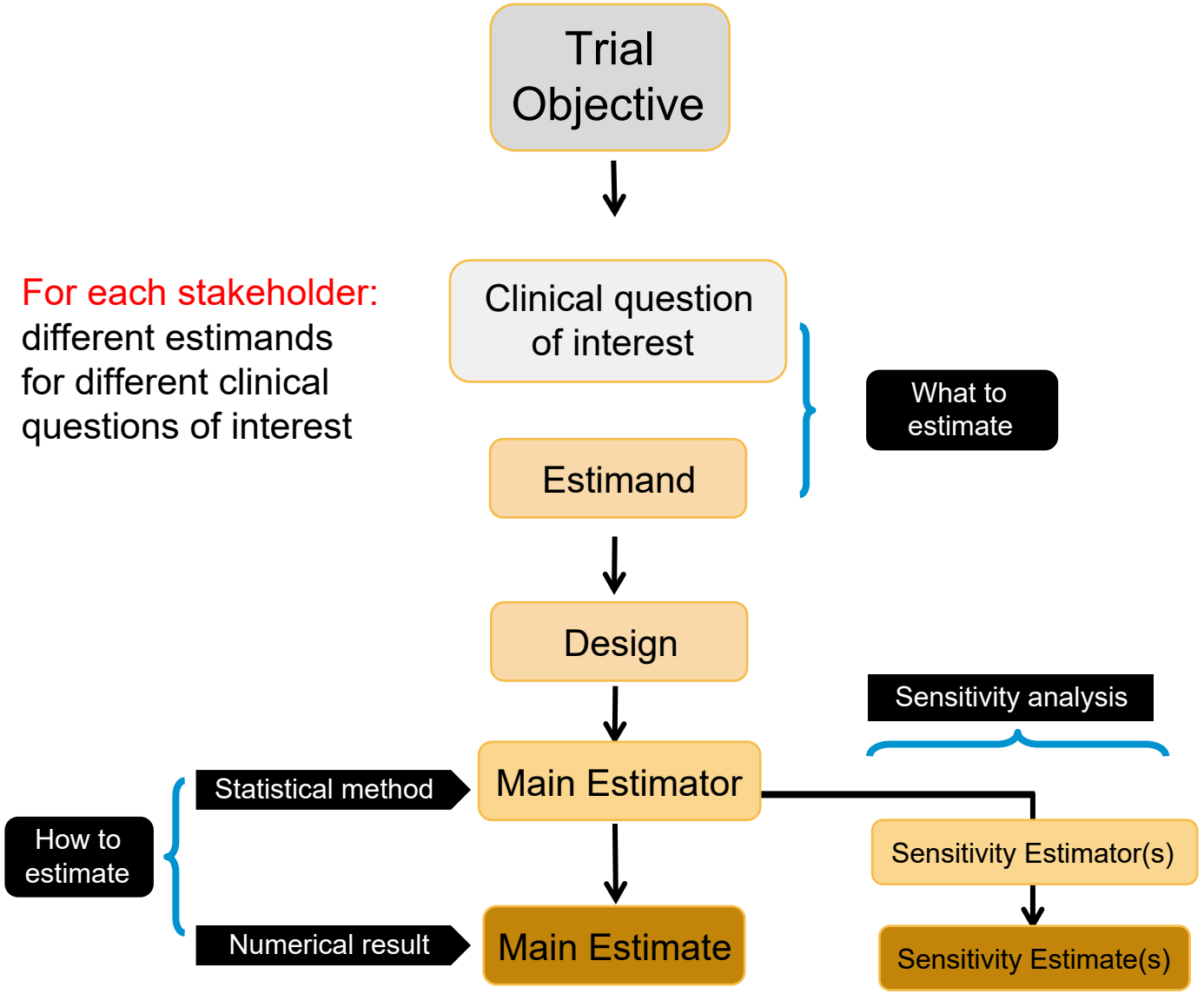
SFDA, Saudi Arabia - Not yet implemented;

Swissmedic, Switzerland - Implemented; Date: 30 November 2019;

TFDA, Chinese Taipei - Implemented; Date: 9 February 2021; Reference: Updated-Announcement for ICH Guidelines Recognition List

TITCK, Turkey - Not yet implemented;

Trial planning framework



Clinical Question - The Five attributes of an estimand

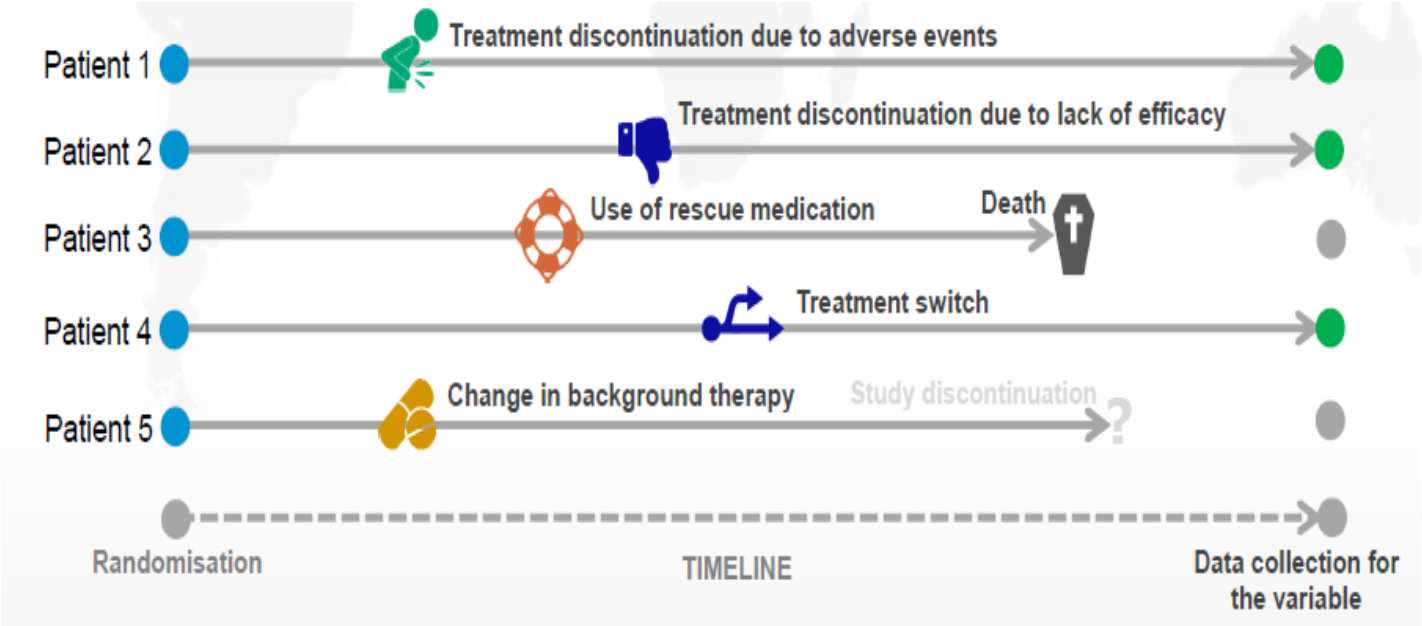
Example of a clinical question of interest from Major Depressive Disorder (MDD)

What is the mean treatment difference	*population-level summary measure*
in change in depression severity at Week 8	*variable*
that can be expected under the assignment to either drug X vs placebo	*study interventions: **treatment** of interest vs **alternative** treatment*
if patients would continue treatment as assigned up to Week 8, without discontinuing treatment or initiating other antidepressant medications	*ICEs and corresponding strategies*
in adults and elderly participants with MDD?	*population*

Bell, J, Hamilton, A, Sailer, O, Voss, F. The detailed clinical objectives approach to designing clinical trials and choosing estimands. *Pharmaceutical Statistics*. 2021

What is considered an Intercurrent Event (ICE)?

Events that occur after treatment initiation and either preclude observation of the variable or affect its interpretation .



- Each identified ICE needs to be addressed by a strategy.
- The chosen strategies need not be the same for all ICEs.

Akacha et al., "Estimands—What they are and why they are important for pharmacometricians" *CPT Pharmacometrics Syst. Pharmacol.* 2021;10:279–282

ICE Handling Strategies Depend on Question of Interest

EXAMPLE: Consider the ICE of treatment discontinuation in a placebo -controlled trial

STRATEGY	DESCRIPTION: How is the ICE addressed?
Treatment Policy Effect of assigning Drug X vs. Placebo, regardless of treatment discontinuation	In general, as part of the **treatment** specification or effect regardless of ICE – NA when values of the variable do not exist after the ICE (e.g. after death) – More generally acceptable to support regulatory decision making
Hypothetical Effect of Drug X vs. Placebo had all patients remain on treatment (without discontinuing treatment)	Hypothetical scenario around the ICE – Consider meaningful scenarios
Principal Stratum Effect of Drug X vs. Placebo in patients who would remain on treatment if prescribed Drug X	As part of the **population** – Target population is a subset determined by the ICE occurrence
Composite (Variable) Effect of Drug X vs. Placebo, where patients who discontinue treatment are considered treatment failures	As part of the **variable** – The ICE itself is meaningful and is thus reflected in the value that will be assigned to the variable (e.g., a non-responder status)
While-on-Treatment Effect Drug X vs. Placebo while patients remain on treatment	As part of the **variable** – Interest is on the response to treatment prior to occurrence of the ICE – Variable is defined such that it is independent or incorporates the patient specific treatment duration (e.g., slope/rate, AUC); summary measure cannot be defined for a fixed time period

Akacha et al., "**Estimands—What they are and why they are important for pharmacometricians**" *CPT Pharmacometrics Syst. Pharmacol.* 2021;10:279–282

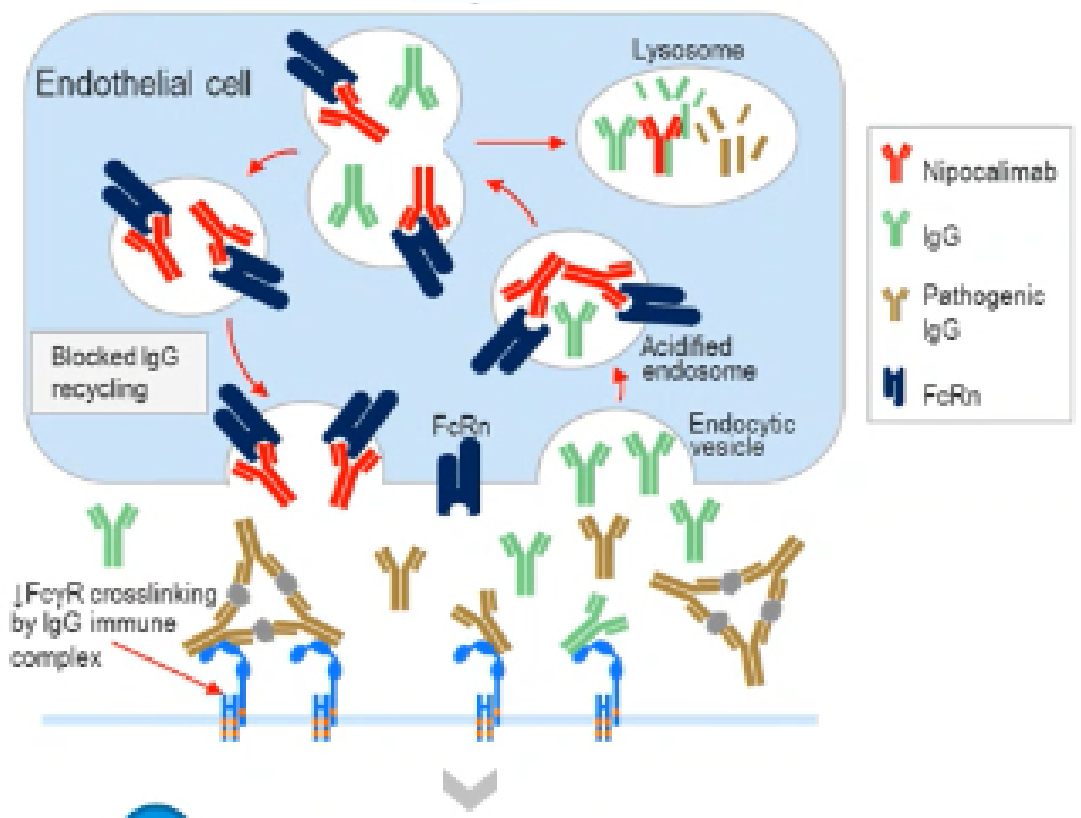
Case Study: Nipocalimab RA
Ph2a Monotherapy

Nipocalimab Lowers IgG and ACPA Primarily Through FCRN Binding

1 Lowering of IgG, ACPA

2 Lowering of IgG containing circulating immune complexes

3 Reduced activation & expression of FcγRs in myeloid cells in blood & synovium



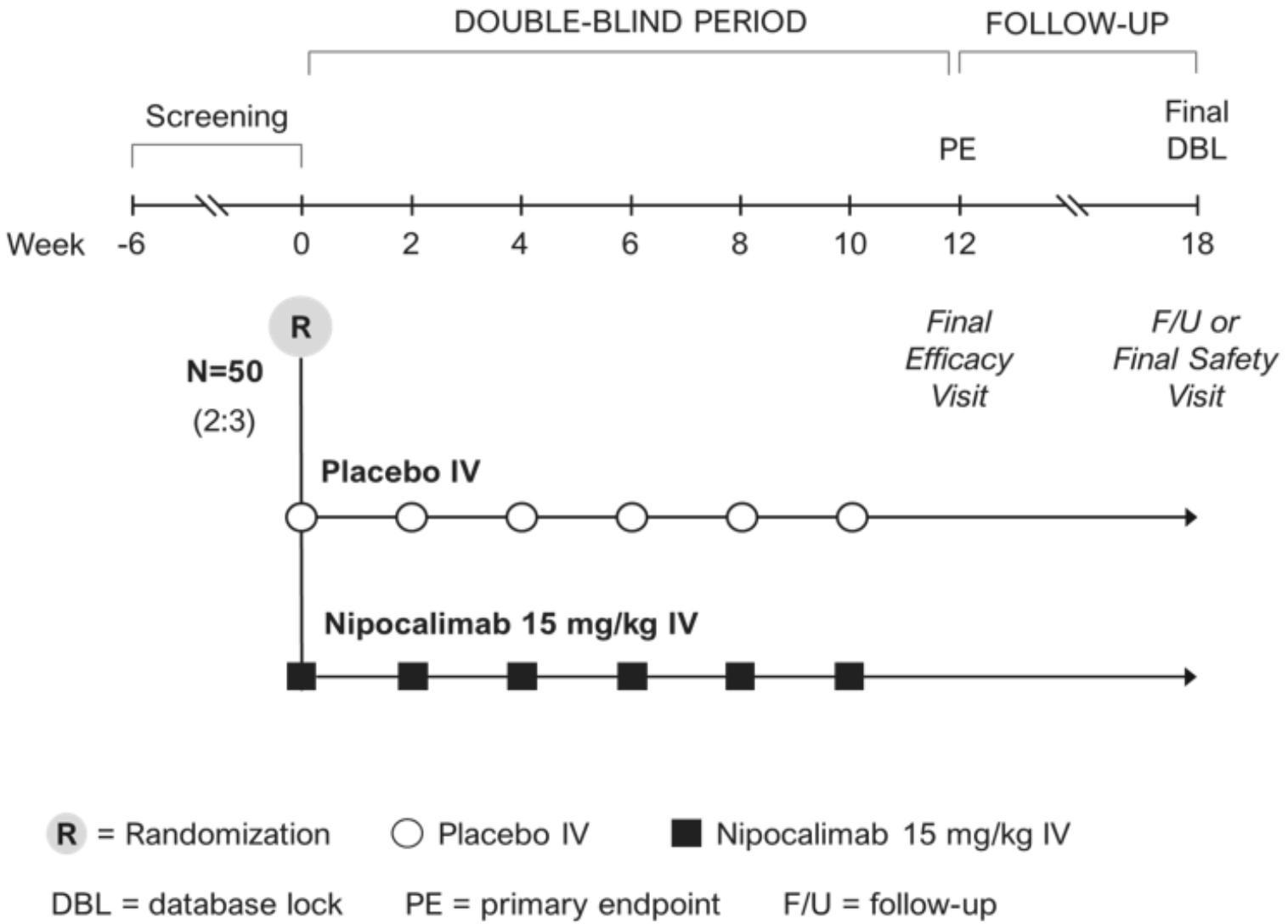
4 Reduction of blood cytokines & inflammatory mediators

5 Normalization of immune complex-trained immune effector cell signatures in blood & synovium

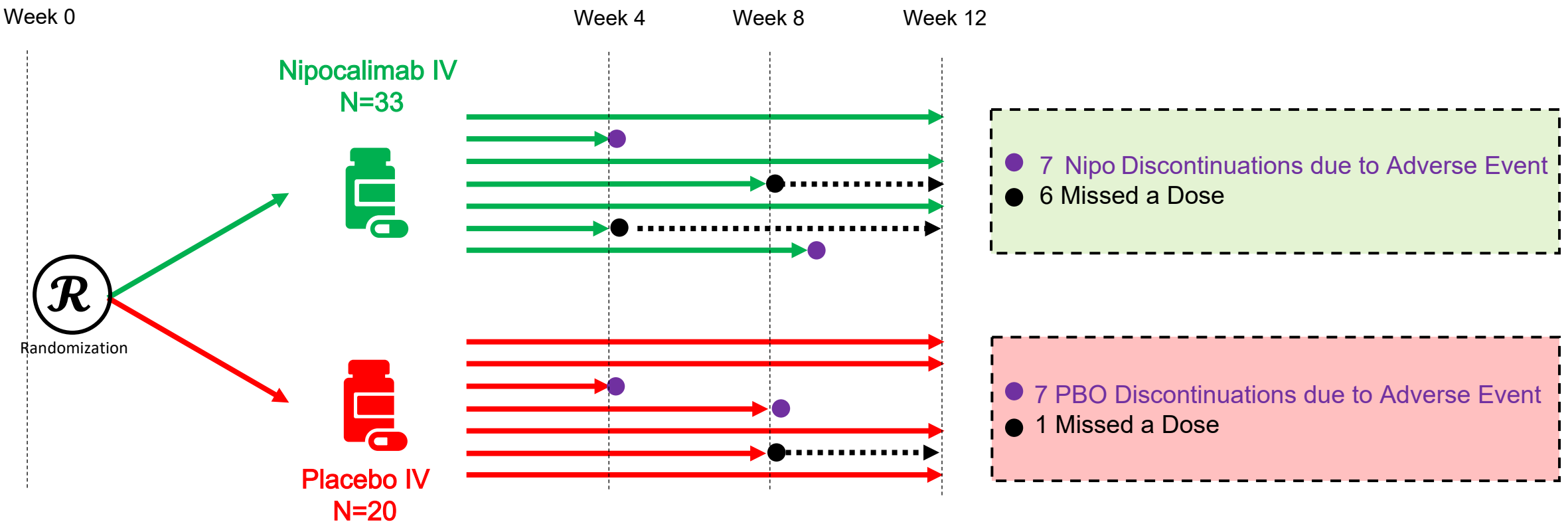
IgG = Immunoglobulin G
FcRn = neonatal Fc receptor
ACPA = Anti-Citrullinated Peptide Antibody

Adopted from Taylor et al., "Efficacy and Safety of Nipocalimab in Patients with Moderate to Severe Active Rheumatoid Arthritis (RA): The Multicenter, Randomized, Double-blinded, Placebo-controlled Phase 2a IRIS-RA Study" *Arthritis Rheumatol.* 2023;75

RA Phase 2a Study Design (ARA2001)



ARA2001 Study Has High Occurrence of ICE



IgG Reduction

Randomization + **Data impacted by ICE/Missed dose** = **Treatment Effect ??**

Key Question: Is There a TRUE Discrepancy Between Previous Model Predictions vs Observed Data?

Observed minimal median % IgG reduction was 54%, which was much smaller than the previous PKPD predicted IgG reduction of 64%

- IgG data was collected for subjects who discontinued treatment or missed dose(s) up to Week 12
  - Patients did not adhere to pre-defined protocol dosing ➔ IgG values being highly variable and diluted

✓ First step to explore the apparent discrepancy

Sensitivity analyses

1. Exclude observations/data points directly impacted
2. Per protocol analysis (excluding all patients who either missed dose or had ICEs)

	% minimal median IgG reduction
Model prediction	64%
Observed	54%
Sensitivity # 1	61%
Sensitivity # 2	62%

Conclusion

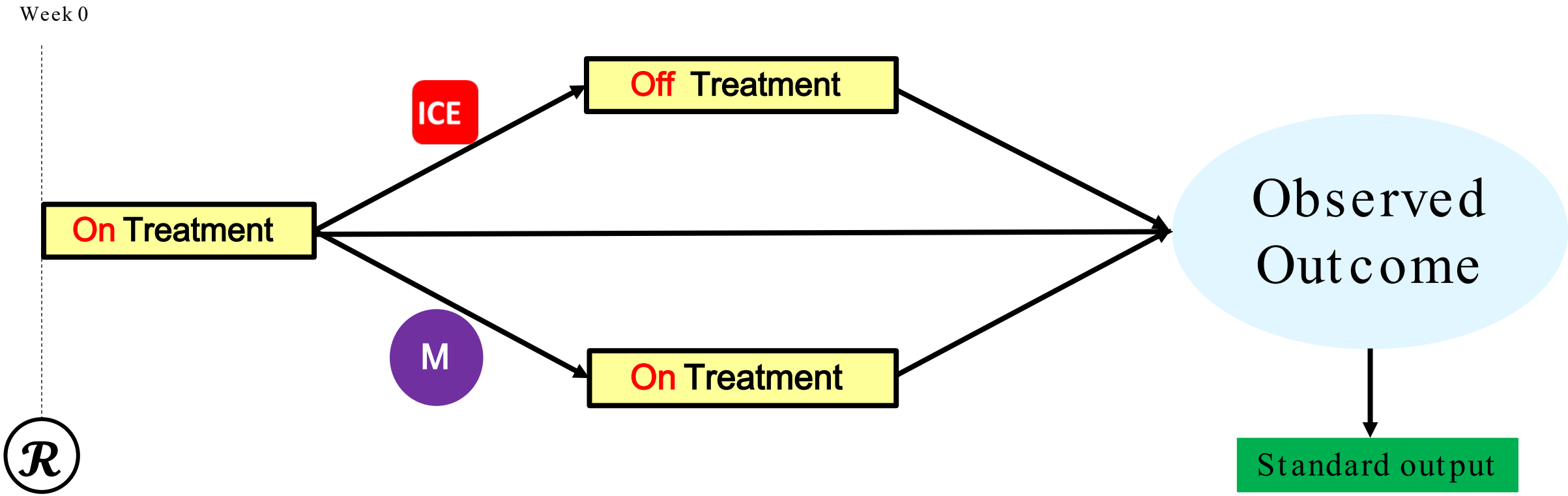
- Excluding treatment discontinuation or missed dose observation aligns with model prediction

However, can we prospectively predict a more realistic treatment effect, based on established PKPD models?

Statistical Analysis of IgG Lowering Using Estimand Framework

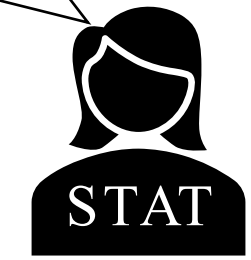
Standard IgG analysis

- IgG is considered as safety parameter
- Observed data is typically presented

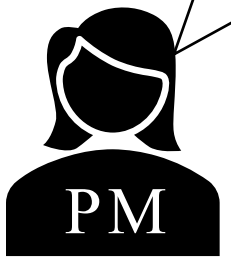


What is an appropriate analysis?

- Handling "IgG" analysis in presence of intercurrent events and missed dose(s) by per protocol analysis?? (potential bias)
- Need to consider the question of interest under the Estimand Framework



- Typically, all the observed data is used to develop and validate PKPD models. However, PKPD simulations generally consider 100% compliance in dosing
- Need to consider realistic dosing scenarios to address impact of ICE on treatment effect



Question of Interest Under Estimand Framework

What is the expected effect in RA patients on % IgG reduction at Week 12 of Nipocalimab 15 mg/kg IV Q2W …

Hypothetical

if taken as directed

i.e as if patients would not have discontinued treatment or missed any dose) up to Week 10

Principal Stratum

in the stratum of patients who, if assigned to Nipo

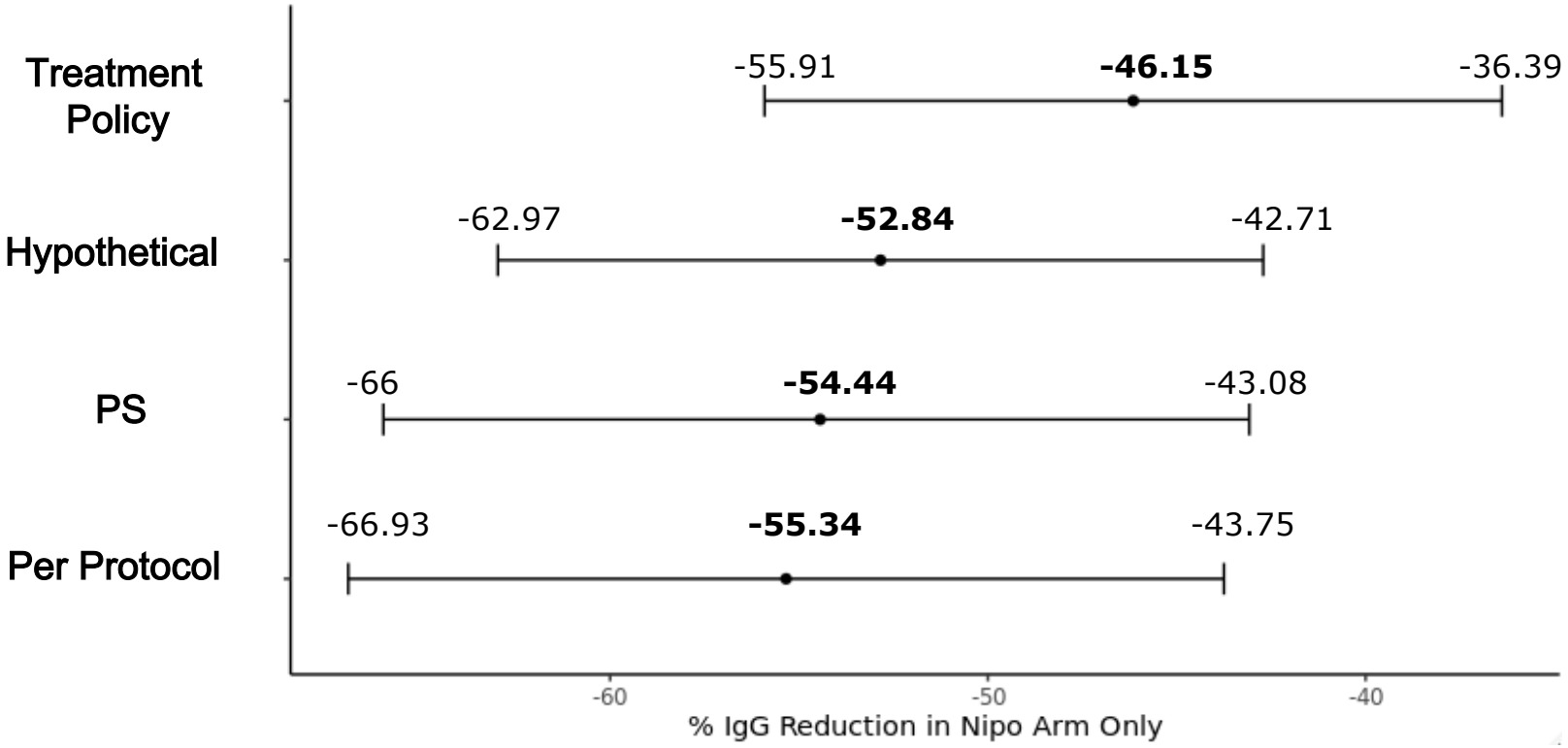
would fully adhere to treatment (i.e., without missing a dose or discontinuing treatment) up to Week 10

Treatment Policy

regardless of treatment discontinuation/ missing a dose

Treatment Effect Estimation

Model: Mixed-Effect Model Repeated Measure



Sample Size*

- Active: 32/33, Control: 20/20
- Active: 26/33, Control: 13/20
- Active: 20/33 (Average), Control: 13/20 (Average)
- Active: 20/33, Control: 12/20

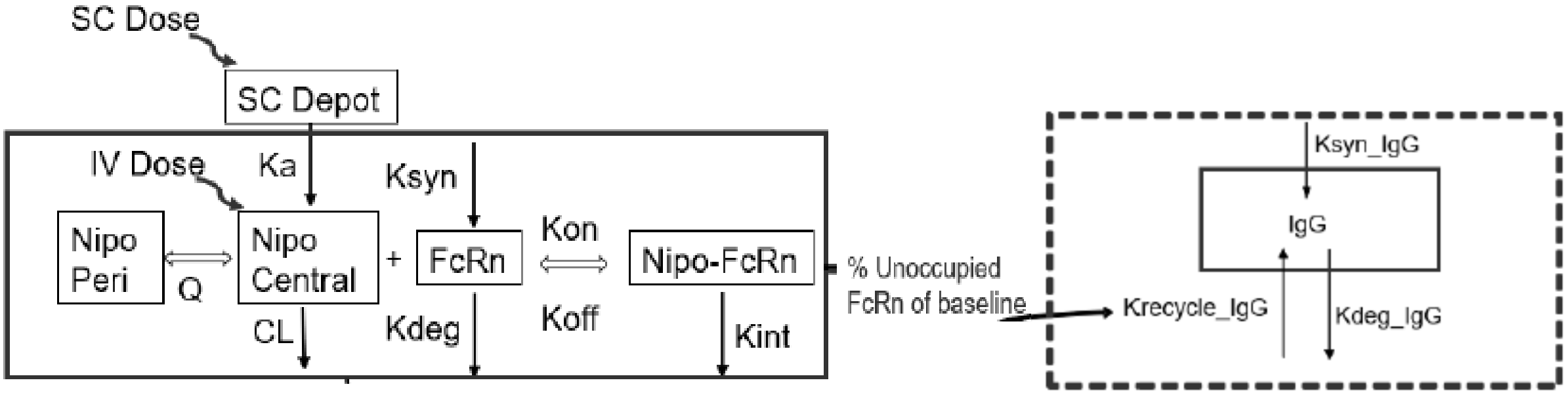
	% Minimal mean IgG reduction
Observed	45%
Sensitivity # 1	53%
Sensitivity # 2	55%

Conclusion: Results of the analyses aligned with different ICE strategies

- Principal Stratum *(PS) sample size averaged over 10,000 imputed datasets*
- *Baseline covariates in model based imputation: (Age, Sex, Baseline MTX use, Baseline Oral Corticosteriod use)*
- *Data points are LS mean and 95% CI at week 12*

Impact of ICE on IgG lowering: PKPD Simulation Results

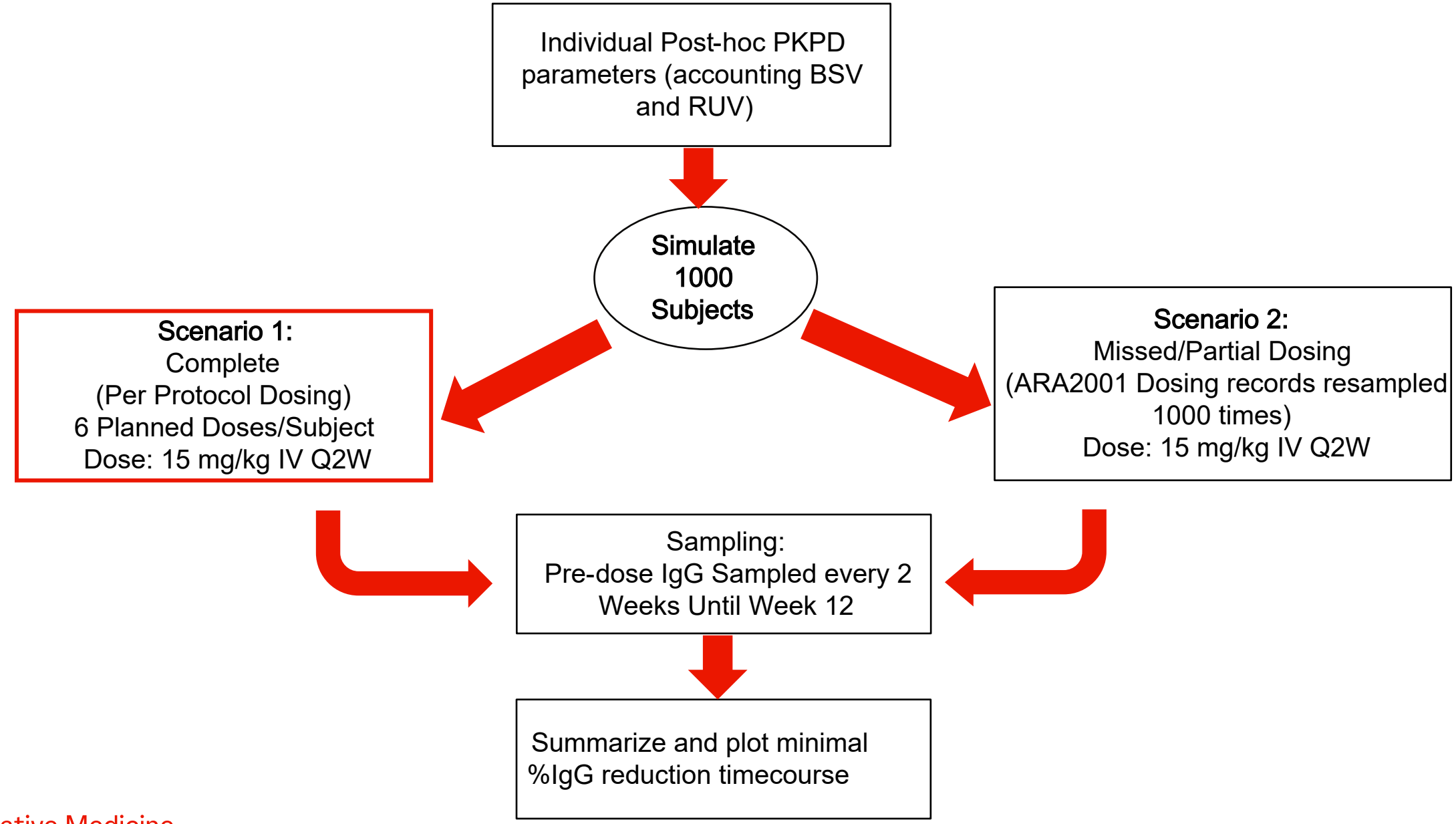
PK-RO-IgG Model Was Constructed Using All Available PK/PD data



- As a first step, a PK-RO model was built using **all the available PK data** from the treatment arms in healthy volunteers (HV) and RA patient population. No subject data was excluded in the PK model building process unless prespecified in the analysis plan
- Once a PK-RO model was built and visually checked for performance, a PK-RO-IgG model as described in the schematic was developed using **all available IgG data** from the placebo and treatment arms in HV and RA patient population. Model was visually checked for performance
- Final PK-RO-IgG model is then used for performing simulations in virtual population with different doses and dosing regimens (assuming 100% compliance) to aid dose selection process for future studies

Zhou et al., *"TMDD Pharmacokinetic and Pharmacodynamic Modeling of the Anti -FcRn Monoclonal Antibody Nipocalimab Administered to Healthy Subjects". 13th American Conference on Pharmacometrics, Colorado, USA (Nov, 2022)*

How Can We Assess Impact of ICE on IgG Lowering Through PKPD Simulations?



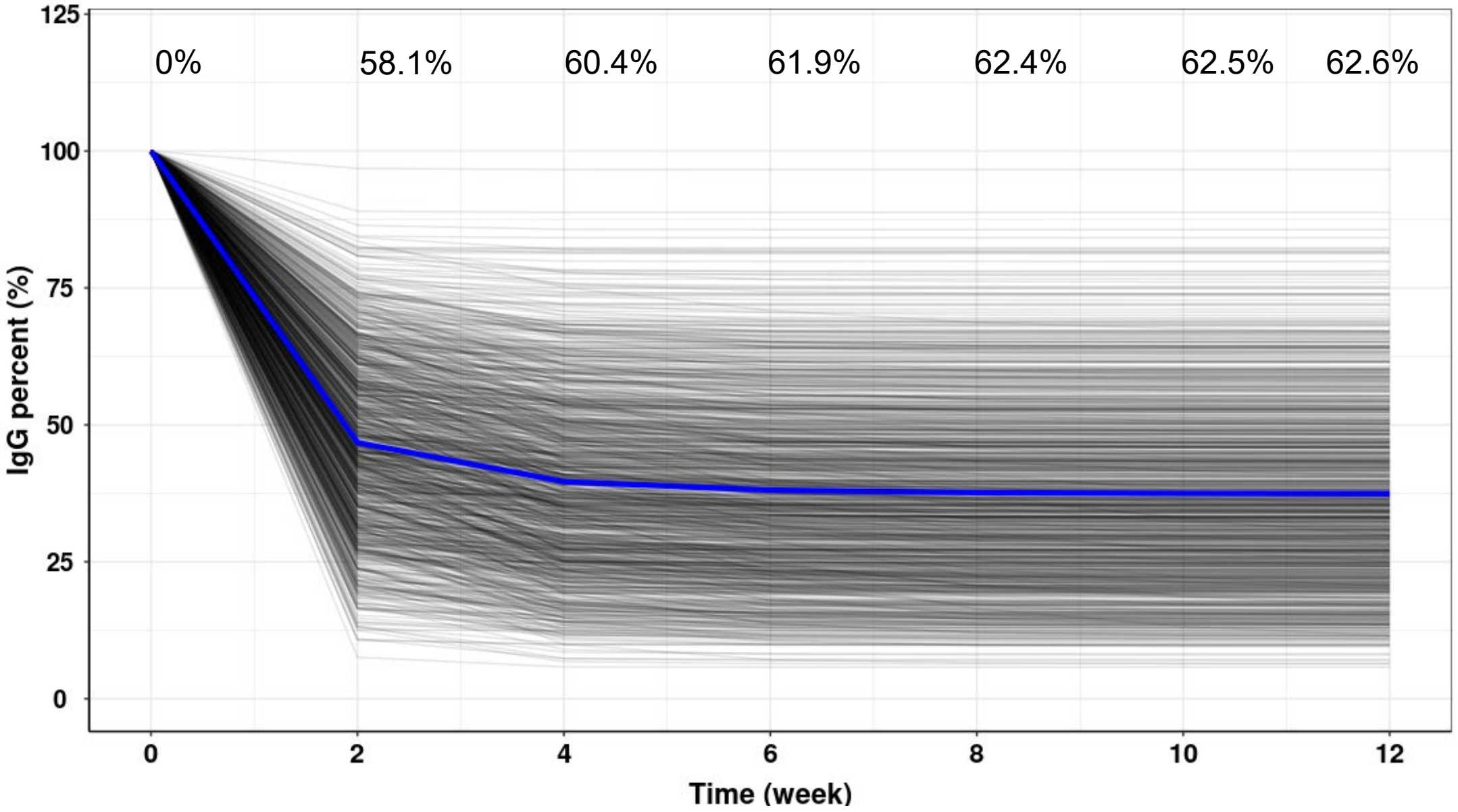
Note: BSV=Between Subject Variability; RUV= Residual Unexplained Variability

For Scenario 1, the Question of Interest is Related to Hypothetical Strategy

What is the expected effect in RA patients on minimal %IgG reduction at Week 12 of Nipocalimab 15 mg/kg IV q2w, if taken as directed for the entire 10 weeks treatment?

What is the	
Treatment effect	Population-level summary measure
on	
Percent IgG Reduction at Week 12	Variable
of	
Nipocalimab 15 mg/kg IV q2w	Study intervention
If taken as directed (i.e as if patients would not have discontinued treatment, modify their standard therapy or initiate any other treatment)	**Intercurrent Events (ICEs) ignored in Hypothetical Strategy**
in	
Patients with moderate to severe active RA, who have an inadequate response to anti-TNFα despite standard therapy	Population

Sustained IgG Reduction is Seen With Complete Dosing Over the Study Duration (15 mg/kg)



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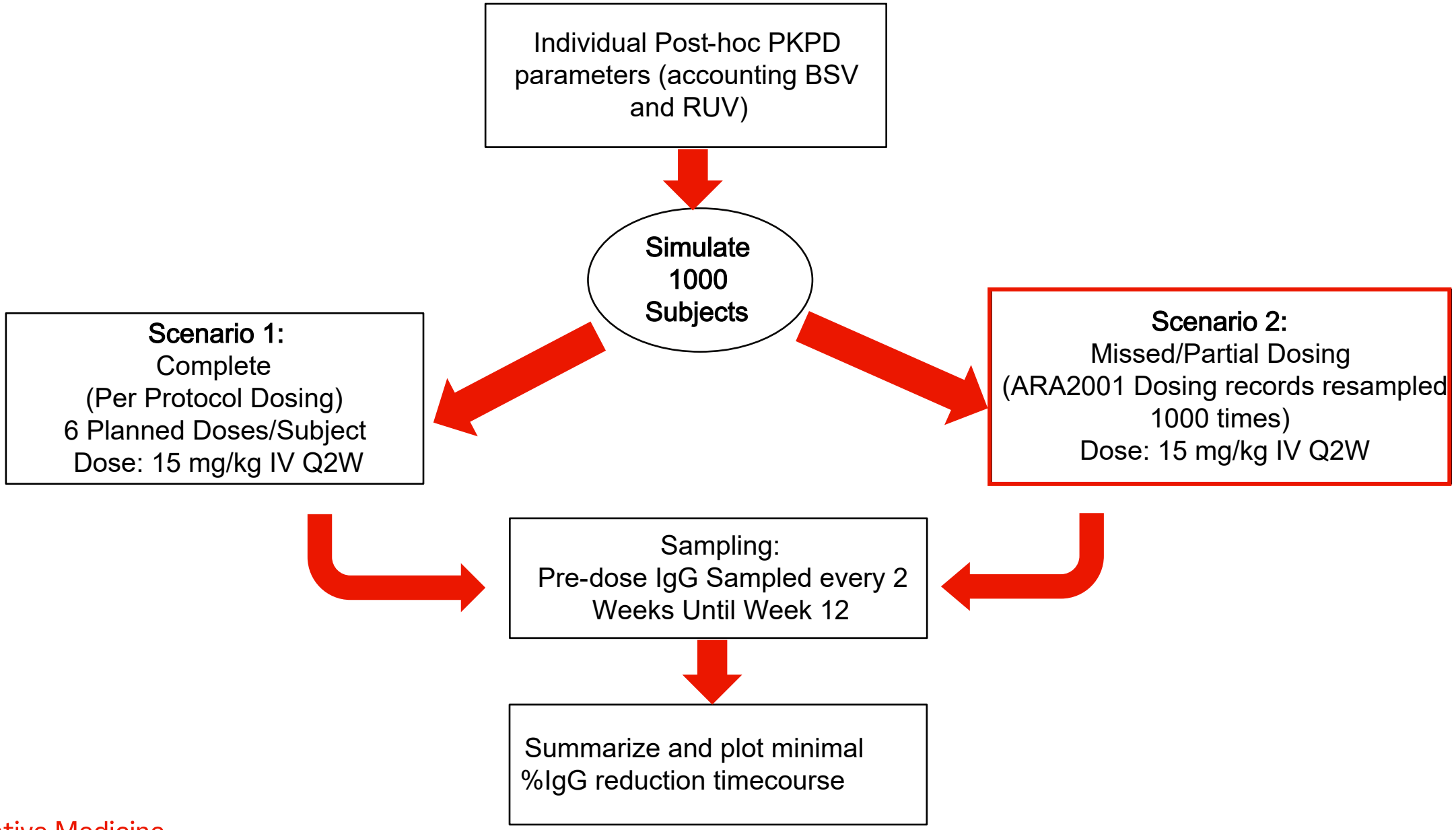


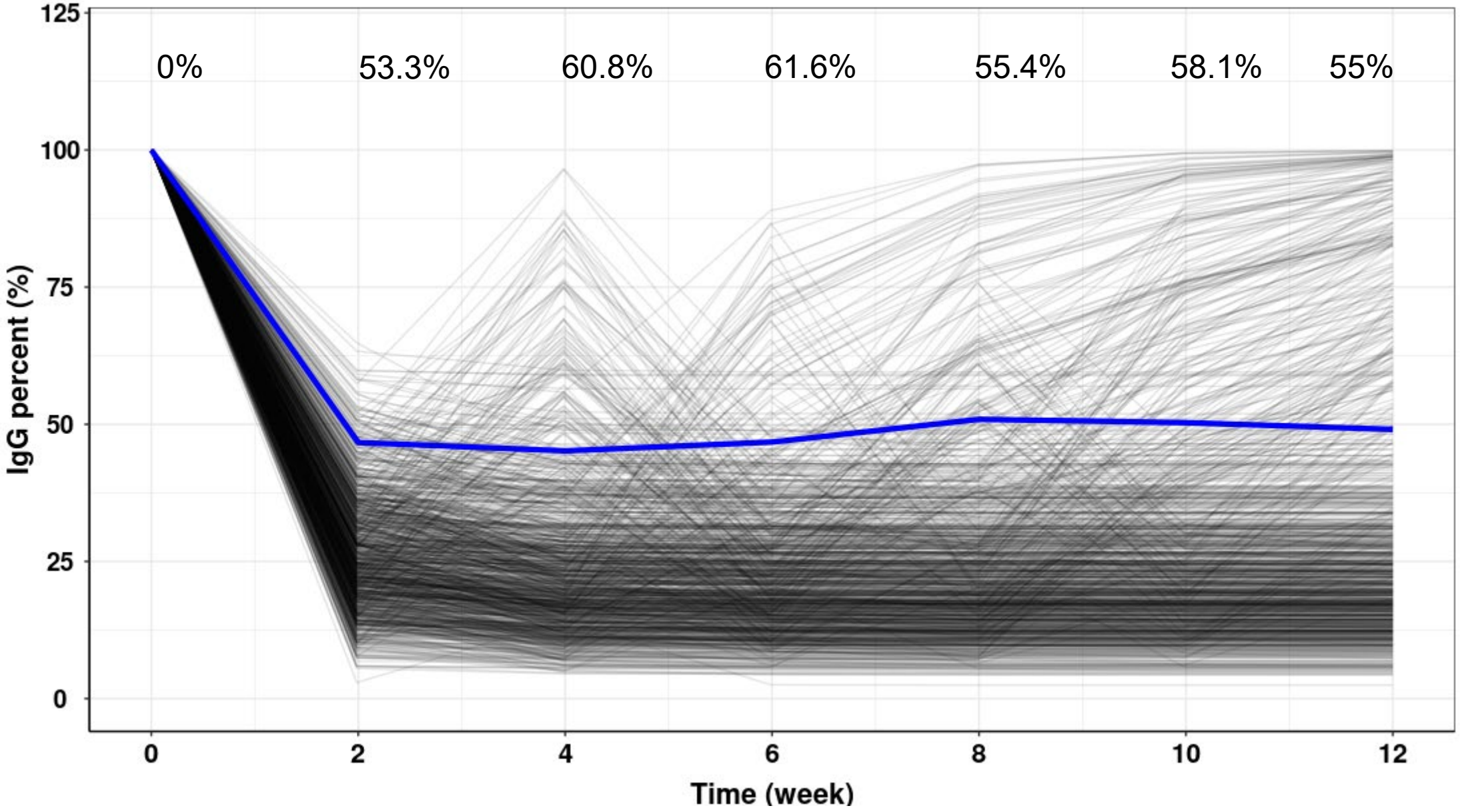
Note: BSV=Between Subject Variability; RUV= Residual Unexplained Variability

For Scenario 2, the Question of Interest is Related to Treatment Policy Strategy

What is the expected effect in RA patients on minimal %IgG reduction at Week 12 of Nipocalimab 15 mg/kg IV q2w, regardless of treatment discontinuation/missing a dose?

What is the	
Treatment effect	Population-level summary measure
on	
Percent IgG Reduction at Week 12	Variable
of	
Nipocalimab 15 mg/kg IV q2w	Study intervention
Regardless of treatment deviations (i.e if some patients would have discontinued treatment or missed their doses)	**Intercurrent Events (ICEs)**
in	
Patients with moderate to severe active RA, who have an inadequate response to anti-TNFα despite standard therapy	Population

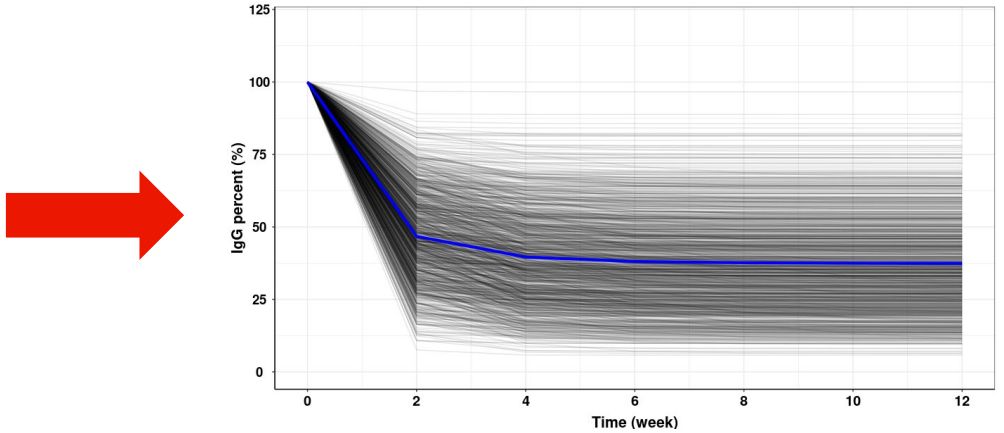
Simulated IgG Reduction Is in Alignment with Observed Data from ARA2001 Study (15 mg/kg)

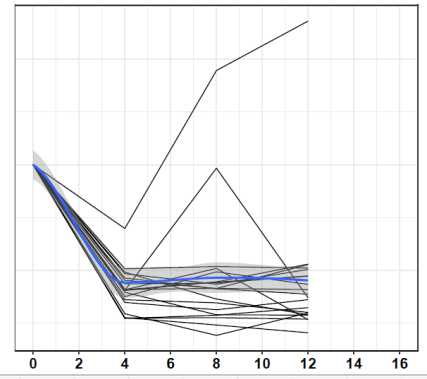


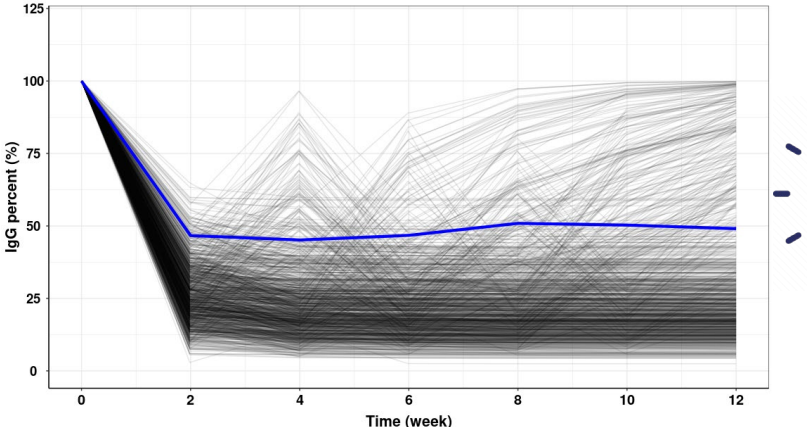
Putting It All Together…

Five ICE Strategies Revisited: How Are They Related to PKPD Simulations?

STRATEGY	DESCRIPTION: How is the ICE addressed?
Hypothetical	A setting is envisaged **in which the ICE would not occur** : the value of the variable to reflect the clinical question of interest is the value that the variable would have taken in the hypothetical scenario defined.
While-on-Treatment	For this strategy, the response to treatment before the occurrence of the ICE is of interest. This strategy hence modifies the variable.
Principal Stratum	The target population is the subpopulation ("principal stratum") **in which the ICE would not occur** .
Composite Variable	An ICE is considered in itself to be informative about the patient's outcome and incorporated into the definition of the variable, usually as an unfavorable outcome. The newly defined variable is then a composite of efficacy and the occurrence of the ICE.
Treatment Policy	Occurrence of an ICE is considered irrelevant in defining the treatment effect of interest: **the value for the variable of interest is used regardless** of whether the ICE occurs.

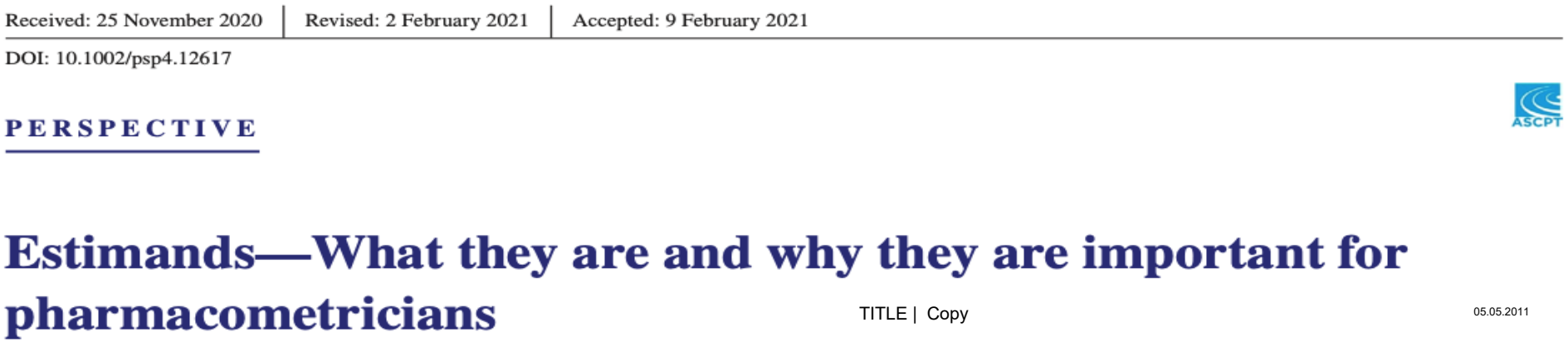






Estimands for Pharmacometricians

- Understanding estimands should be of interest to anyone performing treatment effect estimation, including pharmacometricians.
- Although ICH E9(R1) was primarily written with statistical analysis tradition in mind, the principles outlines in ICH E9(R1) apply more broadly and are relevant whenever a treatment effect is to be estimated.
- ICH E9(R1) introduces a common language that pharmacometricians can use in collaboration with statisticians, clinicians, and other drug development stakeholders.


Received: 25 November 2020 | Revised: 2 February 2021 | Accepted: 9 February 2021

DOI: 10.1002/psp4.12617

PERSPECTIVE

Estimands—What they are and why they are important for pharmacometricians

Akacha et al., "Estimands—What they are and why they are important for pharmacometricians" *CPT Pharmacometrics Syst. Pharmacol.* 2021;10:279–282

Now We Can Understand Each Other Much Better…

Although we always try to report observed safety data as is, for key biomarkers to confirm whether the drug works, alternative ICE strategies can be helpful under the estimand framework

Although our PKPD models are built upon all available data, different simulation approaches considering different estimands can help answer different clinically relevant questions

Thank you

If you have more questions, please contact:
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What are The Five Attributes of an Estimand?

An estimand is a precise description of the treatment effect reflecting the clinical question posed by a given clinical trial objective.