

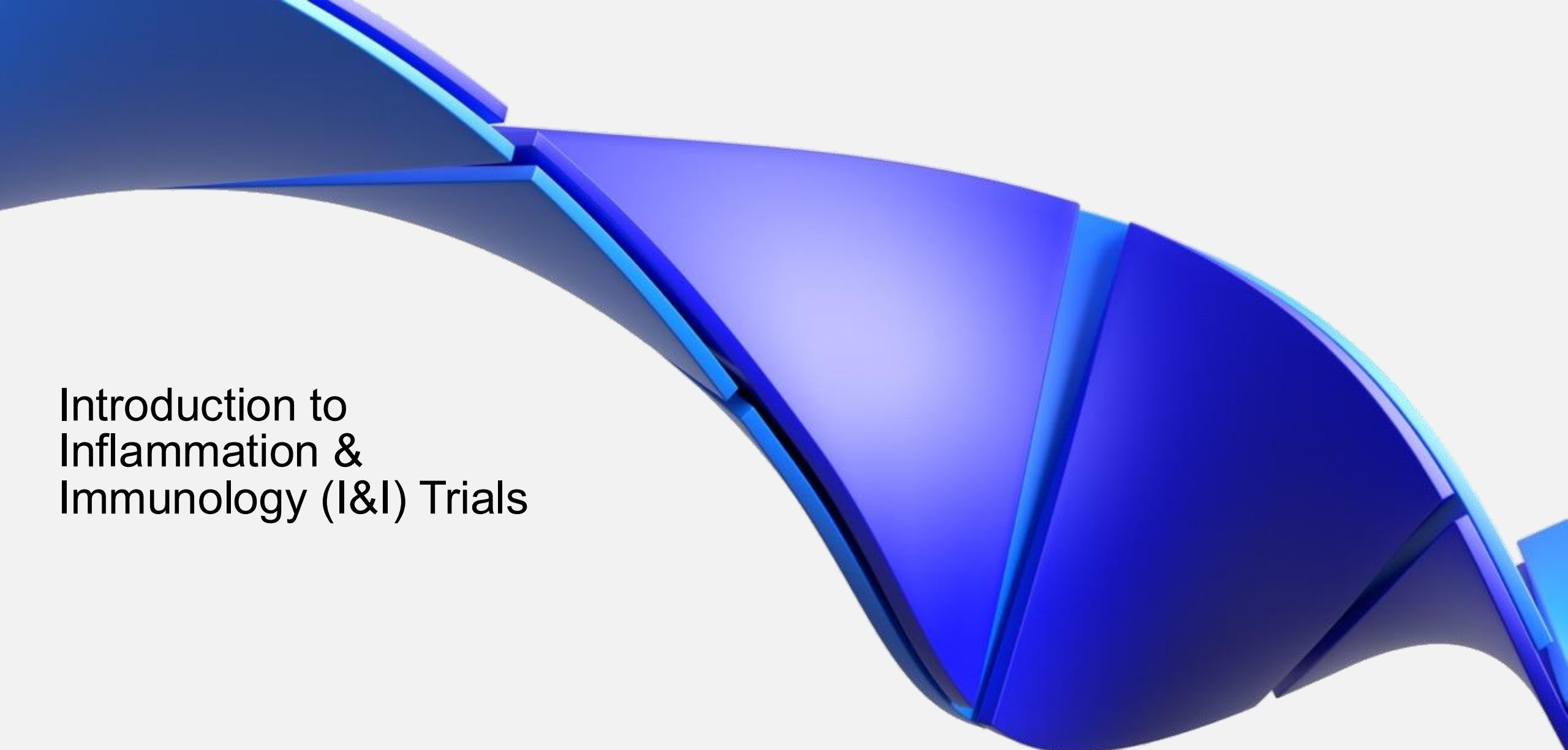


Invisible Influences: Estimands, Assumptions and Sensitivity in Inflammation & Immunologic Trial Interpretation

Author: Sukanya ES

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Introduction to Inflammation & Immunology (I&I) Trials

What Are I&I Trials?

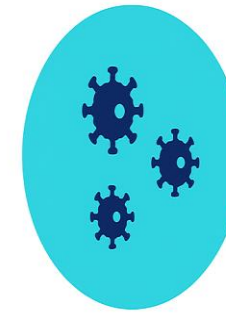
Clinical trials conducted in immune-mediated diseases, where the immune system becomes overactive, dysregulated, or misdirected, leading to chronic inflammation or tissue damage. I&I is one of the fastest-growing and scientifically complex therapeutic areas in drug development.

Includes:

- **Autoimmune diseases** (e.g., rheumatoid arthritis, lupus, ulcerative colitis)
- **Autoinflammatory disorders** (e.g., sJIA, Still's disease)
- **Allergic & Type-2 inflammatory diseases** (e.g., atopic dermatitis, asthma)
- **Immune-driven dermatologic diseases** (e.g., psoriasis, alopecia areata)



Autoimmune



Auto-inflammatory



Allergic & immune-driven dermatologic

Common Features Across I&I Diseases

- Long-standing, relapsing–remitting disease course
- Driven by cytokine imbalances (IL-1, IL-4, IL-6, IL-17, IL-23, TNF, JAK/STAT pathways)
- Require long-term or biologic therapies
- Involve immune-mediated tissue damage (skin, joints, bowel, systemic)



Long-standing,
relapsing-remitting
disease course



Driven by cytokine
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Require long-
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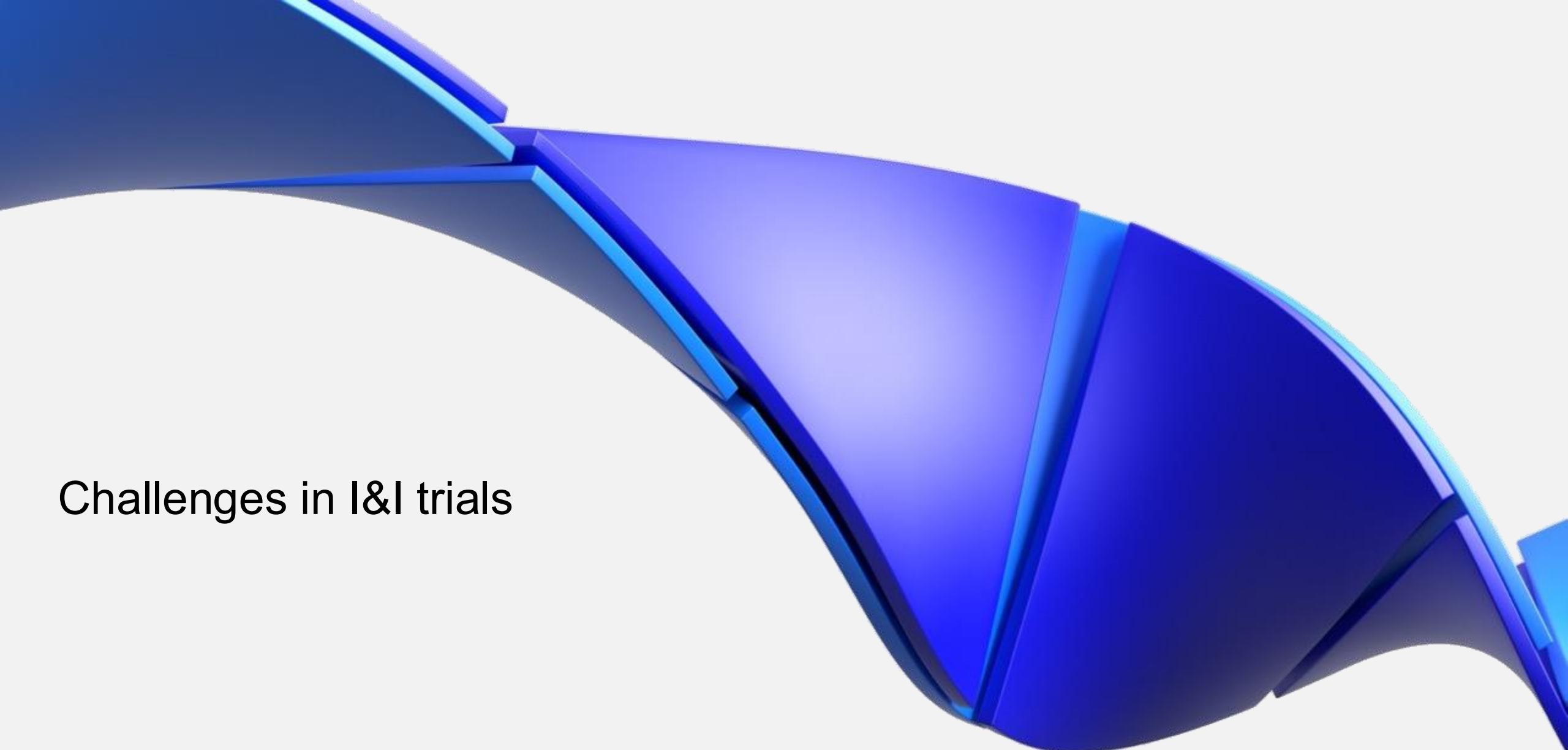


Involve immune-
mediated tissue
damage (skin,
joints, bowel,
systemic)



Why I&I Trials Are Unique?

- Diseases follow **flare–remission cycles**, not a stable pattern.
- Treatments are often biologics or **JAK inhibitors**, requiring time for immune modulation.
- **Immunogenicity (ADA formation)** can reduce exposure or neutralize drug effect.
- **Rescue medications** are frequently needed to control flares.
- **High discontinuation** due to lack of efficacy, adverse events, or symptom worsening.
- Heavy use of **patient-reported outcomes** (itch, pain, fatigue, function).

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Challenges in I&I trials

OVERVIEW OF PRE-ESTIMAND CHALLENGES



Lack of Standardized Objectives

Pre-estimand trials had vague goals, failing to specify treatment conditions or population definitions clearly.

Ad Hoc Handling of Intercurrent Events

Treatment changes and rescue medication were inconsistently managed, causing uncertainty in trial results.

Challenges with Missing Data

High dropout rates led to biased analyses due to unclear justification of imputation methods.

Poor Communication and Transparency

Trial results reports lacked clarity on assumptions, confusing clinicians and regulators.

UNCLEAR TREATMENT EFFECT



Vague Trial Objectives

Trial objectives often asked broad questions without specifying the conditions for treatment effects clearly.

Lack of Consensus on Parameters

No agreement on accounting for rescue medication, target population definitions, or missing data handling.

Impact on Interpretation

Ambiguity led to inconsistent interpretations and reduced confidence among clinicians, statisticians, and regulators.

Scientific Validity Challenges

Unclear treatment effect definitions complicated comparisons and undermined scientific conclusions.

NO STANDARD FOR INTERCURRENT EVENTS



Inconsistent Event Handling

Intercurrent events were handled inconsistently leading to unreliable and biased clinical trial outcomes.

Impact on Trial Results

Arbitrary censoring or imputation creates uncertainty about whether results reflect true drug efficacy or real-world effectiveness.

Need for Standardization

Lack of a standardized framework introduced bias and hindered comparability across studies emphasizing urgent need for clear guidelines.

INCONSISTENT MISSING DATA HANDLING



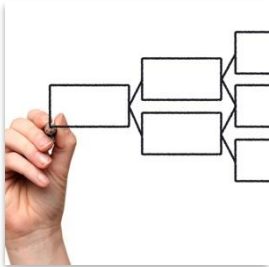
Pre-Estimation Methods

Earlier methods like LOCF and multiple imputation lacked clear rationale and often relied on unverifiable assumptions.



Impact on Trial Results

Inconsistent missing data handling reduced result transparency and led to biased treatment effect estimates.



Need for Standardization

A framework linking data handling to estimands and objectives enhances scientific coherence and interpretability.

OPAQUE SENSITIVITY ANALYSES



Lack of Clear Objectives

Pre-Estimand sensitivity analyses often lacked clear objectives and were conducted post hoc without scientific rigor.

Opaque Assumptions

Assumptions behind analyses were rarely explained, reducing interpretability and stakeholder confidence.

Variability Across Trials

Lack of systematic planning caused wide variability in sensitivity analyses across different trials.

Estimand Framework Benefits

The Estimand framework fosters structured, transparent sensitivity analyses aligned with trial objectives.

POOR COMMUNICATION OF RESULTS



Lack of Clarity in Reports

Trial results often lacked clear assumptions, causing confusion among clinicians, statisticians, and regulators.

Impact on Interpretation

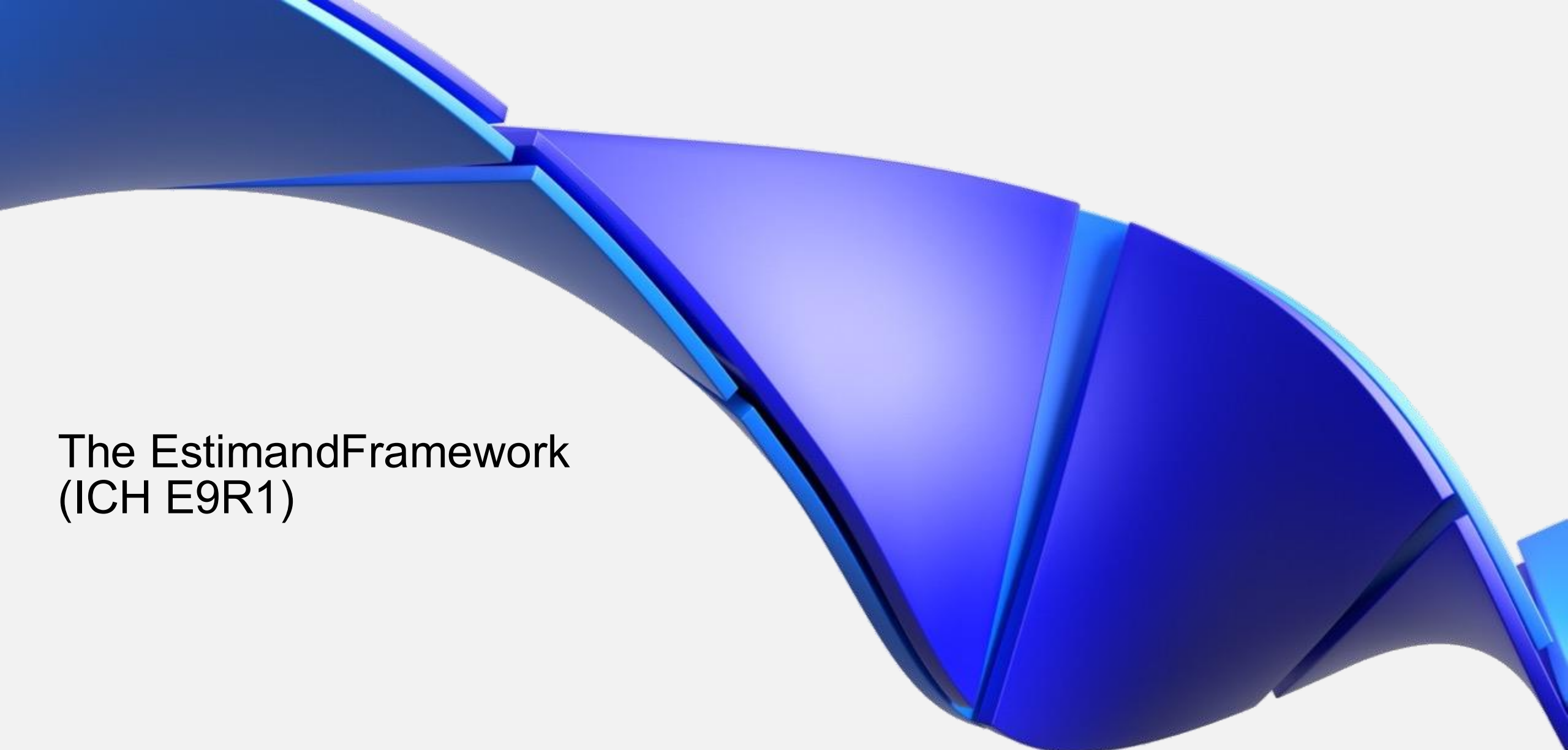
Without transparent data on factors like patient discontinuation, treatment effects could be misinterpreted.

Regulatory Challenges

Poor communication complicated regulatory review, making it hard to verify alignment with trial goals.

Need for Standardization

A standardized framework improves clarity by clearly linking assumptions and analyses to scientific questions.

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The EstimandFramework (ICH E9R1)



ICH E9(R1) Definition of an Estimand

Estimand Concept Overview

An estimand precisely describes the treatment effect reflecting the clinical question and trial objective.

Bridge Between Objective and Analysis

Estimands guide design, conduct, and analysis by clarifying how to handle intercurrent events in trials.

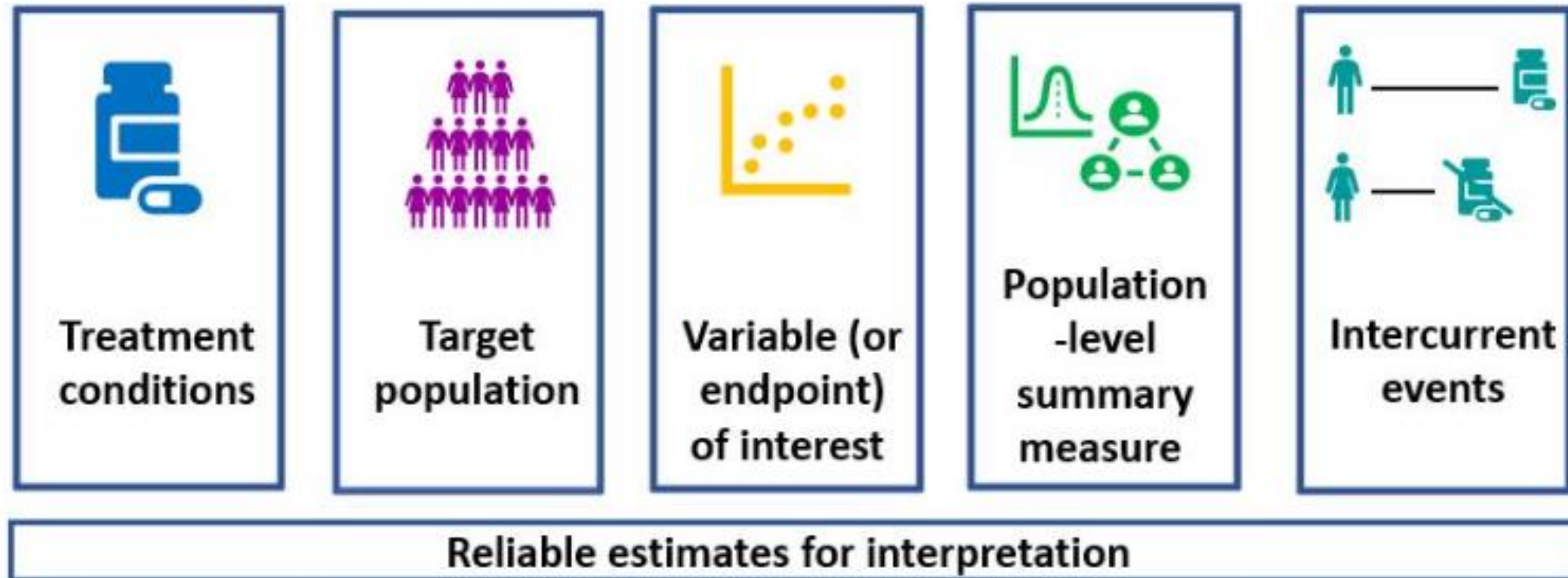
Promoting Consistency and Transparency

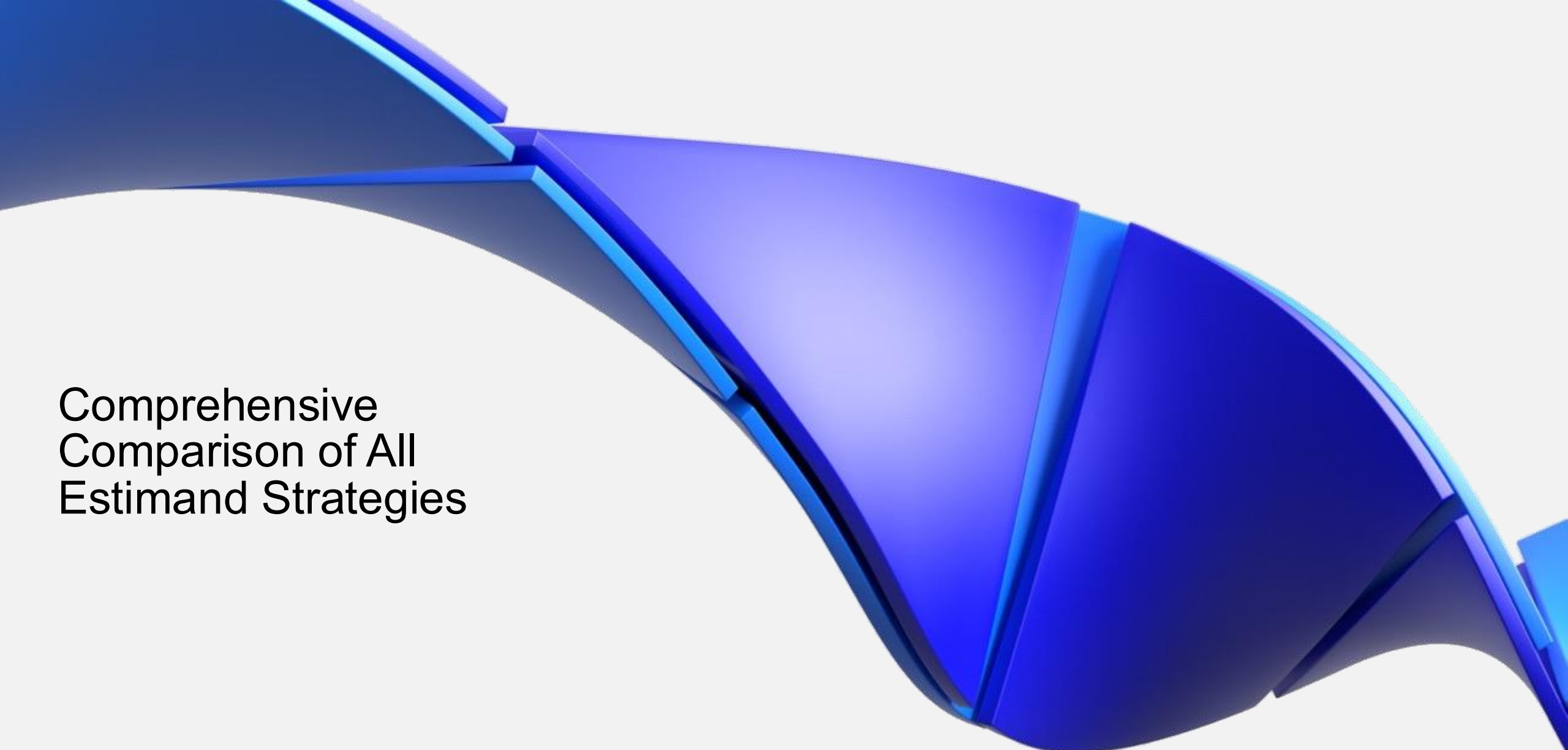
ICH E9(R1) formalizes estimands to enhance consistency, reduce ambiguity, and support regulatory submissions.

Avoiding Bias in Trial Planning

Early estimand definition helps prevent post-hoc decisions that may bias trial conclusions.

What is the Estimand Framework?

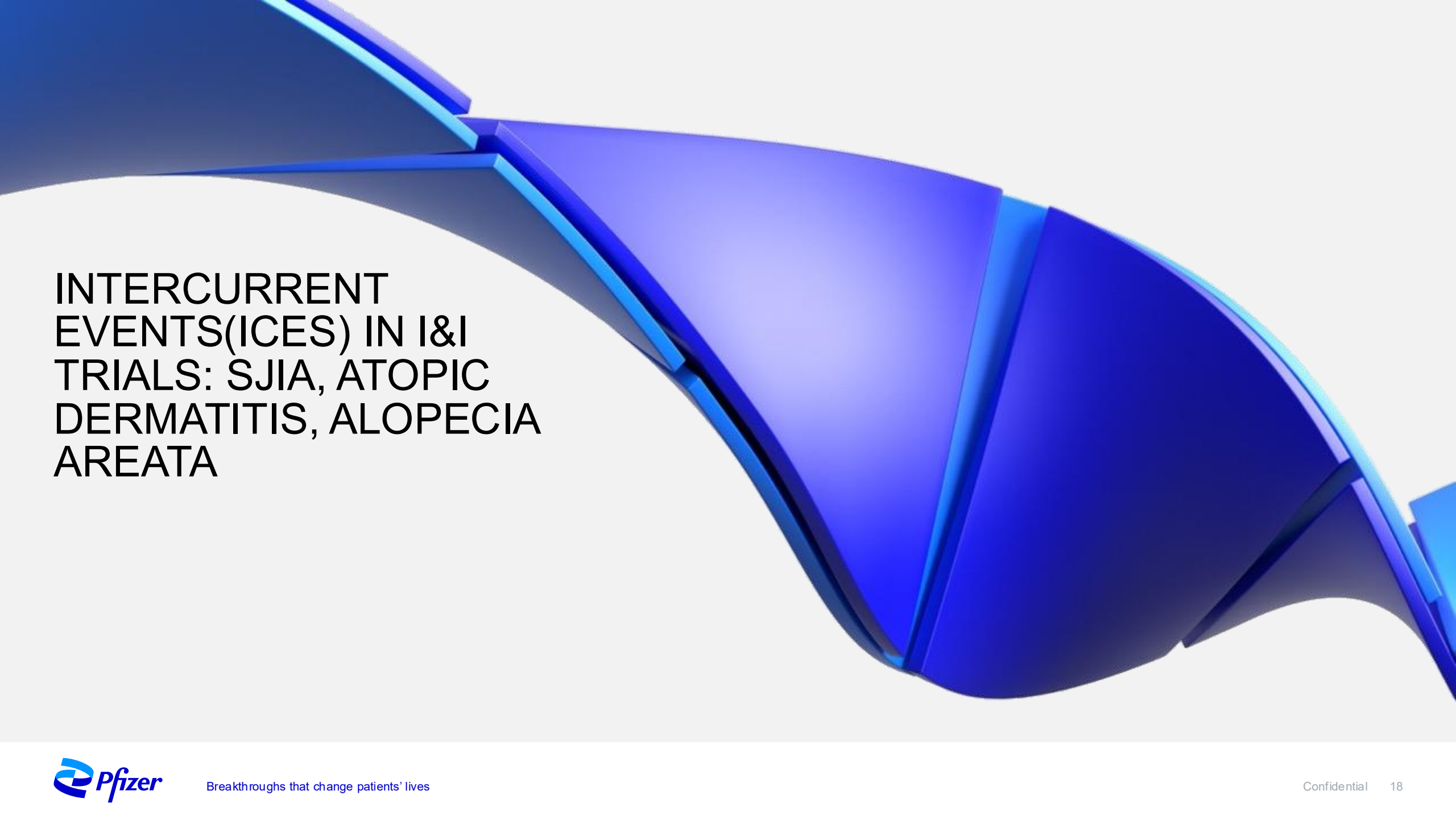


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Comprehensive Comparison of All Estimand Strategies

COMPARISON OF ALL ESIMAND STRATEGIES

Aspect	Treatment Policy	Hypothetical	Composite	While-on-Treatment	Principal Stratum
Philosophy	Real-world effectiveness	Pure, mechanistic efficacy	ICE becomes part of the endpoint	Effect only while treatment continues	Effect in subgroup defined by potential ICE occurrence
Handling of ICE	Include all post-ICE data “as observed”	Assume ICE did not occur, estimate outcome	Treat ICE as outcome event	Censor or truncate at ICE	Analyse only patients who would (counterfactually) not have the ICE
Scientific Question	What is the effect of assigning treatment?	What is the effect if all adhered/no ICEs occurred?	How does treatment affect a combined endpoint including ICE?	What is effect of treatment before ICE happens?	What is effect in patients with a particular underlying ICE behaviour?
Statistical Methods	MMRM, ANCOVA, GEE, mixed models using all data	MI, Bayesian models, pattern-mixture, MAR/MNAR models	Time-to-event, logistic/Cox models	On-treatment MMRM, survival models with censoring	Causal inference: IV, structural models, principal stratification
Treatment Effect Interpretation	Effectiveness in routine clinical use	Efficacy under ideal adherence	Risk of clinically meaningful (bad) events	Effect while patient is actually treated	Causal contrast for “latent” subpopulation



INTERCURRENT EVENTS(ICES) IN I&I TRIALS: SJIA, ATOPIC DERMATITIS, ALOPECIA AREATA

UNDERSTANDING ICES AND THEIR IMPACT



Definition and Importance of ICES

ICES occur after treatment starts and affect the assessment and interpretation of clinical trial outcomes.

Examples in Immune & Inflammatory Trials

ICES such as disease flares, rescue therapies, and missed assessments affect diseases like sJIA, AD, and AA differently.

Strategies to Address ICES

Approaches like composite estimands, treatment-policy, and hypothetical imputations help maintain scientific integrity in trials.

Regulatory and Trial Design Impact

Understanding ICES ensures trial design robustness and compliance with regulatory clarity and transparency requirements.

COMMON ICEs AND ESTIMAND STRATEGIES IN SJIA

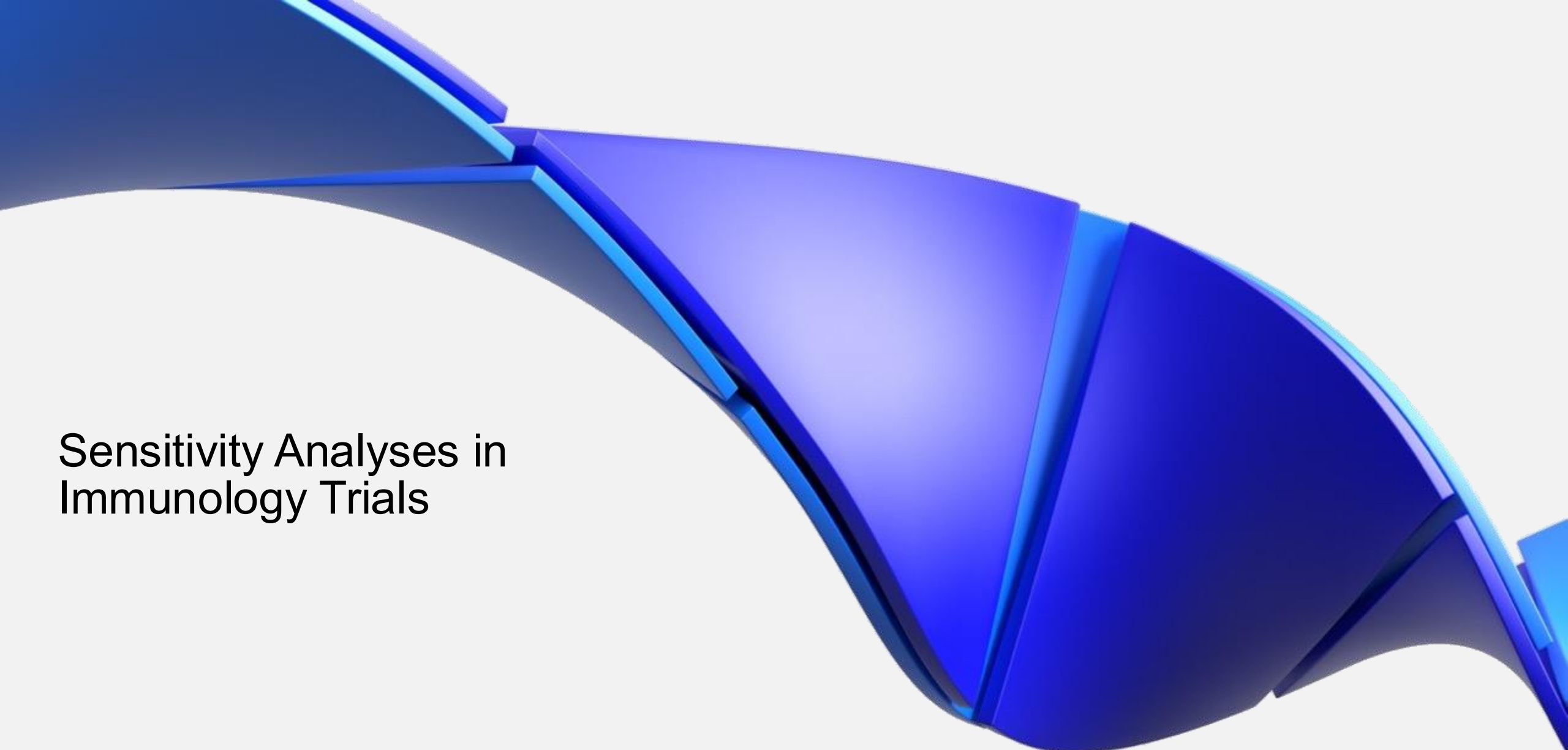
INTERCURRENT EVENT	DEFINITION / CONTEXT	ESTIMAND STRATEGY	REGULATORY INTERPRETATION
Disease Flare	Recurrence of fever + worsening JIA variables	Composite	Treatment failure
Sustained Inactive Disease Discontinuation	Stopping after prolonged remission	While-on-treatment	Not failure; data until discontinuation
Other Discontinuations	AEs, lack of efficacy, patient decision	Composite	Treatment failure
Rescue Medication Use	Additional therapy for disease control	Composite	Treatment failure
Missing Visits	Operational disruptions	Hypothetical	Impute as if occurred
Extension Phase Transition	Move to open-label	While-on-treatment	Exclude extension data

ICES IN ATOPIC DERMATITIS TRIALS

INTERCURRENT EVENT	DEFINITION / CONTEXT	ESTIMAND STRATEGY	REGULATORY INTERPRETATION
Prohibited Medications	Use of disallowed therapies	Treatment-policy / Composite	Failure if composite
Rescue Medication	Additional therapy for symptom control	Composite	Treatment failure
Discontinuation (Lack of Efficacy)	Stopping due to poor response	Composite	Non-response
Discontinuation (AEs)	Stopping due to safety issues	Principal-stratum / Composite	Depends on objective
Forbidden Skin Products	Non-approved moisturizers	Treatment-policy / Hypothetical	Data retained or imputed
Non-Adherence	Missed doses	Treatment-policy	Included in effect
Missing PRO Data	Incomplete diaries	Hypothetical	Imputed
Operational Disruptions	Missed visits	Hypothetical	Imputed
Open-Label Switch	Extension phase entry	While-on-treatment	Exclude extension data

ICEs IN ALOPECIA AREATA TRIALS

INTERCURRENT EVENT	DEFINITION / CONTEXT	ESTIMAND STRATEGY	REGULATORY INTERPRETATION
Rescue Therapy	Additional treatment for regrowth	Composite	Treatment failure
Prohibited Medications	Non-allowed systemic agents	Treatment-policy / Composite	Failure if composite
Discontinuation (Lack of Efficacy)	Stopping due to poor response	Composite	Non-response
Discontinuation (AEs)	Stopping due to safety issues	Principal-stratum / Composite	Depends on objective
Cosmetic Procedures	Haircut, dye, camouflage	Hypothetical / Treatment -policy	Imputed or retained
Missing SALT/PRO Data	Incomplete assessments	Hypothetical	Imputed
Operational Disruptions	Missed visits	Hypothetical	Imputed
Open-Label Switch	Extension phase entry	While-on-treatment	Exclude extension data
Non-Adherence	Missed doses	Treatment-policy	Included in effect

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Sensitivity Analyses in Immunology Trials

SENSITIVITY ANALYSIS IN I&I trials

Sensitivity analyses in immunology must address the reality that patients who discontinue early do not behave like patients who stay on treatment—especially in fluctuating conditions like sJIA, AD, or AA.

- **RBI** is one of the most relevant families of sensitivity analyses for this context.
- **Delta Adjusted Models.**
- **Tipping Point Analysis.**

SENSITIVITY ANALYSIS



Reference-Based Imputation (RBI): What It Does

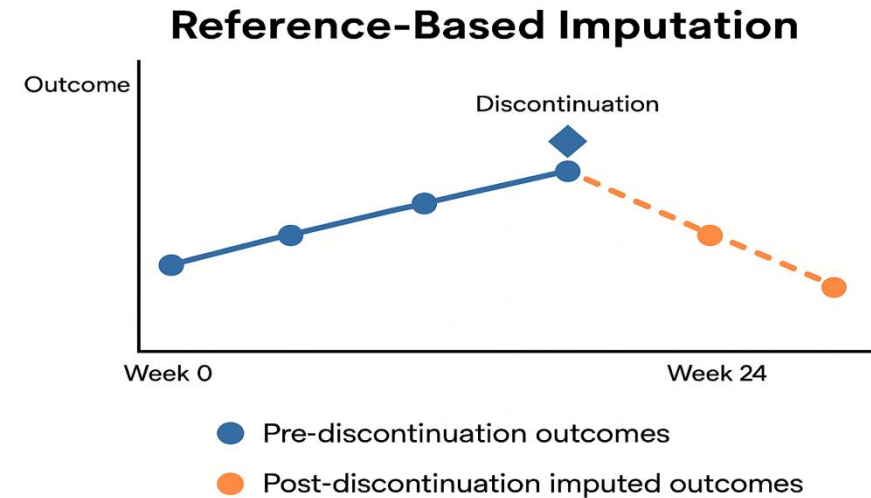
RBI is a post-discontinuation imputation framework in which missing values after treatment discontinuation are imputed using data from a reference group, typically:

- Placebo arm, or
- Matched population with similar post-withdrawal clinical

Why RBI is useful in Immunology

- Patients often discontinue due to:
- Lack of efficacy
- Adverse events
- Needing rescue medication
- Flares

- → After this point, they no longer follow the expected treatment effect trajectory of the randomized arm.
- → MAR assumptions (e.g., standard MMRM/MI) become unrealistic.



RBI - Jump-to-Reference (J2R)

Concept

After discontinuation, patient outcomes immediately “jump” to follow the control arm distribution.

When used

Regulatory-friendly conservative estimand

Reflects de-facto effectiveness if patients cannot benefit after stopping treatment

EXAMPLE-

A patient on active drug discontinues at Week 8 due to lack of efficacy.

- Observed data: EASI-75 improvement = 52% at discontinuation.

J2R imputes post-Week-8 data:

- Patient's Week 12 and 16 EASI scores are imputed from placebo patients who reached Weeks 12 and 16.

Interpretation:

- After stopping treatment, they lose all drug benefit instantly → **consistent with worsening AD.**

RBI - Copy-Reference (CR)

Concept:

- After discontinuation, the patient follows the same mean trajectory as the reference arm starting from their discontinuation level.

Different from J2R:

- J2R → immediate jump to reference mean
- Copy-reference → maintain their current value, but future change mirrors reference

Example – Atopic Dermatitis

- A patient has EASI improvement 60% at Week 8 before discontinuation.

CR imputation:

- Week 8 = 60%
- Post-Week-8 change follows placebo trajectory
- (e.g., placebo may worsen by 10%, so impute 50% → 40%...)

Interpretation:

- Allows for gradual loss of treatment effect.



RBI - Copy-Increment-from-Reference (CIR)

Concept:

The patient maintains the incremental treatment benefit they had at discontinuation, but future response change follows reference arm.

Example — Alopecia Areata

Placebo: average change from Week 12 → Week 24 = +3% SALT improvement.
Active treatment patient had: 40% improvement at Week 12.

CIR imputes:

+3% added → 43% at Week 24

Interpretation:

Allows maintained benefit while mirroring placebo change rate.



RBI - Return-to-Baseline (RtB) / Return-to-Reference (RtR)

Typically used when the clinical assumption is "benefit stops completely" once treatment stops.

Example — sJIA

- A patient discontinues due to flare at Week 10 (disease inactive before).

RtB imputes:

- Return to baseline inflammatory markers and joint counts
- Represents full loss of disease control

Interpretation:

- Useful in sensitizing flare-protection analyses.

DELTA- ADJUSTED MODELS

Delta-adjustment applies a prespecified shift to imputed values to reflect plausible MNAR mechanisms such as immunogenicity or adherence issues. For example, anti-drug antibodies might reduce expected benefit; a negative delta can be applied to post-dropout imputations for antibody-positive patients to assess impact on primary conclusions.

Delta Type	Description	Typical ICE(s) Imputed in I&I Trials
Constant Delta	Same Δ for all post-ICE values	Treatment discontinuation; mild AE dropout
Tipping-Point Δ	Range of Δ values tested	All ICEs causing missing data (discontinuation; rescue)
Group-Specific Δ	Δ varies by subgroup	ADA+; rescue; non-adherent; lack of efficacy (LOE)
Time-Varying Δ	Δ increases over time	Biologic discontinuation; long drug-interruption gaps
Pattern-Mixture Δ	Δ applied by ICE pattern	AE dropout; LOE dropout; rescue; protocol deviation
Reference-Based + Δ	Δ layered on J2R/CR/CIR	Rescue initiation; discontinuation; treatment switching
Bayesian Δ	Δ has prior distribution	ADA-driven dropout; adherence-related discontinuation
Effect-Size Δ	Δ shifts treatment effect	Meta-analytic sensitivity analyses



Tipping Point Analysis

Tipping-point analyses are a global MNAR sensitivity analysis framework where assumptions about missing data are systematically varied—typically through a grid of delta-adjustments—until the study’s primary conclusion “tips” (i.e., loses statistical significance or loses clinical relevance).

They answer the question:

- “How extreme must the missing-data bias be to overturn our conclusion?”
- This makes tipping-point analyses particularly **valuable in immunology**, where missingness is often associated with flares, rescue medication, immunogenicity, adherence issues, or slow-to-reverse disease dynamics.



Why tipping point analysis Matters in Immunology Trials?

Immunology endpoints (EASI, vIGA, SALT, ACR, flare, PROs) are sensitive to deterioration after:

- Rescue medication use
- ADA development
- Loss of adherence
- Withdrawal flares
- Intermittent improvement/worsening patterns

Thus tipping-point analyses provide regulators and clinicians with a robustness map of how assumptions about post-dropout worsening could impact results.

Detailed Explanation of the Tipping-Point Example (Atopic Dermatitis, EASI-75)

Scenario:

- In an AD trial, 12% of patients in the active arm dropped out.
- MAR-based MI assumes their missing EASI-75 responses behave like patients who stayed on treatment.
- But in reality, people who discontinue early often have worse outcomes.
- Tipping-point analysis tests how much worse these missing outcomes would have to be to overturn the study results.

A grid of deltas is applied:

- Δ_{active} : -5%, -10%, -15%, -20%, -25%
- Δ_{placebo} : +0%, +5%, +10%

Interpretation:

- Treatment remains statistically significant for all $\Delta_{\text{active}} \geq -18\%$
- Treatment loses significance when $\Delta_{\text{active}} = -20\%$ and $\Delta_{\text{placebo}} = +5\%$

Conclusion:

- The effect is robust unless active-arm dropouts would have had outcomes 20% worse than MAR predicts, while placebo dropouts would need to be modestly better.
- This is biologically unlikely → robust result.

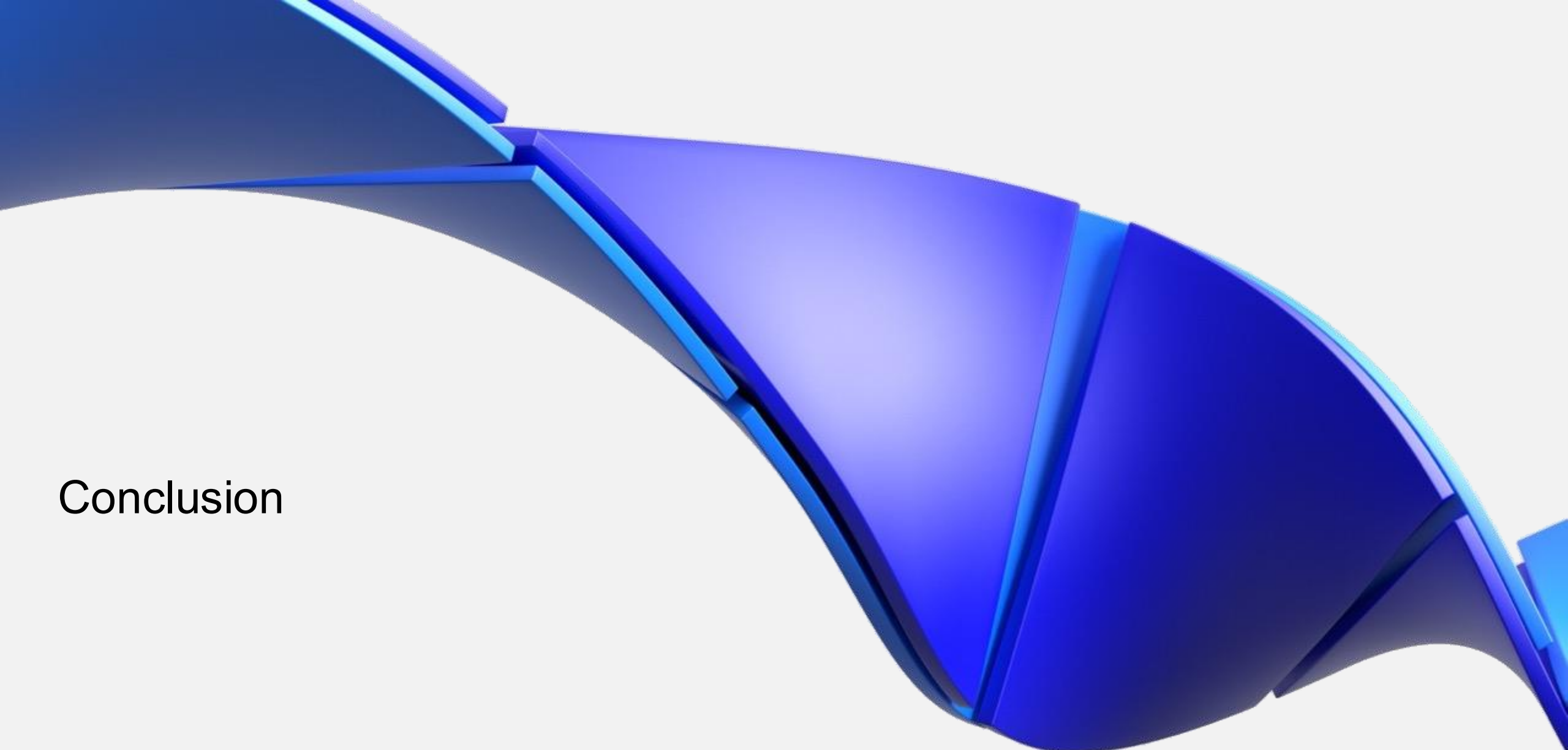
How MAR vs Δ changes the final responder rate

Arm	Observed responders / observed	Missing (dropouts)	MAR: Imputed responders among missing	Δ -adjusted: Imputed responders among missing
Active	44 / 88	12	6 (50% of 12)	4 (30% of 12)

What this implies for the overall Week-24 responder rate

MAR overall responders = $44 + 6 = 50/100 = 50\%$

Delta overall responders = $44 + 4 = 48/100 = 48\%$

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Conclusion



Conclusion: Invisible Influences in Inflammation & Immunologic Trials

Clear estimands define the question

- Align analysis with clinical objectives
- Make explicit what effect is being targeted

Assumptions shape interpretation

- Identify assumptions underlying causal claims
- Acknowledge complexities (intercurrent events, heterogeneity)

Sensitivity analyses reveal robustness

- Test alternative plausible scenarios
- Distinguish true biological signals from analytical artifacts

Transparency strengthens decisions

- Improves credibility of trial results
- Ensures patient-relevant, interpretable evidence



Thank You

