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2026 Europe Interchange

THE FUTURE IS CONNECTED: STANDARDS AND AI POWERING DIGITAL TRANSFORMATION

Connecting the Dots: Future of Estimand Implementation

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Speakers

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Disclaimer and Disclosure

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Agenda

- Why We're Still Not Connected
- Why Estimands Still Feel "Disconnected"
- Where The Dots Actually Are In The Lifecycle
- Implementation Reality:
  What's Working Vs What's Messy
- Future State:
  What "Connected" Estimands Could Look Like and What Teams Can Do Now

Why We’re Still Not Connected

Why We're Still Not Connected

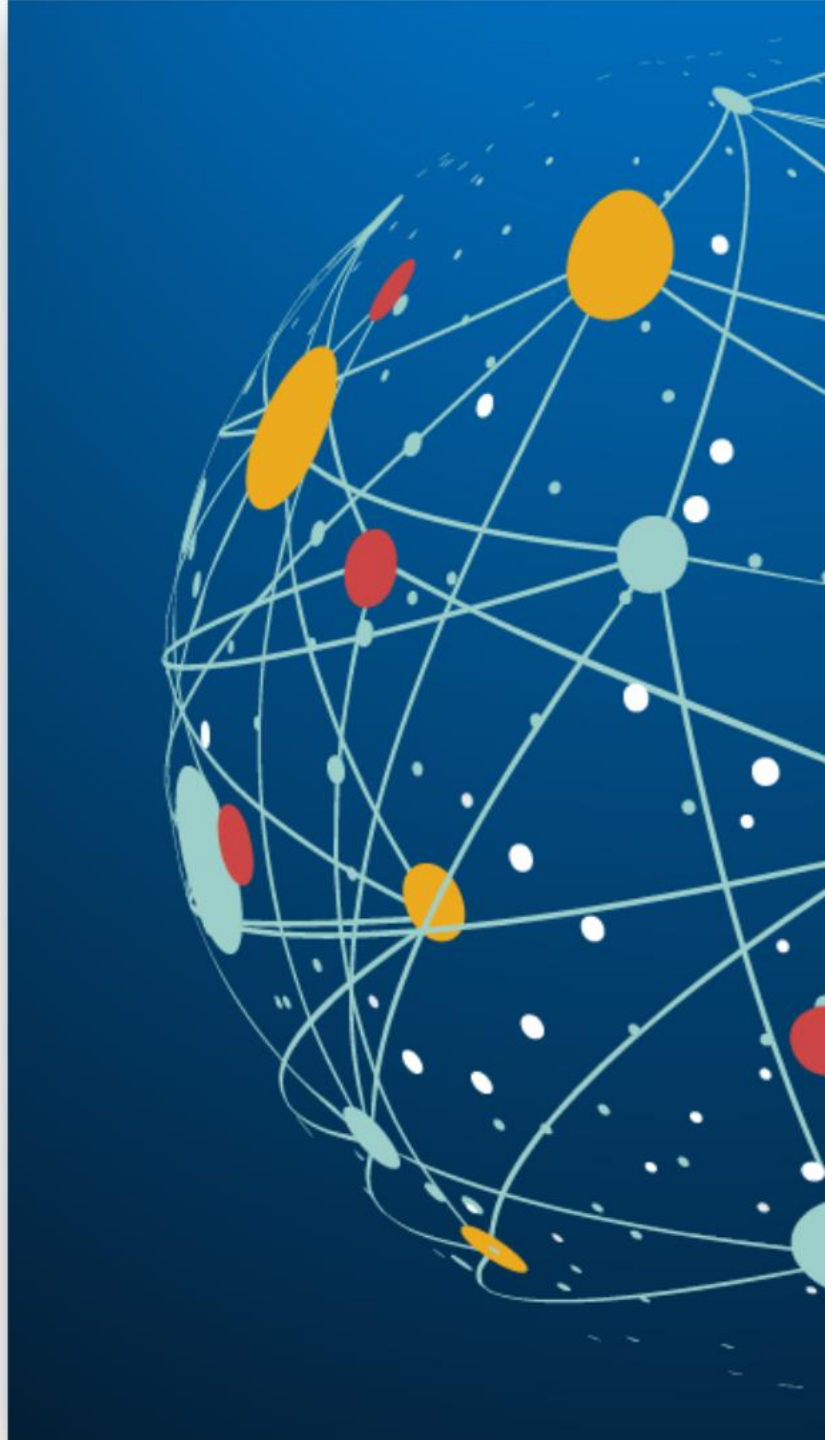
****We've defined estimands...**

So why are we still not estimating what we think we are?**

- ICH E9(R1)
- PHUSE, PSI, EFSPI/EFPIA Estimand Implementation Working Groups, and
- CDISC ADaM estimand initiatives

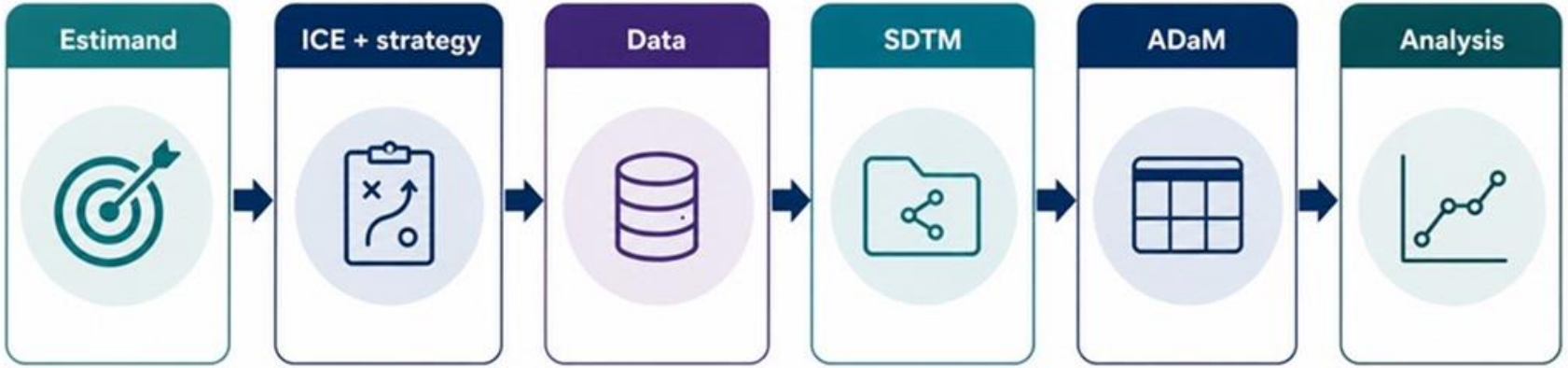
And yet …

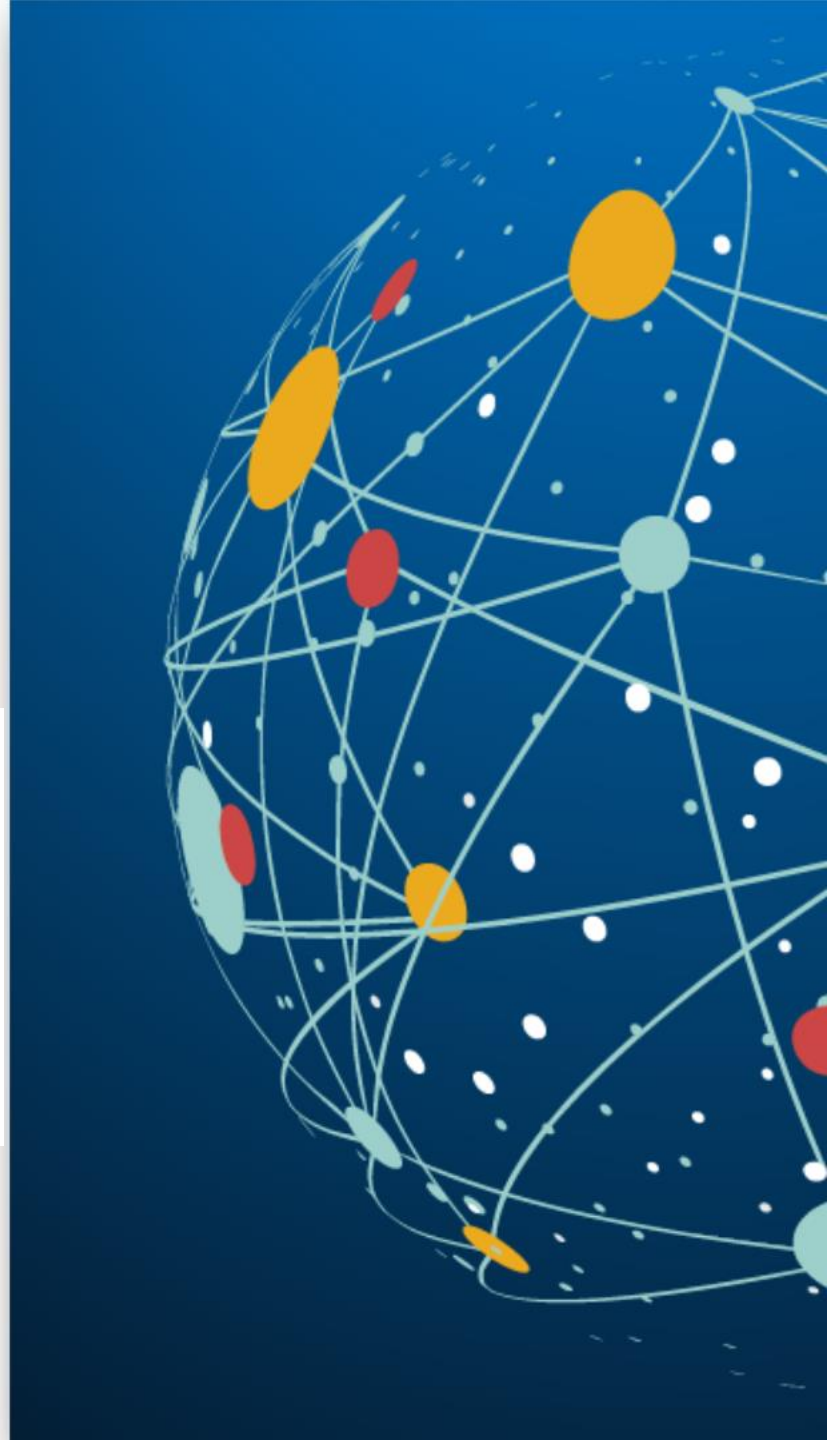
- Estimands are still:
  - inconsistently implemented,
  - hard to trace through datasets,
  - and sometimes re-defined unintentionally during analysis



Why We're Still Not Connected

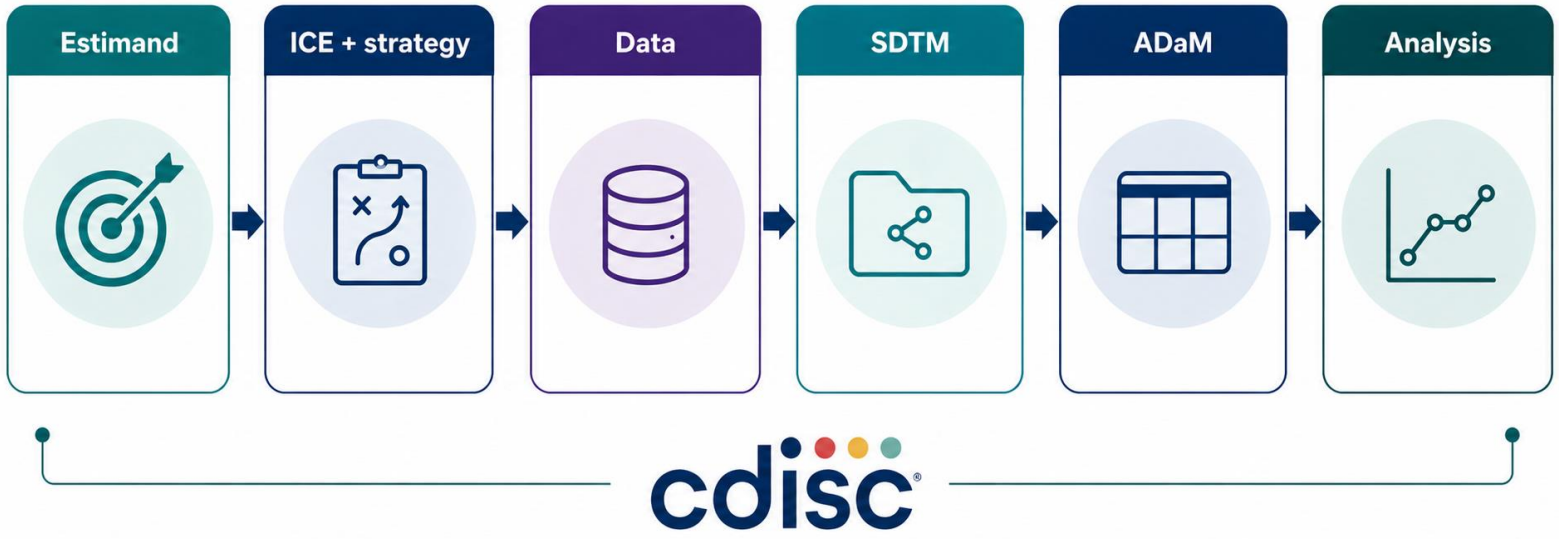
The uncomfortable truth...

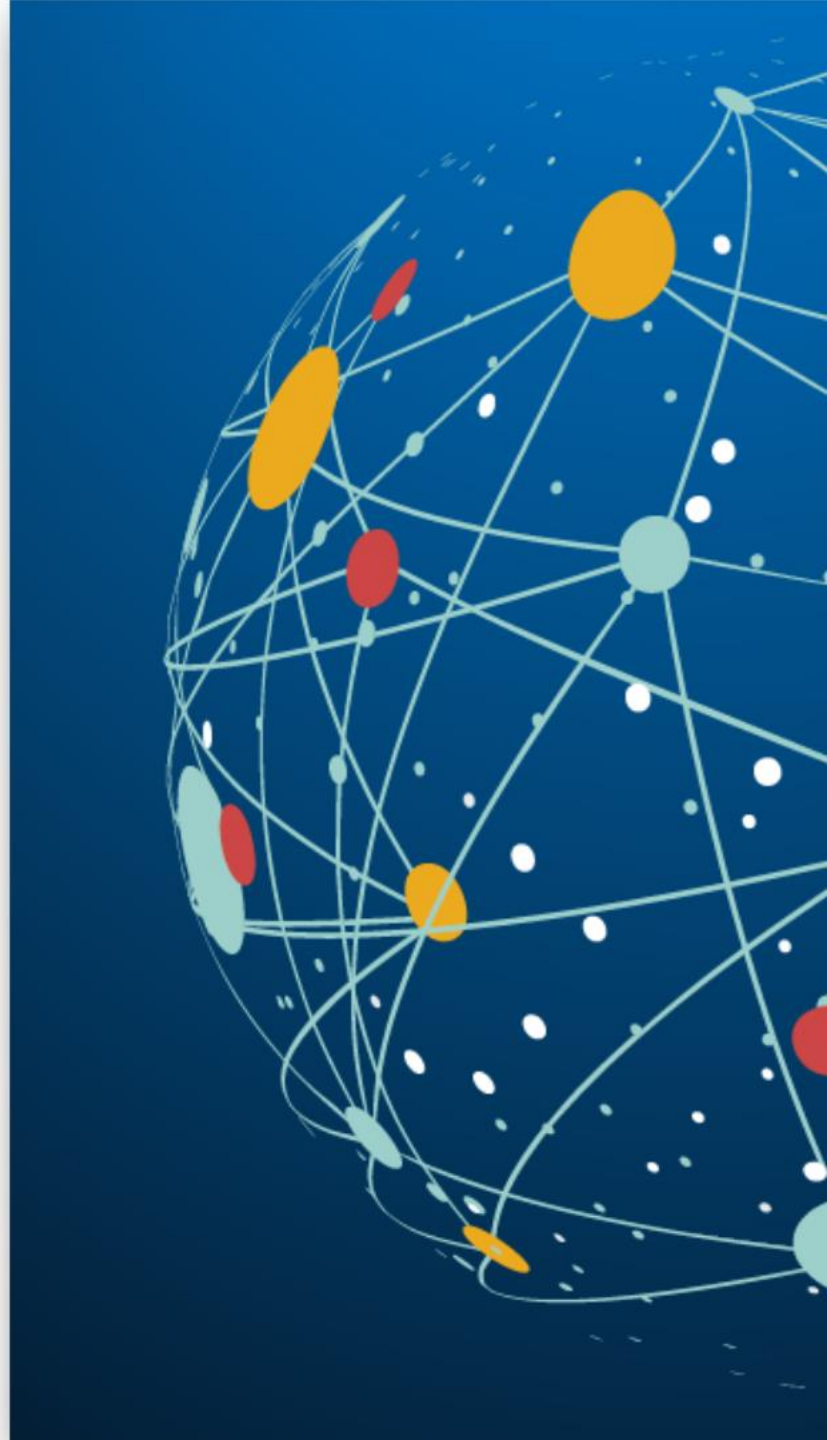




Why We're Still Not Connected

Why this matters...



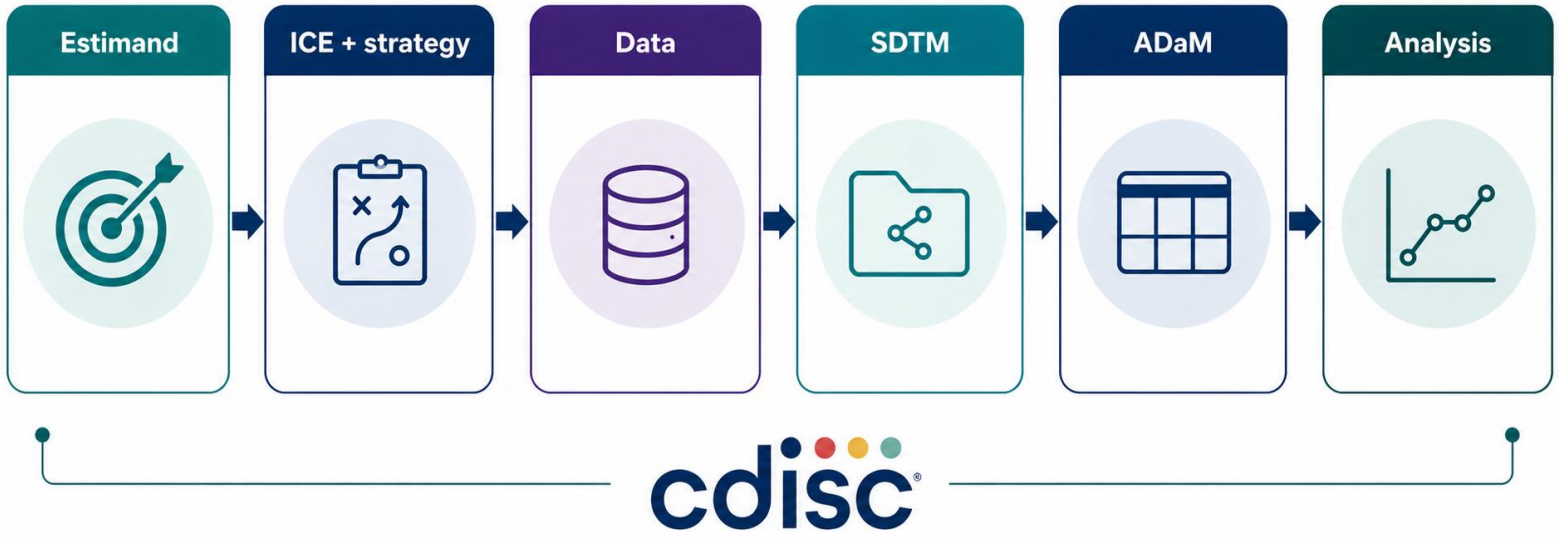


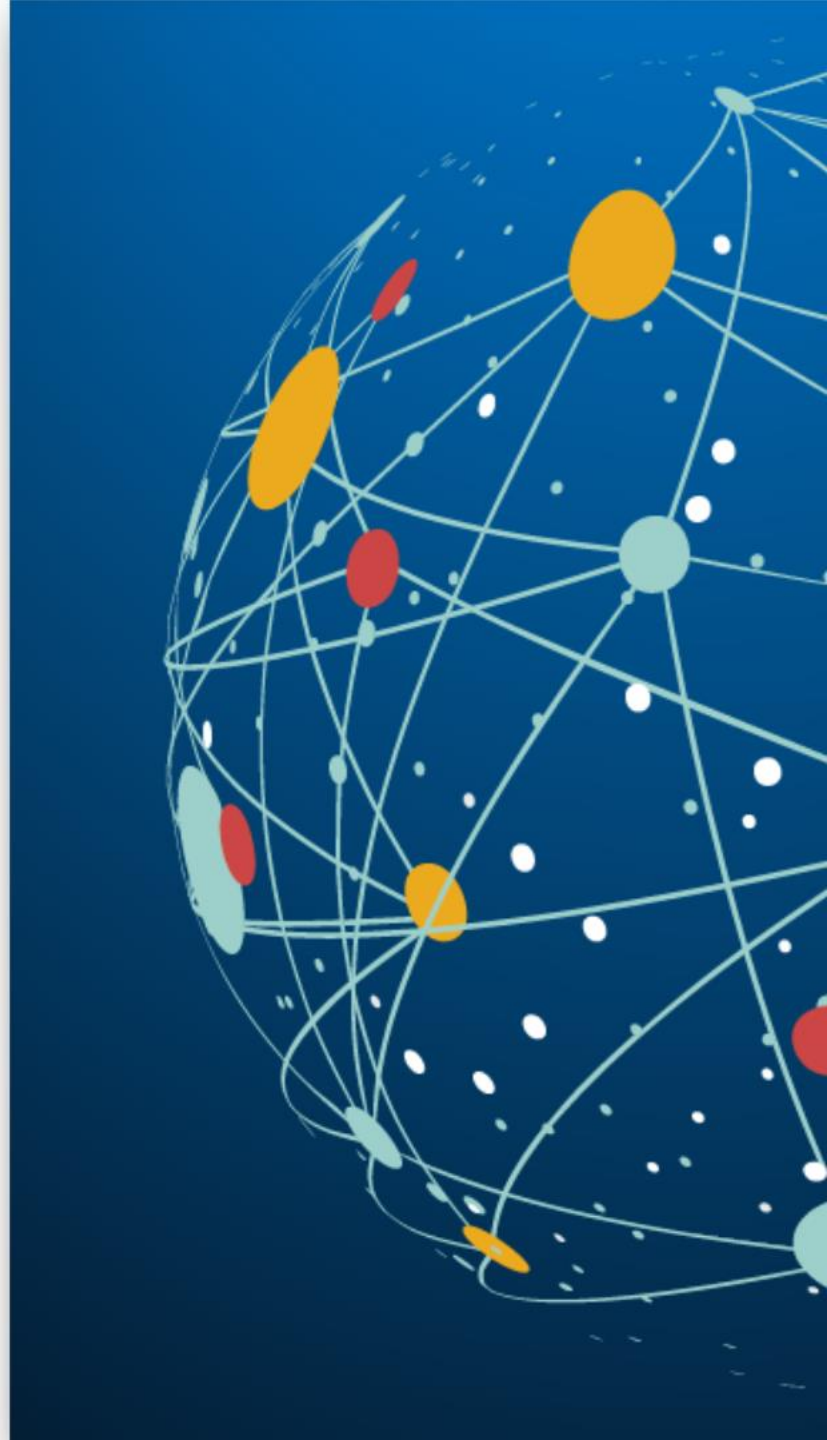
Why We're Still Not Connected

What this session is really about

Not redefining estimands, Not proposing another framework

But exposing where the gaps still exist

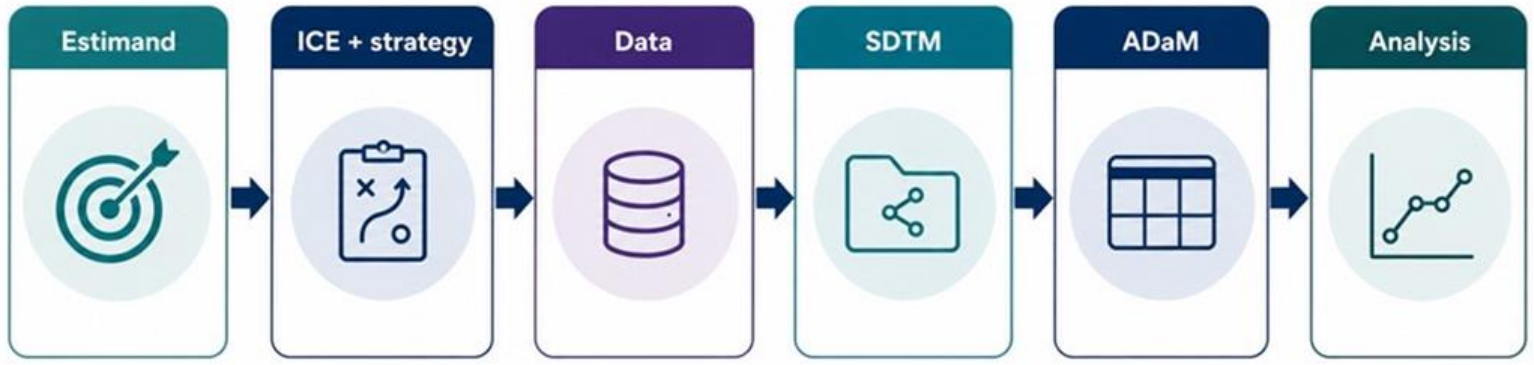


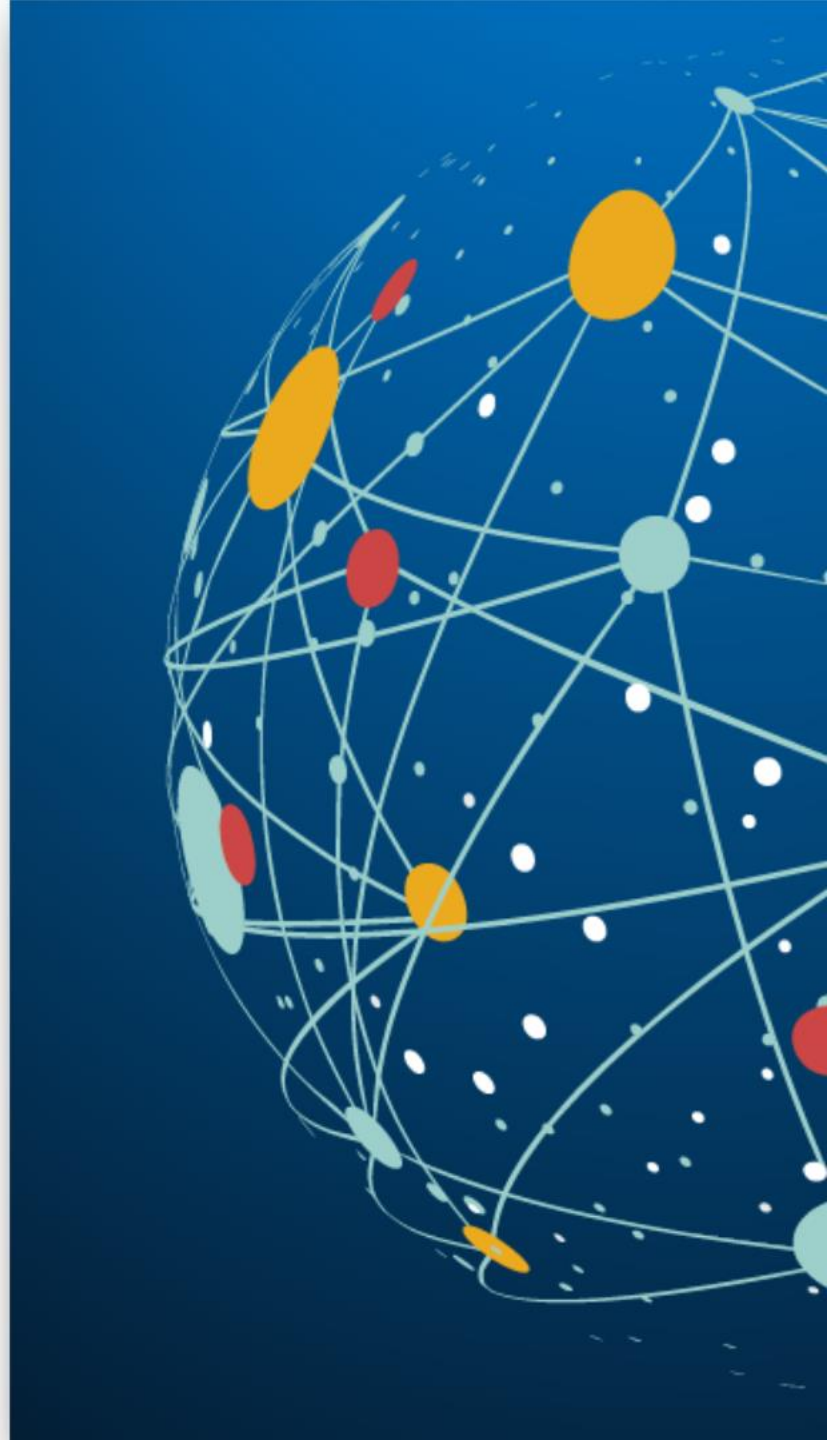


Why Estimands Still Feel “Disconnected”

Where The Disconnects Start

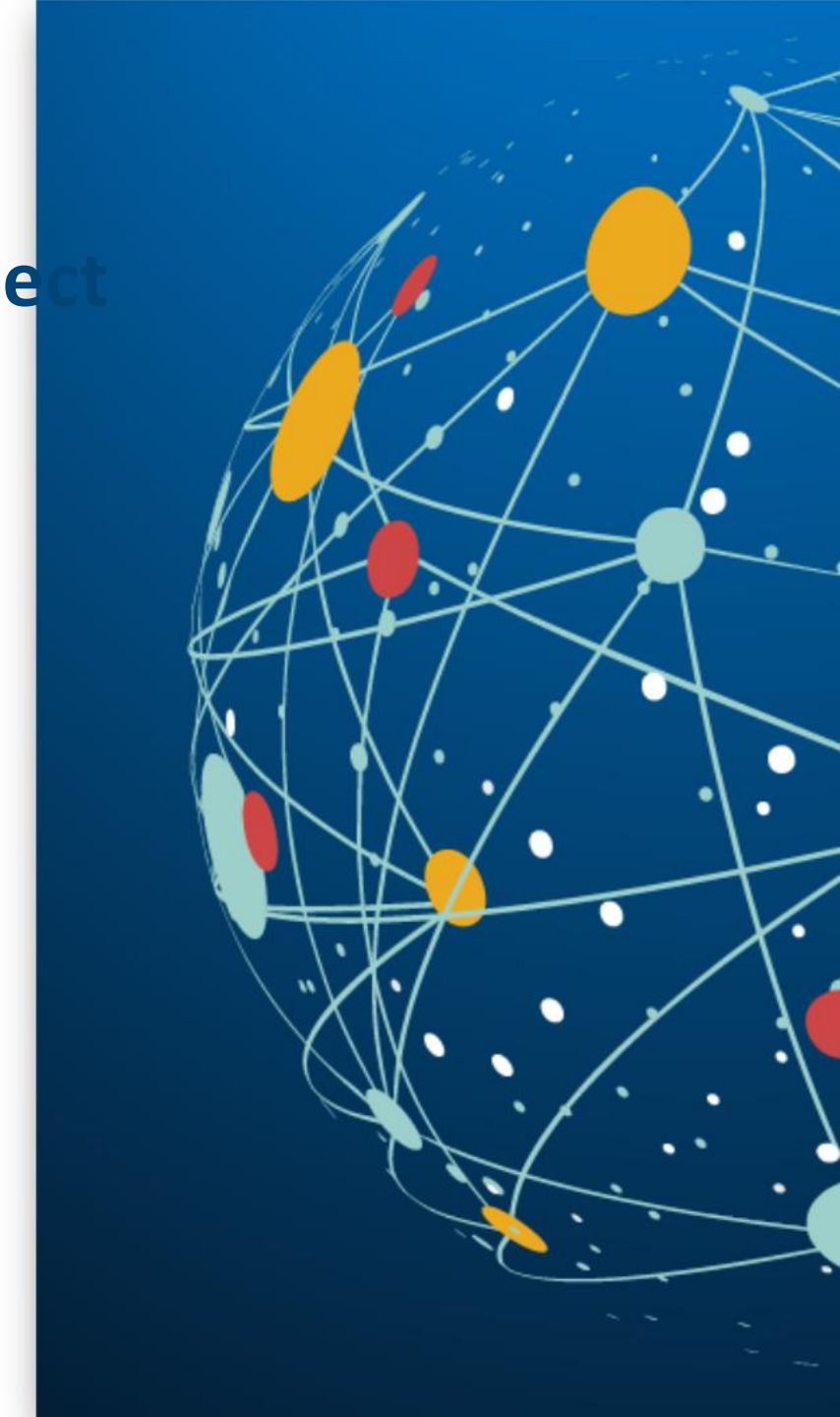
- Estimands exist on paper; implementation is fragmented
- Protocol intent ≠ what ends up in ADaM
- Ambiguity around intercurrent events
- Defaults quietly replace intent





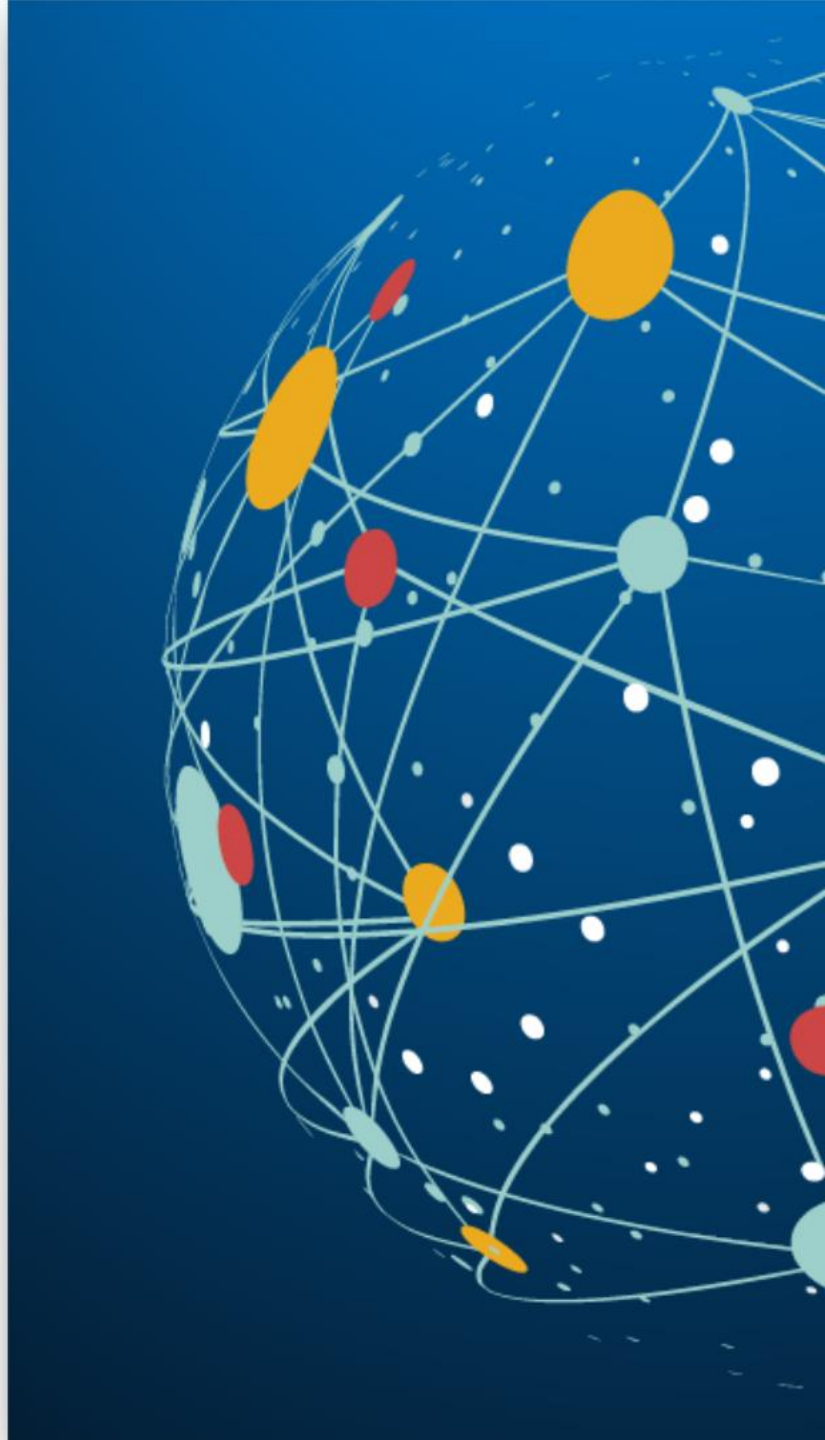
Common Misunderstandings That Drive Disconnect

- Estimand ≠ Estimator
- Estimand ≠ Endpoint
- Sensitivity ≠ New Estimands
- Assuming that all missing data is accounted for by the Estimand (result of an ICE)



Awareness ≠ Understanding

- Estimands mean different things to different roles
- Gaps remain even among experts
- Implementation requires role-specific understanding



What's Helping - And Why It's Not Enough

- ADICE is a major step forward and makes intercurrent events explicit
- Improves traceability across estimands
- Exposes real-world implementation complexity

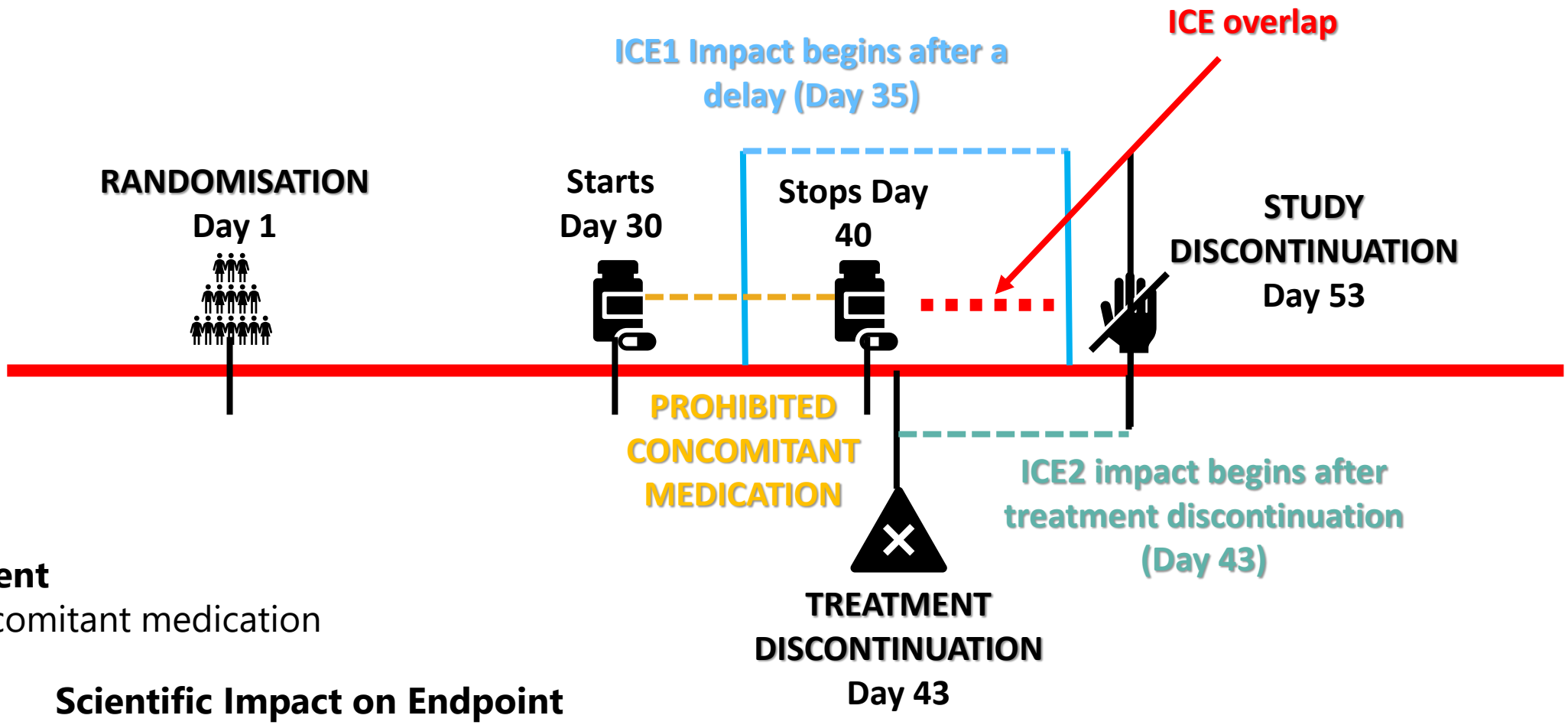
Row	USUBJID	ASEQ	ATERM	ADECOD1	ACAT1	VISIT	VISITNUM	ASTDT	AENDT	SRCDOM	SRCSEQ	EST01STP	EST02STP
1	ABC001	1	Started rescue medication	Starting other pharmacological treatment	Concomitant Medication	WEEK 4	5	2022-04-15		CM	12	TREATMENT POLICY	HYPOTHETICAL
2	ABC001	2	Treatment discontinued – AE	Treatment discontinuation due to AE	Treatment Discontinuation	WEEK 6	7	2022-04-29		DS	4	TREATMENT POLICY	HYPOTHETICAL
3	ABC002	1	Treatment discontinued – logistics	Treatment discontinuation due to logistical issues	Treatment Discontinuation	WEEK 2	3	2022-03-30		DS	3	TREATMENT POLICY	HYPOTHETICAL
4	ABC003	1	Started prohibited medication	Starting other pharmacological treatment	Concomitant Medication	WEEK 3	4	2022-04-06		CM	7	TREATMENT POLICY	HYPOTHETICAL
5	ABC003	2	Temporary interruption	Temporary treatment interruption	Treatment Interruption	WEEK 5	6	2022-04-20	2022-04-27	DS	5	TREATMENT POLICY	HYPOTHETICAL
6	ABC004	1	Treatment discontinued – AE	Treatment discontinuation due to AE	Treatment Discontinuation	WEEK 5	6	2022-04-20		DS	2	TREATMENT POLICY	HYPOTHETICAL
7	ABC004	2	Started rescue medication	Starting other pharmacological treatment	Concomitant Medication	WEEK 7	8	2022-05-04		CM	10	TREATMENT POLICY	HYPOTHETICAL
8	ABC005	1	Lack of efficacy	Treatment discontinuation due to lack of efficacy	Treatment Discontinuation	WEEK 4	5	2022-04-13		DS	6	TREATMENT POLICY	HYPOTHETICAL
9	ABC005	2	Dose reduction	Treatment dose modification	Dose Modification	WEEK 6	7	2022-04-27		DS	9	TREATMENT POLICY	HYPOTHETICAL

PSI Workshop 2024
ICH E9(R1)

Why Implementation Gets Hard

Overlapping Intercurrent Events Reveal Hidden Complexity

Intercurrent Event Timing vs Impact Window



Intercurrent Event

- Prohibited concomitant medication
- Start: **Day 30**
- Stop: **Day 40**

Scientific Impact on Endpoint

- ICE1 begins **after a delay** (Day 35 through Day 47)
- ICE2 impact begins **after treatment discontinuation date on Day 43** (through Day 53)
- Impact of **treatment discontinuation** persists until **study discontinuation** (NO FOLLOW-UP)

Analysis Datasets – Impact Variable Example and Details

per intercurrent event categorisation modalities

USUBJID	ASEQ	ATERM	ADECOD1	ACAT1	ASTDT
ABC003	1	ANTIDEPRESSANT	Starting other pharmacological treatments	Starting other pharmacological treatments	2022-04-06
ABC003	2	LACK OF EFFICACY	T…ent discontinuation due to lack of efficacy	Treatment discontinuation due to lack of efficacy	2022-04-27

USUBJID	PARAMCD	ADT	AVISIT	AVAL	BASE	CHG	ICC1	ICC2S	ICCDOM	ICCVAR	ICC1F	ICC2F	ICC1N	ICC2N
ABC003	HAMD118	2022-03-16	BASELINE	26	26					ASEQ				
ABC003	HAMD118	2022-03-23	WEEK 1	21	26	-5			ADICE	ASEQ				
ABC003	HAMD118	2022-03-30	WEEK 2	19	26	-7			ADICE	ASEQ				
ABC003	HAMD118	2022-04-06	WEEK 3	16	26	-10			ADICE	ASEQ				
ABC003	HAMD118	2022-04-13	WEEK 4	19	26	-7	1		ADICE	ASEQ	Y		1	
ABC003	HAMD118	2022-04-20	WEEK 5	15	26	-11	1		ADICE	ASEQ	Y		1	
ABC003	HAMD118	2022-04-27	WEEK 6	21	26	-5	1		ADICE	ASEQ	Y		1	
ABC003	HAMD118	2022-05-04	WEEK 7	18	26	-8	1	2	ADICE	ASEQ	Y	Y	1	1
ABC003	HAMD118	2022-05-25	WEEK 8	16	26	-10	1	2	ADICE	ASEQ	Y	Y	1	1

Based on ACAT1 categories

Source domain and source variable

Flag variables

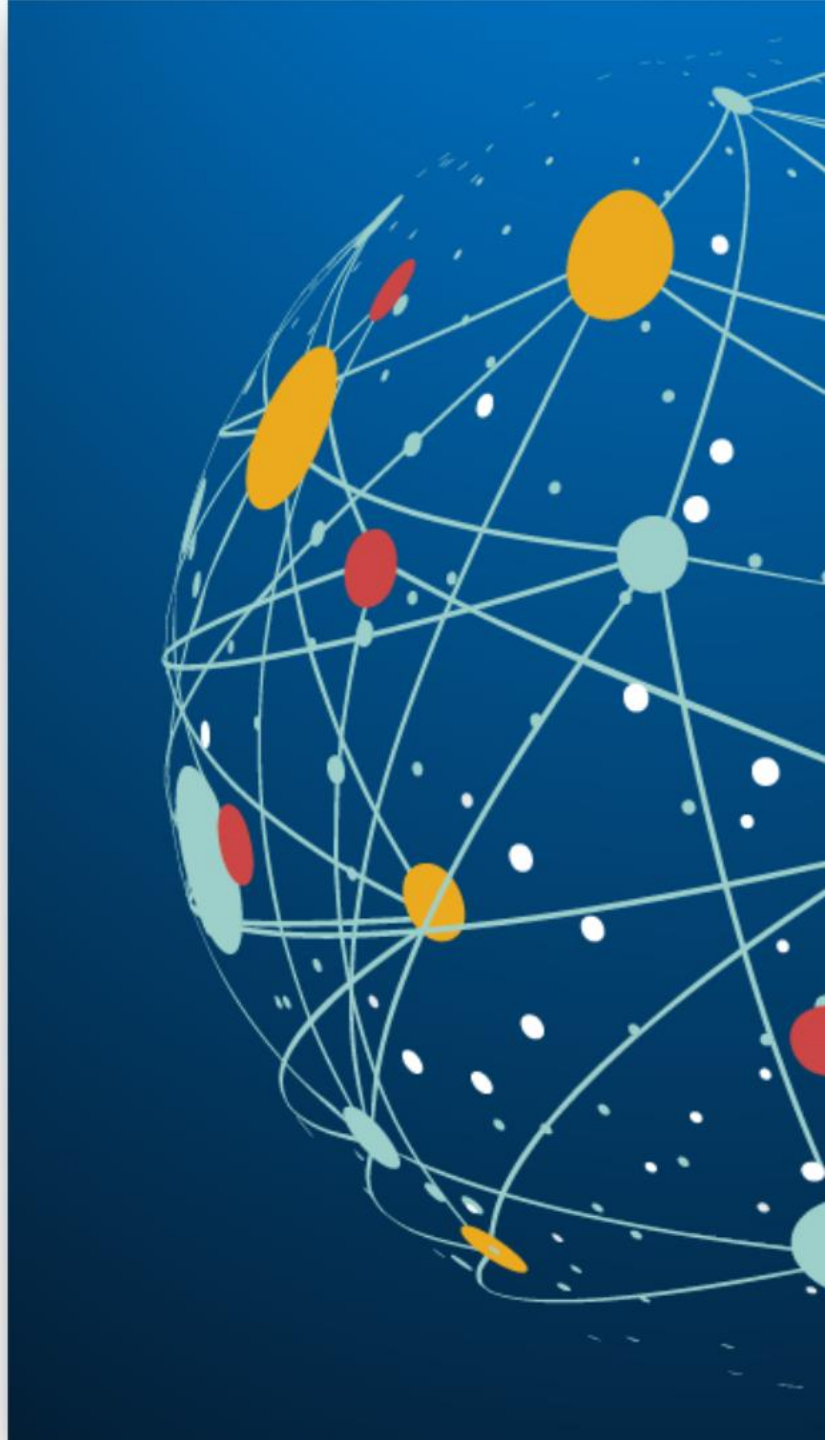
Same Estimand, Different Action

ICE strategies say what questions we are answering

Estimators say what we do with the data to answer it

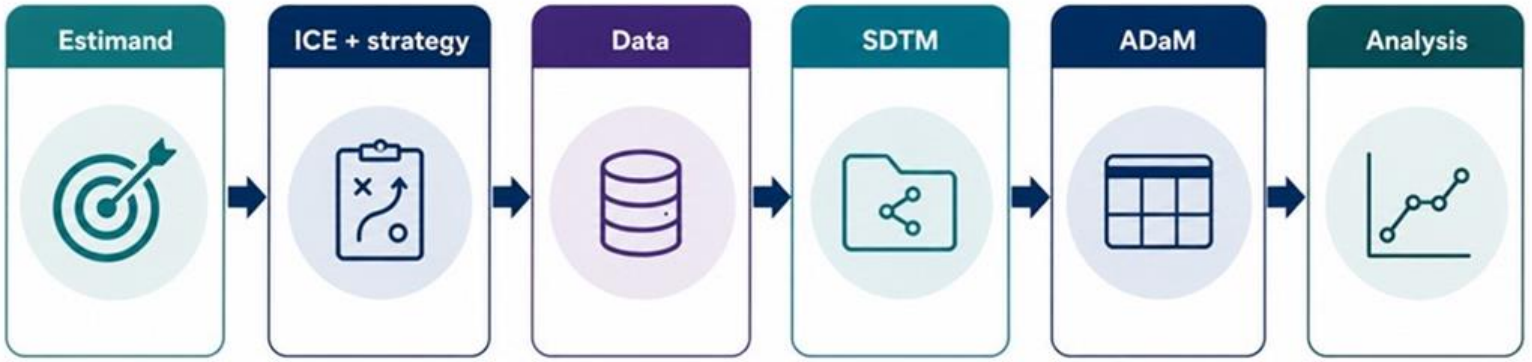
Are the actions a function of the “estimator” and not the estimand?

- One estimand
- Multiple valid estimators
- Very different data actions
- Estimand remains fixed



The Core Problem

Estimands don’t usually fail in theory.
They fail when intent, data, and implementation drift apart.



Where The Dots Actually Are In The Lifecycle

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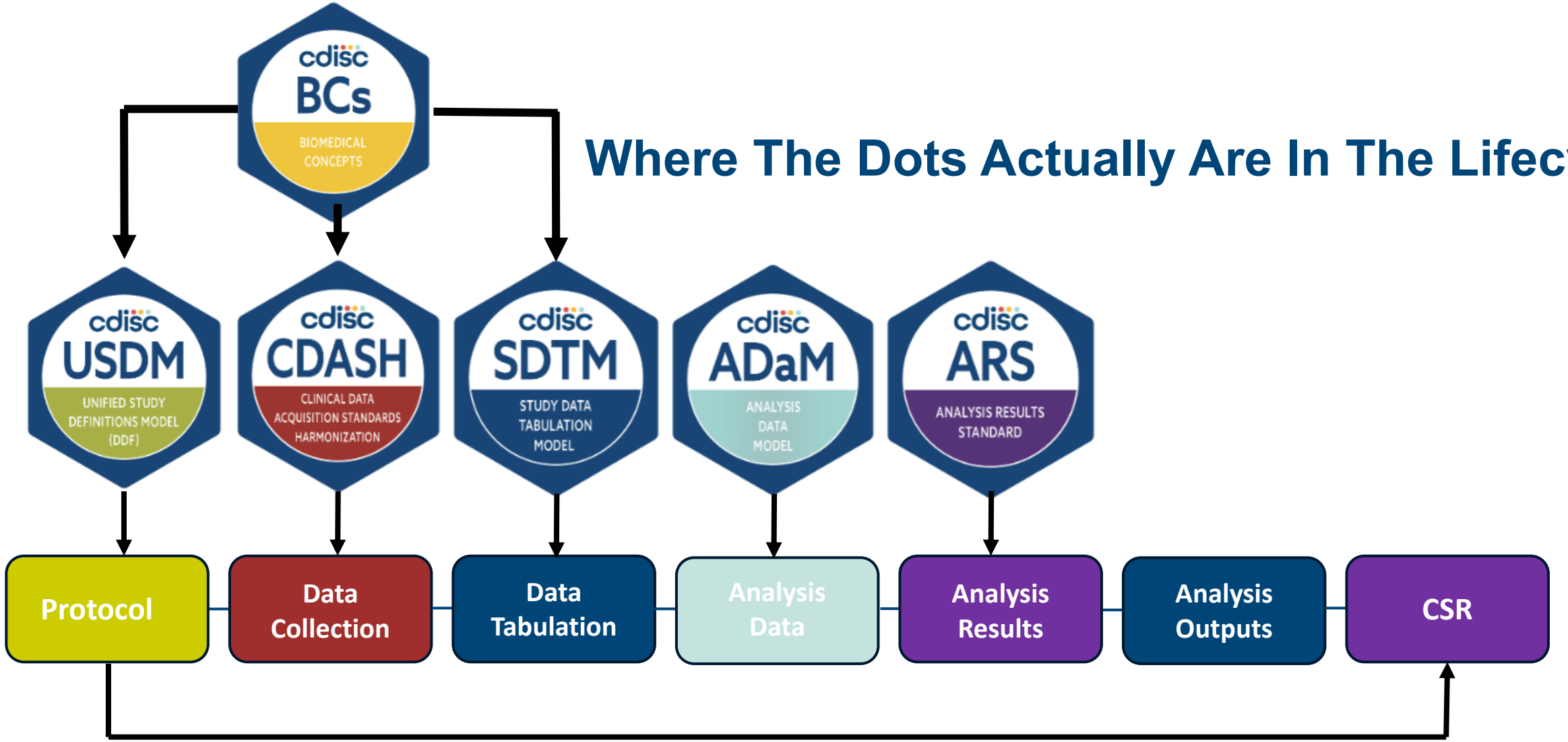
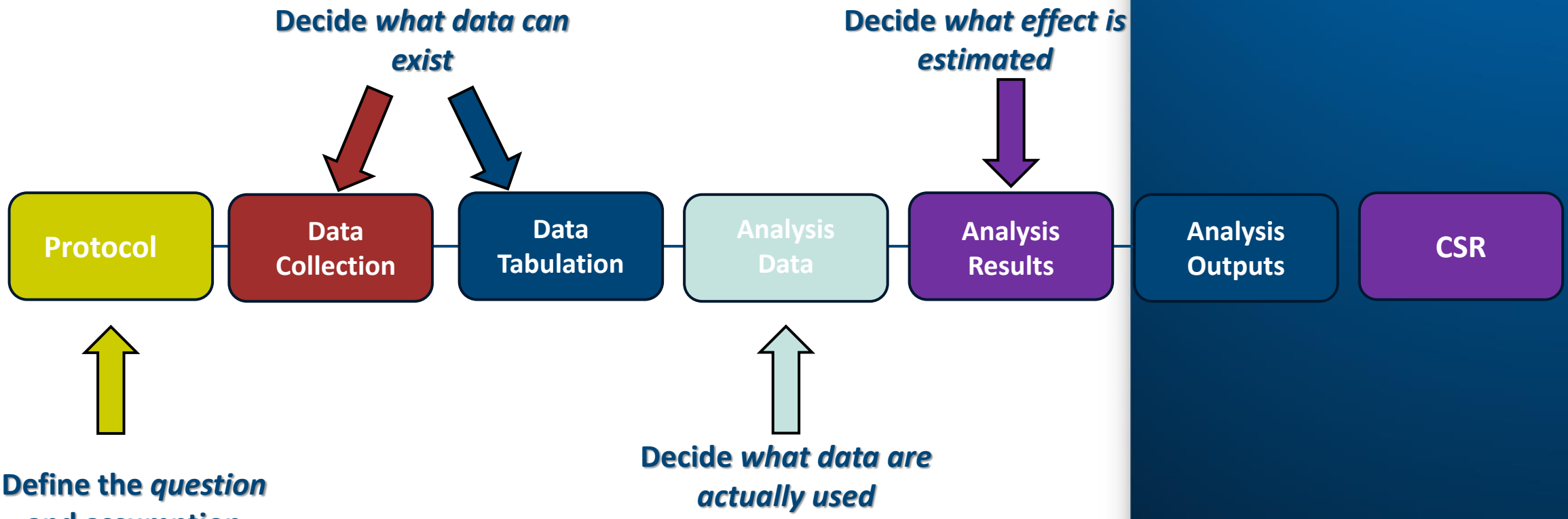
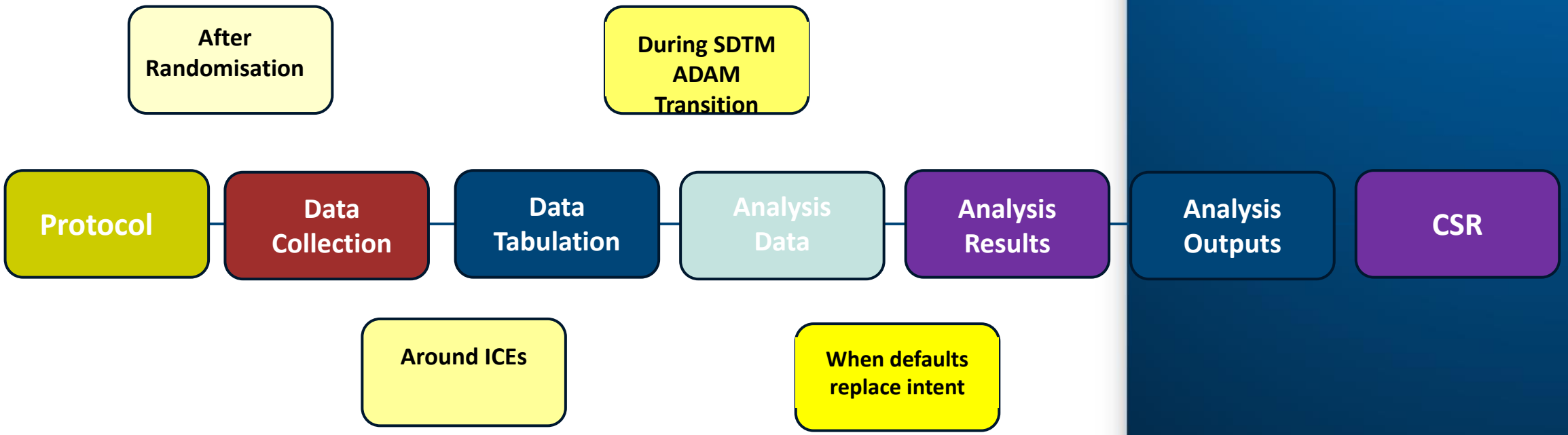


Where The Dots Actually Are In The Lifecycle
What Each Stage Really Does To The Estimand



Where The Dots Actually Are In The Lifecycle

Where Gaps Typically Appear



Implementation Reality:

What's Working Vs What's Messy

Implementation Reality:

What's Working Vs…

- Strong traceability across SDTM → ADaM
- Structured datasets that support reproducibility
- Clear population-level flags (e.g. FAS vs PP)
- Increasing consistency across studies and vendors

Implementation Reality:

…What's Messy

Traceability does not always equal interpretability

Record-level exclusions cause major confusion
- some teams expect records to be dropped
- statisticians need them set to missing and handled via estimand strategy

Order-of-operations ambiguity
- impute then subset?
- subset then impute?
- pool studies before or after imputation?

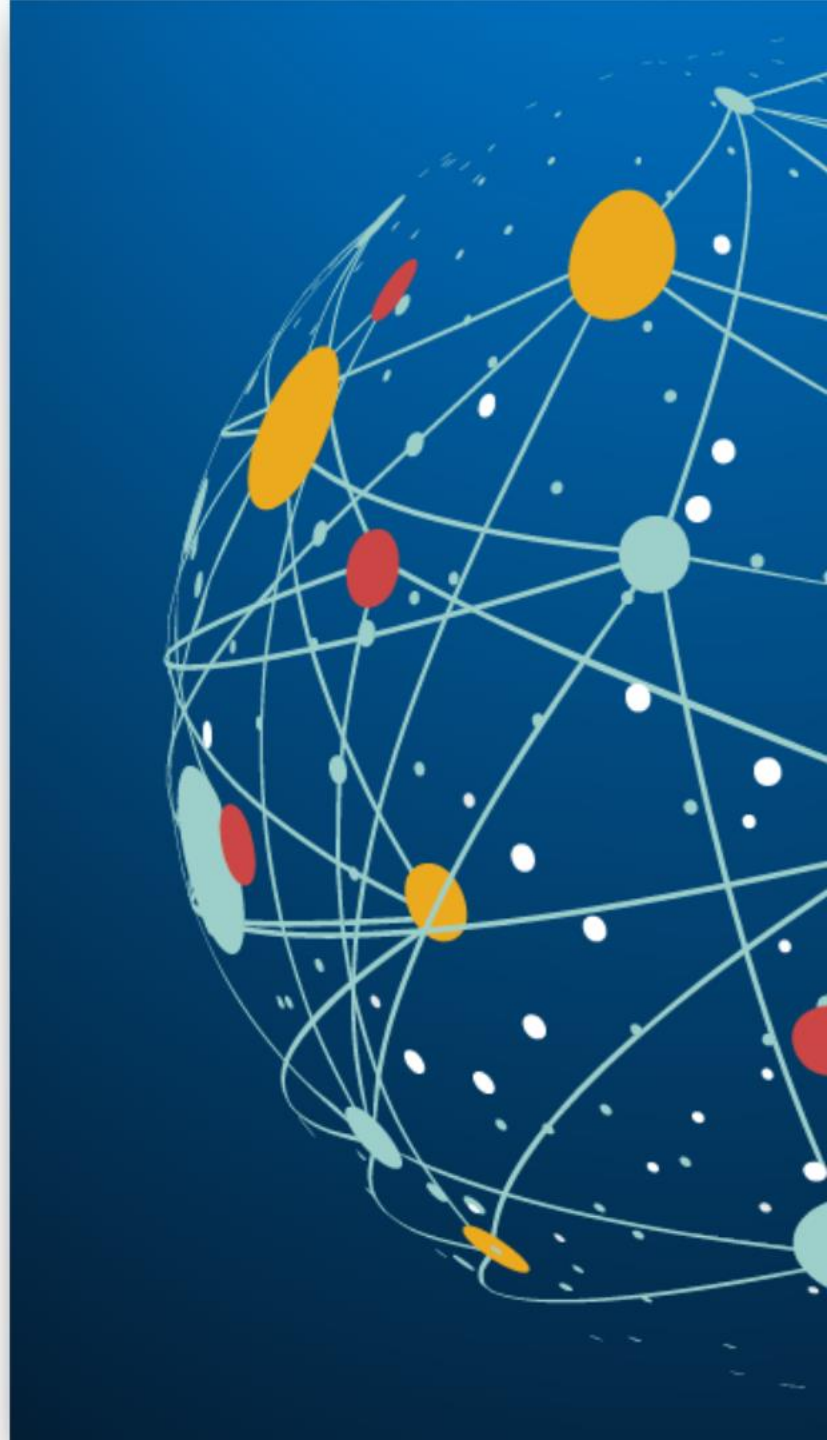
Same intercurrent event handled differently depending on:
- estimand
- endpoint
- efficacy vs safety objective

Where Implementation Becomes Fragile

Implementation Reality:
Communication Breakdown

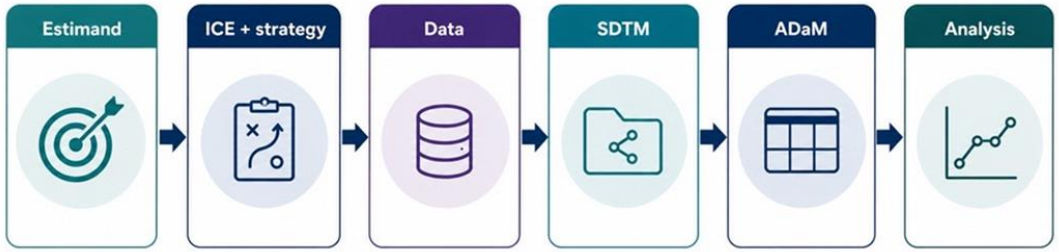
Communication Gaps Between Statistics and Programming

- Analysis datasets often not self-documenting
- Variable labels and flags are too subtle
- Estimand flags differ by non-intuitive suffixes
- Errors don’t “jump off the page” during review



Implementation Reality:
Why This Matters

- ADaM does not just reflect the estimand
- ADaM encodes the estimand
- Small data decisions can silently redefine the treatment effect



Estimands are implemented through data decisions, not words

If your SDTM and ADaM don't align, the estimand in your protocol is not the estimand you are analysing

Future State:

What “Connected” Estimands Could Look Like
And What Teams Can Do Now

From Discussion to Action: What Teams Can Do Now

Study Teams

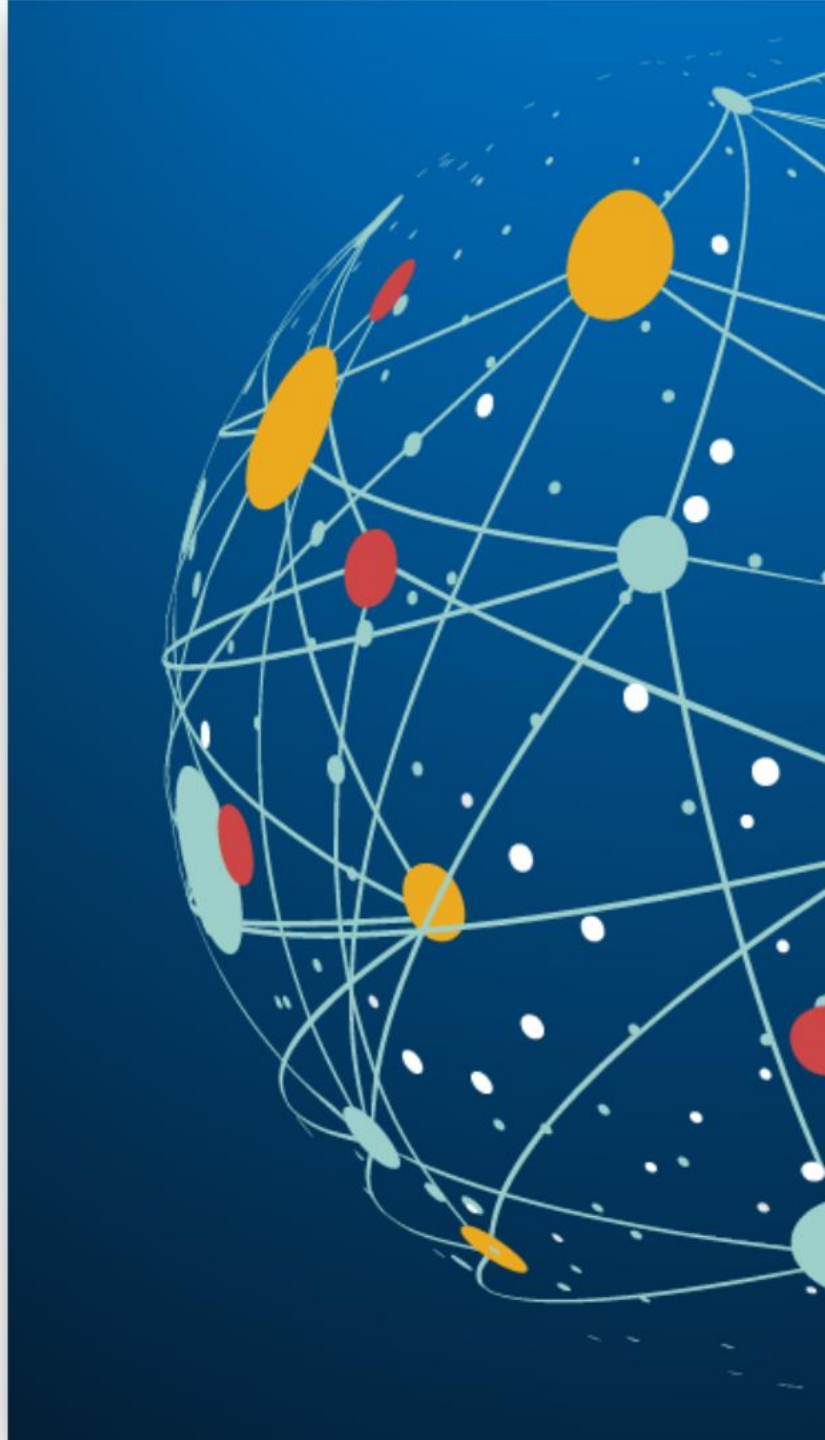
- Finalise estimand before CRF/SDTM
- Capture ICEs explicitly
- Distinguish *treatment discontinuation* vs *study withdrawal*

Statisticians

- Align estimand wording with inclusion rules
- Avoid default *while-on-treatment* without justification
- Plan sensitivity around missingness, not convenience

Programmers

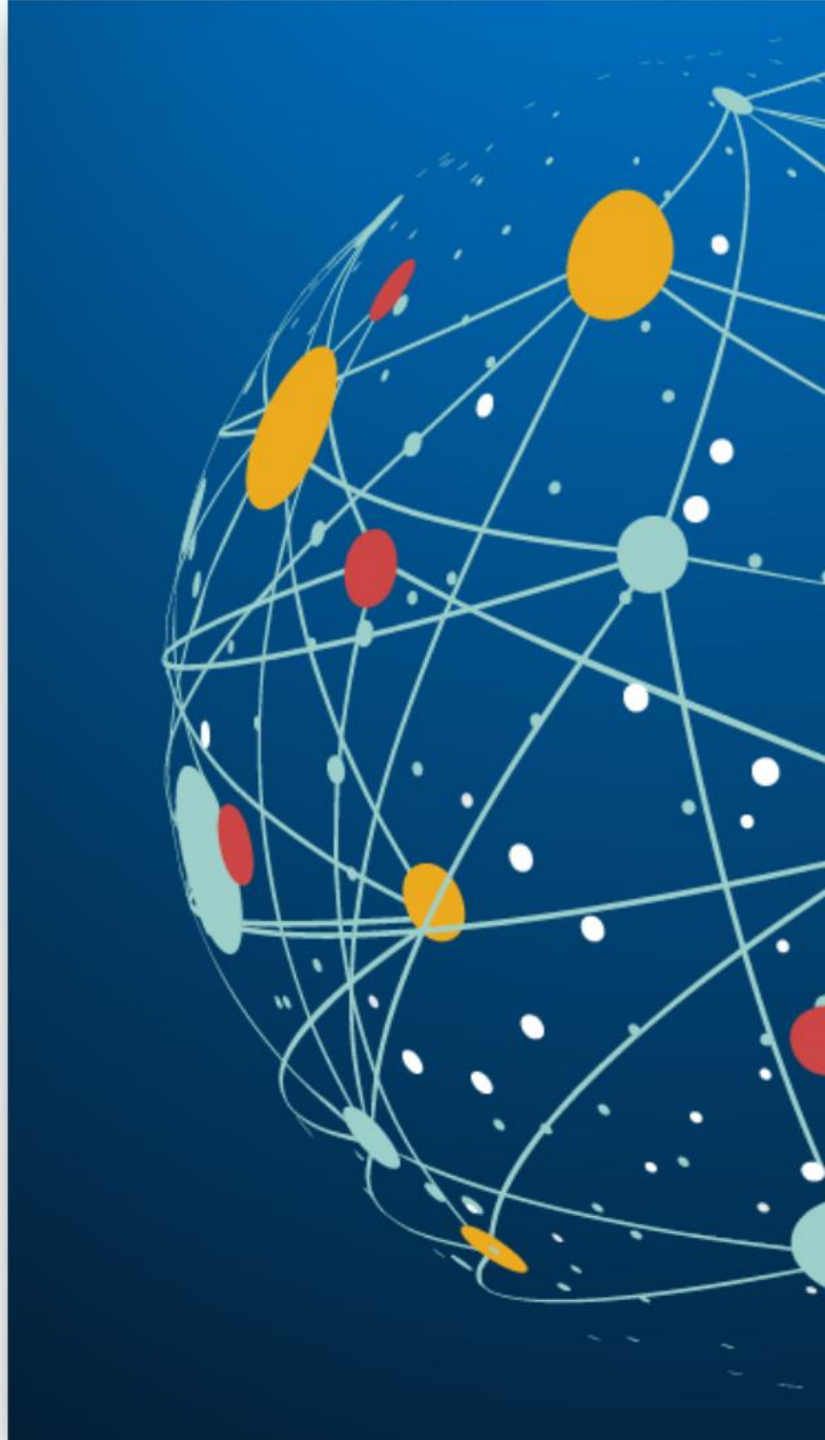
- Demand explicit include/exclude rules
- Tie flags directly to estimands
- Build traceability: estimands → variables → flags



Ravel et al., 2026

Estimands Are Now A Reporting Expectation

- Regulators require estimands globally
- SPIRIT & CONSORT explicitly reference estimands
- ICH E9(R1) defines *what* is estimated
- ICH E3 defines *how* results are reported, but predates estimands



Estimands must be defined, implemented, and reported coherently across the full trial lifecycle

Kahan et al., 2024
Chan et al., 2025
Hopewell et al., 2025
ICH E3
ICH E9(R1)

Regulatory Feedback

Hypothetical Strategy for a Primary Estimand

- Phase III, Rare disease, confirmatory setting
- Hypothetical strategy proposed for treatment discontinuation
- ~40 weeks individual study duration
- Limited or no follow-up after discontinuation
- Regulatory concern raised:
  hypothetical strategies are rarely of interest for primary analyses in confirmatory settings

Estimand choice must be supported by trial design and data collection

Flemming et al., 2025
Estimands and regulatory interaction – APF Workshop, Hiller, November 2025

Regulatory Feedback

Hypothetical Strategy for Rescue Medication

- Placebo-controlled Phase III study
- Chronic disease with available SoC
- Hypothetical strategy used for rescue medication
- ~800 participants
- ~15 weeks
- Post-ICE data collected but excluded from analysis
- Regulators requested treatment-policy analysis

Collecting data is not enough, how it is used defines the estimand

Regulatory Feedback

Composite Strategy for Death in Oncology

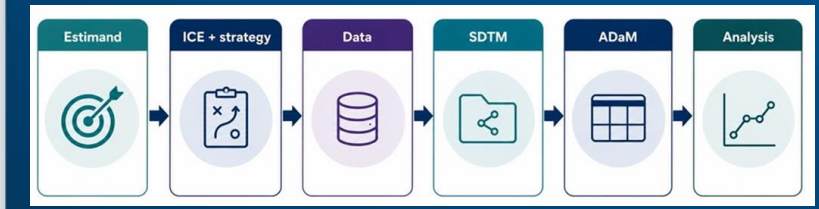
- Oncology Phase II/III study
- Experimental intervention vs. placebo + background systemic anticancer therapy
- Complex handling proposed for death
- ~300 participants
- ~12 weeks
- Cause-specific imputation rejected
- Worst-outcome composite recommended

Some intercurrent events require clinical, not hypothetical, handling

Regulatory Feedback

What These Regulatory Examples Tell Us

- Estimands are assessed end-to-end
- Trial design and data collection determine what can be estimated
- Hypothetical strategies face high scrutiny as primary estimands
- Implementation details silently redefine estimands



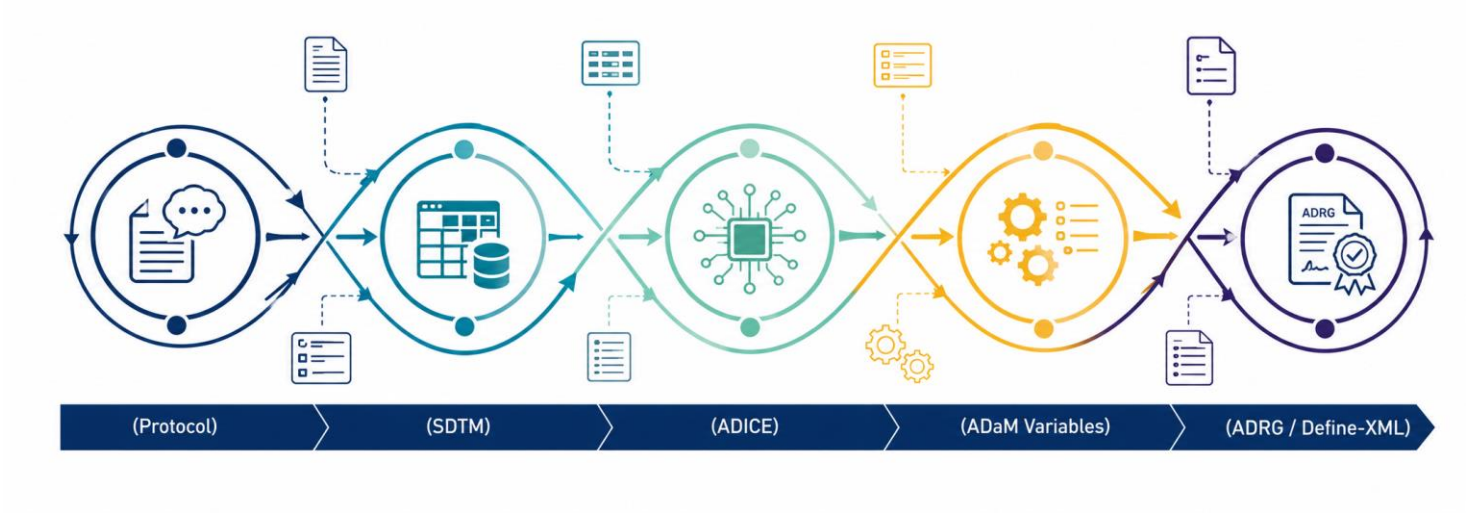
Regulatory feedback is where estimands are tested in practice

Estimands Are End-to-End: The Chain Must Stay Intact

Small choices at any step can change what is estimated:

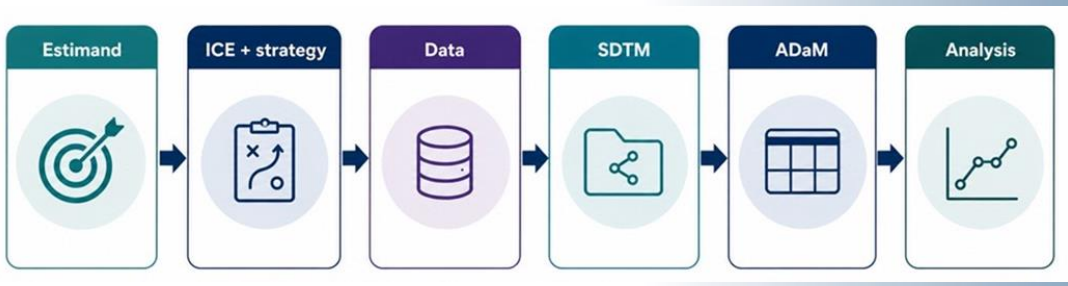
Estimand implementation is no longer a downstream activity.

- It shapes protocol objectives and ICE strategies
- It determines what data must be collected and when
- It governs how SDTM and ADaM are constructed
- It ultimately defines what effect is estimated



The goal isn't complexity - it's coherence.

The Physical Manifestation of Clinical Intent



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Questions?

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