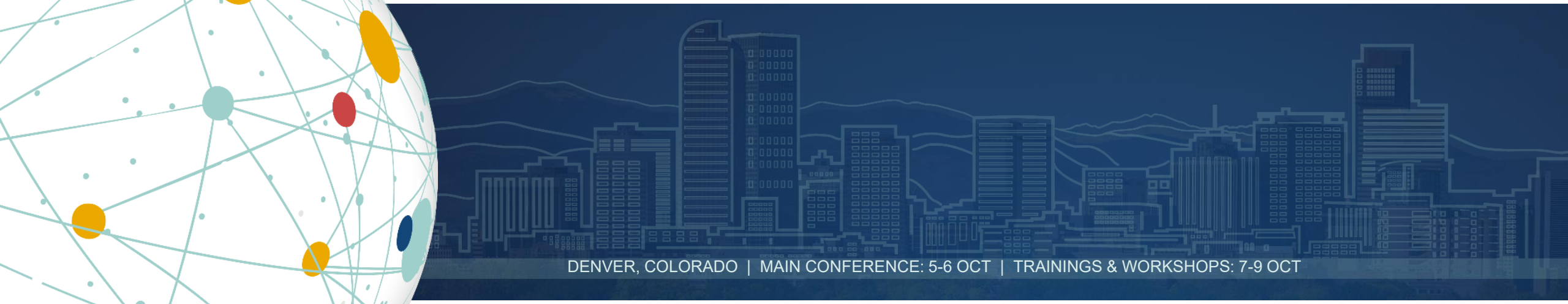


2026 US Interchange

THE FUTURE IS CONNECTED: STANDARDS AND AI POWERING DIGITAL TRANSFORMATION



Seeking Validation: Verified or Truly Vetted? Challenges on the Path to Regulatory Approval

Julie Ann Hood, Principal CDISC Consultant, Pinnacle 21 by Certara

Agenda

1. Introduction of the Illusion
2. The Pledge: Artifact
3. The Turn: Relationship
4. The Prestige: Evidence

Speaker



1. **Julie Ann Hood**
2. Principal CDISC Consultant
3. Pinnacle 21 by Certara

Julie Ann Hood is a Principal CDISC Consultant at Pinnacle 21 by Certara, where she contributes to thought leadership, product training, data quality initiatives, and regulatory submission review. She also serves as an FDA subcontractor, providing Data Fitness Analyst support to CBER and CDER.

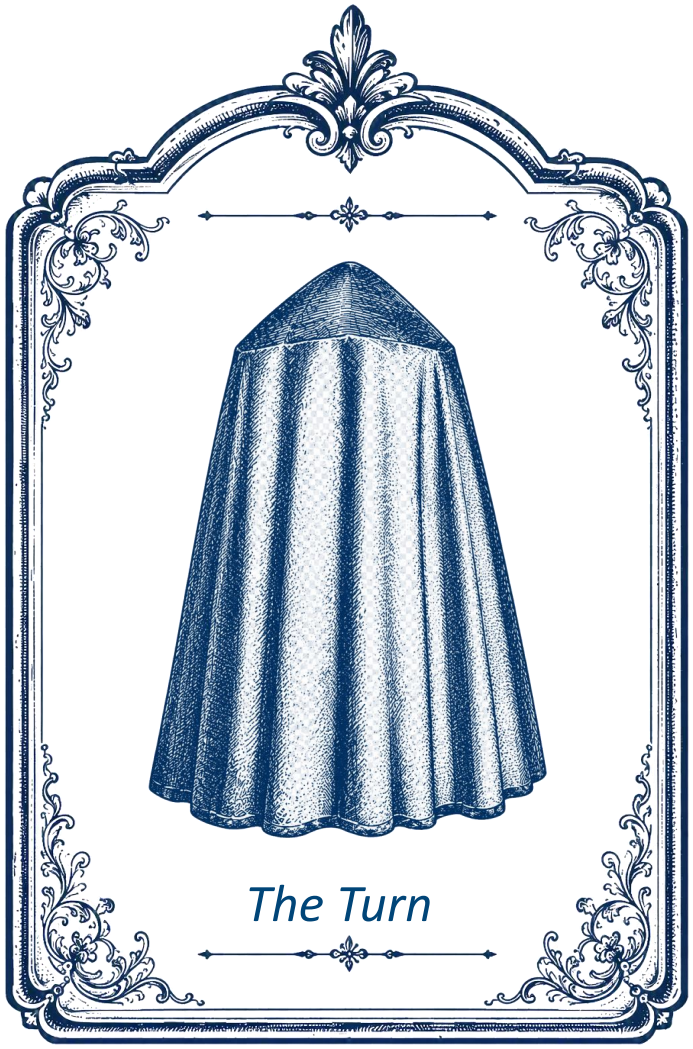
Her professional journey began with preclinical drug development research at the Research Institute on Addictions. After completing the Behavioral Neuroscience program at the University at Buffalo, she earned a master's degree in psychology. Throughout her career, she has developed broad, practical experience across the submission lifecycle, spanning preclinical research, clinical data management, and clinical and nonclinical data standards. She is actively involved in standards development initiatives and regularly speaks at industry conferences.

Disclaimer and Disclosures

- *The views and opinions expressed in this presentation are those of the author and do not necessarily reflect the official policy or position of CDISC, Certara, or FDA.*

The Parts of a Magic Trick





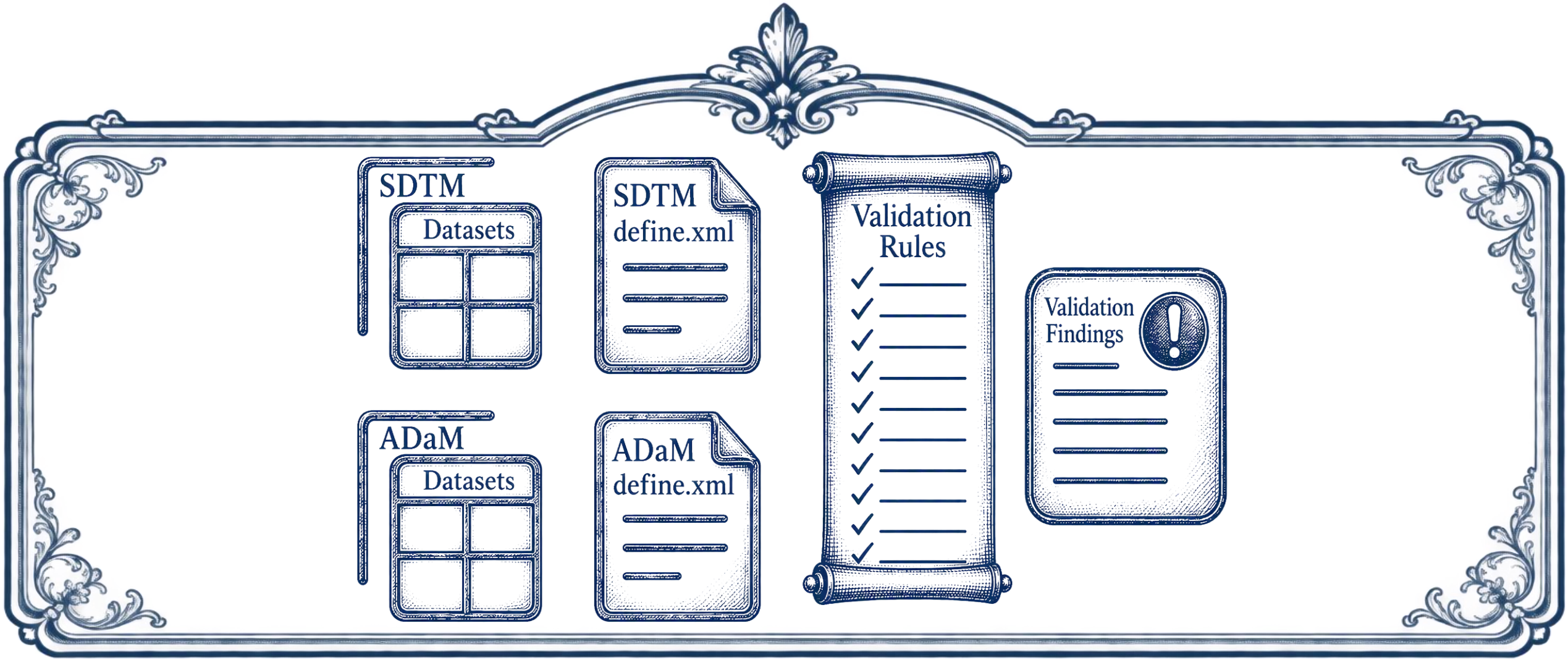


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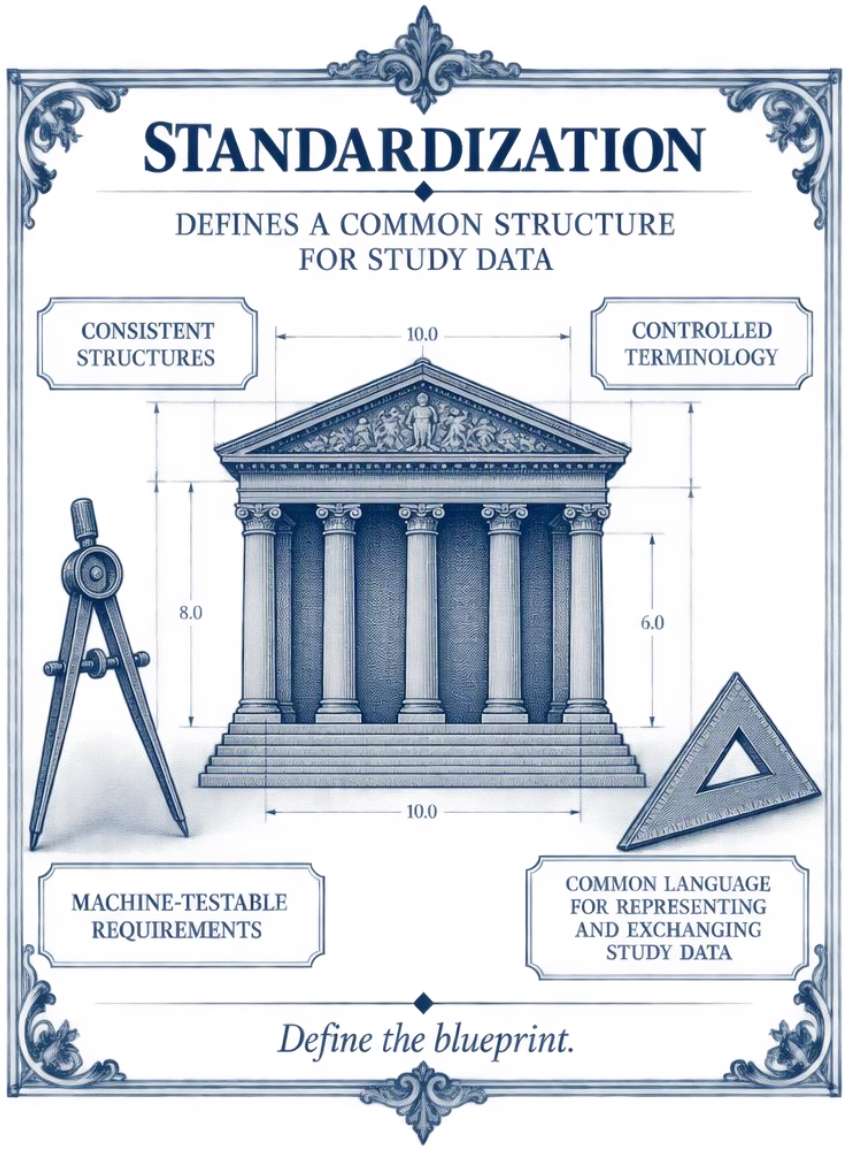
The Pledge

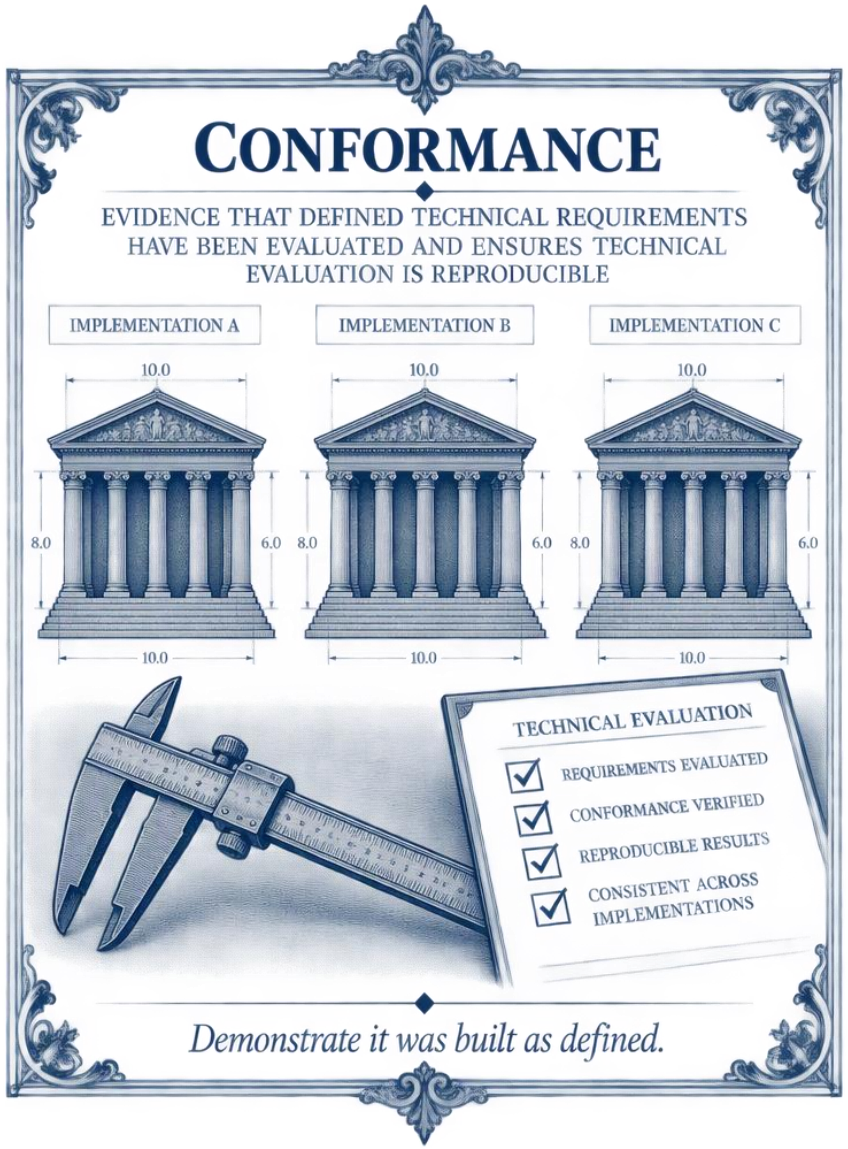


The Pledge

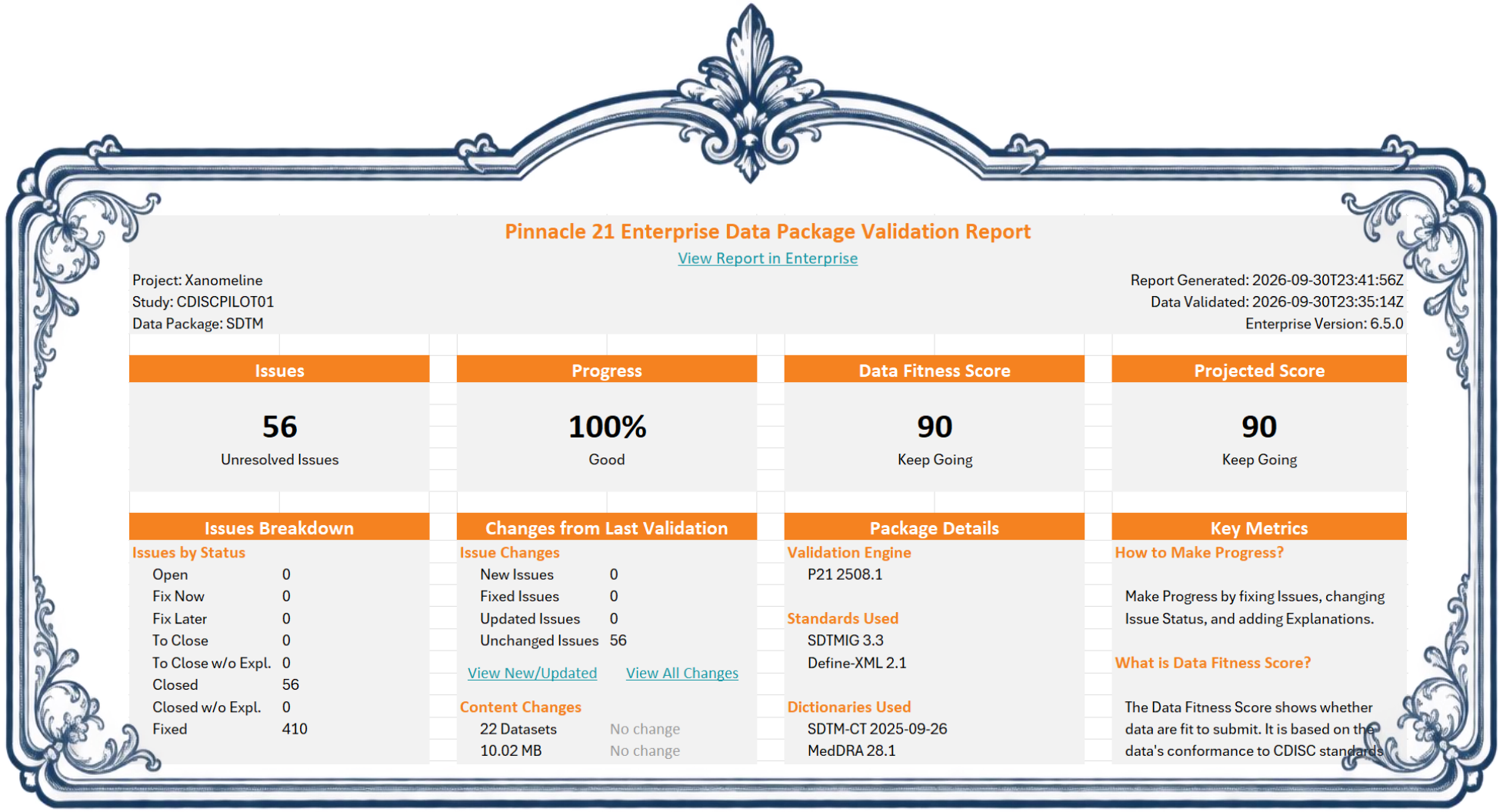

SDTM
Datasets
SDTM
define.xml
Validation
Rules
Validation
Findings
ADaM
Datasets
ADaM
define.xml

What Standardization and Conformance Give Us





A Realistic Validation Report



Pinnacle 21 Enterprise Data Package Validation Report

View Report in Enterprise

Project: Xanomeline
Study: CDISCPILOT01
Data Package: SDTM

Report Generated: 2026-09-30T23:41:56Z
Data Validated: 2026-09-30T23:35:14Z
Enterprise Version: 6.5.0

Issues	Progress	Data Fitness Score	Projected Score
56	100%	90	90
Unresolved Issues	Good	Keep Going	Keep Going

Issues Breakdown

Issues by Status

Open	0
Fix Now	0
Fix Later	0
To Close	0
To Close w/o Expl.	0
Closed	56
Closed w/o Expl.	0
Fixed	410

Changes from Last Validation

Issue Changes

New Issues	0
Fixed Issues	0
Updated Issues	0
Unchanged Issues	56

View New/Updated View All Changes

Content Changes

22 Datasets	No change
10.02 MB	No change

Package Details

Validation Engine
P21 2508.1

Standards Used
SDTMIG 3.3
Define-XML 2.1

Dictionaries Used
SDTM-CT 2025-09-26
MedDRA 28.1

Key Metrics

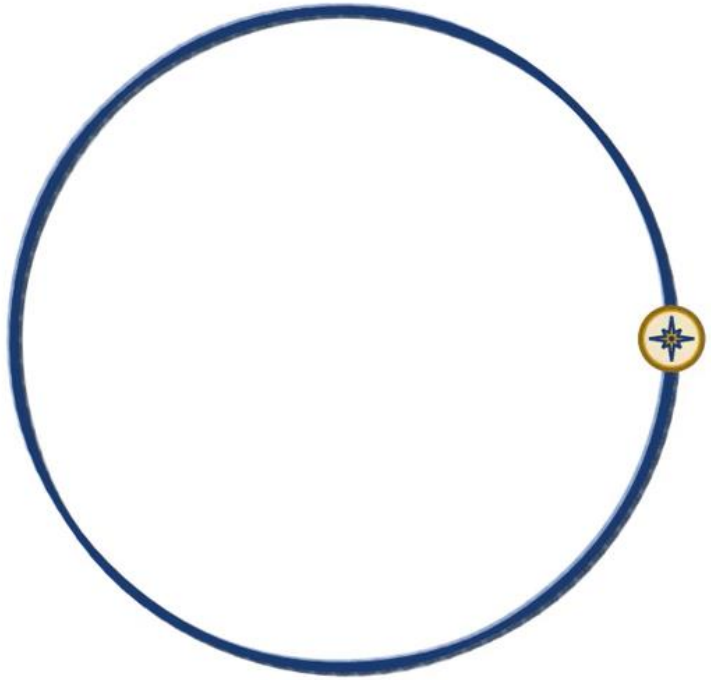
How to Make Progress?

Make Progress by fixing Issues, changing Issue Status, and adding Explanations.

What is Data Fitness Score?

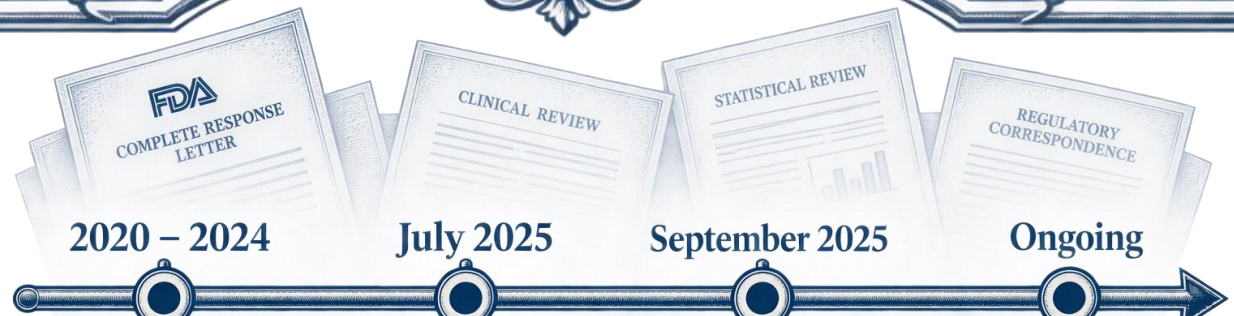
The Data Fitness Score shows whether data are fit to submit. It is based on the data's conformance to CDISC standards

Views Matter



Top-down view

Background



2020 – 2024

Applications from 2020–2024

CRLs cover a range of therapeutic areas and application types.

July 2025

200+ CRLs

FDA released 200+ Complete Response Letters in July 2025.

September 2025

89 Additional CRLs

FDA released 89 additional CRLs in September 2025.

Including pending or withdrawn applications.

Ongoing

Releases Continue

Still being released as an active, ongoing effort.

Available on openFDA, partially redacted while remaining informative.

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The Question We Started With



What the CRL Review Became

Two phases. Two different questions.

	Initial Review	Presentation Review*
Timing	Beginning October 2025	April 2026 – September 2026
Scope	~100 CRLs	32 CRLs
Application	Approved & Nonapproved	Nonapproved
Selection	Exploratory set	Filenames containing 2026
Question	Could deficiencies inform validation rule development?	What categories of reasons for non-approval are present?
Output	N/A	Categorization of issues

*The 32-CRL set was a pragmatic focused subset, not a statistically designed sample

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The Breadth of Categories



Facilities



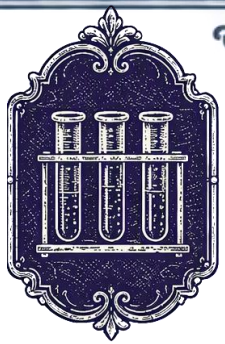
Product Quality



Nonclinical Evidence



Clinical Efficacy and Safety



Clinical Pharmacology and Bridging



Study Design



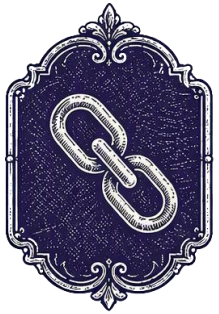
Study Conduct and Analysis Integrity



Human Factors/Use-Related Risk

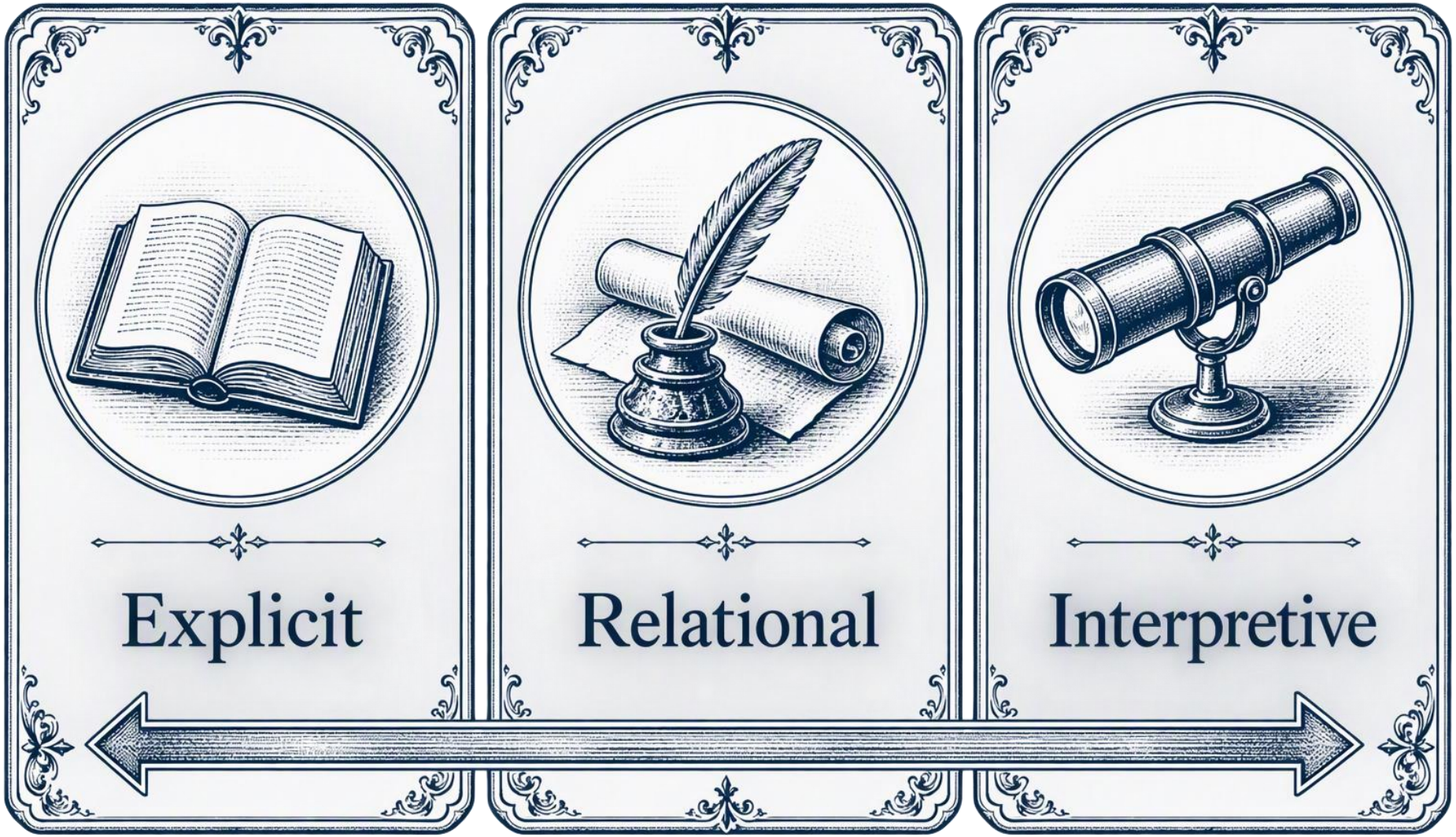


Labeling and Administrative



Other/Linked Regulatory Status

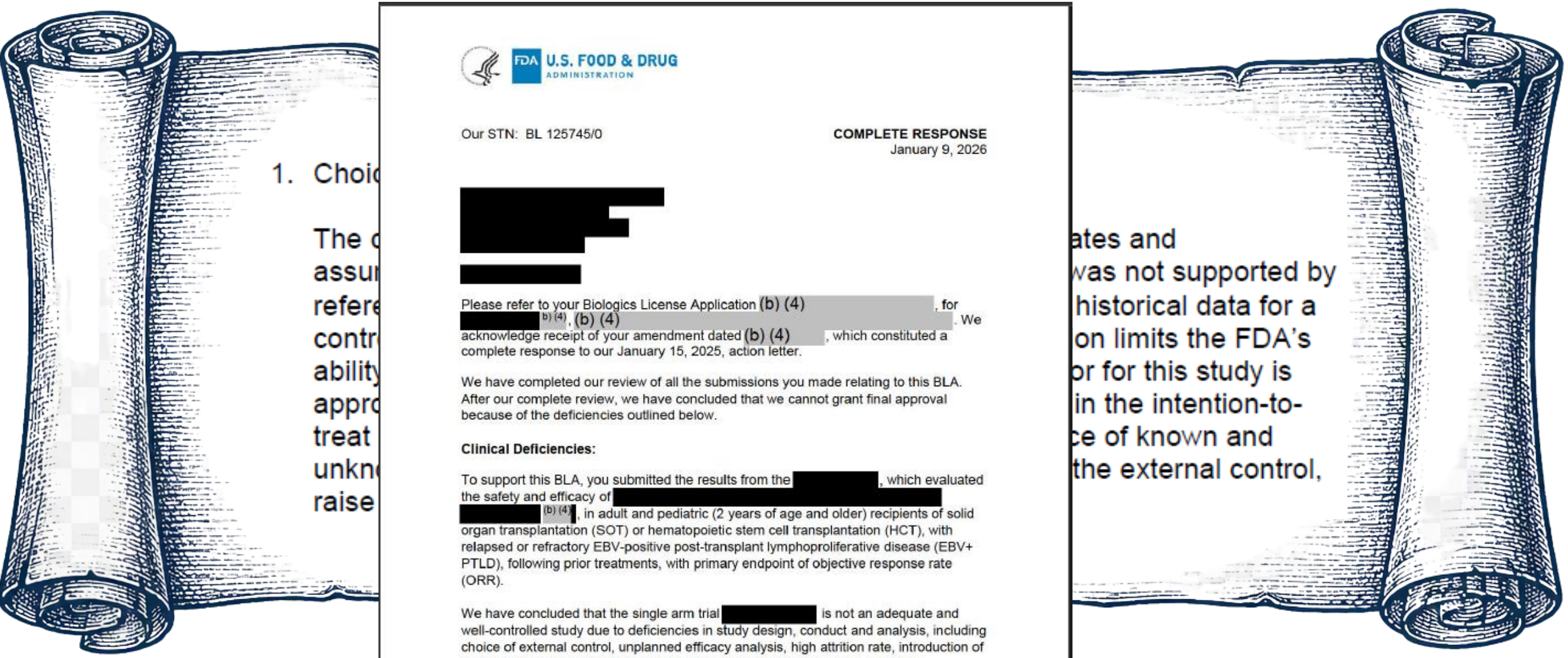
The Distance to a Rule



The Turn



CRL Example #1: Clinical Efficacy & Safety



FDA U.S. FOOD & DRUG ADMINISTRATION

Our STN: BL 125745/0

COMPLETE RESPONSE
January 9, 2026

[redacted]

Please refer to your Biologics License Application (b) (4) , for [redacted] (b) (4), (b) (4) . We acknowledge receipt of your amendment dated (b) (4) , which constituted a complete response to our January 15, 2025, action letter.

We have completed our review of all the submissions you made relating to this BLA. After our complete review, we have concluded that we cannot grant final approval because of the deficiencies outlined below.

Clinical Deficiencies:

To support this BLA, you submitted the results from the [redacted], which evaluated the safety and efficacy of [redacted] (b) (4), in adult and pediatric (2 years of age and older) recipients of solid organ transplantation (SOT) or hematopoietic stem cell transplantation (HCT), with relapsed or refractory EBV-positive post-transplant lymphoproliferative disease (EBV+ PTLD), following prior treatments, with primary endpoint of objective response rate (ORR).

We have concluded that the single arm trial [redacted] is not an adequate and well-controlled study due to deficiencies in study design, conduct and analysis, including choice of external control, unplanned efficacy analysis, high attrition rate, introduction of selection bias, and concomitant treatment interventions which confounded the interpretability of study results. For these reasons, the data from the [redacted] are insufficient to demonstrate substantial evidence of effectiveness of [redacted] (b) (4) to treat relapsed or refractory EBV+ PTLD.

BLA 125745, Jan 9, 2026 (ref. 1)

CRL Example #1: Clinical Efficacy & Safety

2. Quality of the [redacted] study

   a. Unplanned efficacy analyses with smaller sample size

   Unplanned changes to the sample size in an ongoing single arm study in your revised statistical plan submitted on (b) (4) [redacted], and subsequently revised on (b) (4) [redacted], resulted in reduction in sample size from 99 treated subjects (in 3 cohorts) to 44 treated subjects (in 2 cohorts). Due to lack of pre-specification of this analysis and lack of Type I error control, the results within this submission are considered descriptive and not statistically inferential. The unplanned efficacy analyses may have introduced a random chance of a successful primary efficacy outcome in a smaller data set.

   b. High attrition rate

   A substantial proportion of ITT population (n=130) with an available matching cell lot were excluded from treatment with any version of the product (55/130; 42%). A smaller subset of ITT population was treated with the intended product version (44/130; 34%). This high attrition rate further challenged data interpretability. The lack of information about subject disposition impacted our ability to assess the reason for high attrition rate, raising further concerns for introduction of selection bias.

BLA 125745, Jan 9, 2026 (ref. 1)

CRL Example #1: Clinical Efficacy & Safety

3. Persuasiveness and interpretability of the efficacy data

a. Limited sample size of complete responders (CR)

The small number of subjects (12/44 or 27%) who achieved complete response (CR) as the best response post (b) (4) treatment, limits the certainty of the efficacy data.

b. Limited durability of partial response (PR)

Although PR was observed in 10 of 44 treated subjects, (23%, 95% CI: 11.5-37.8) and contributed to the ORR of 50%, the short median duration of PR (2.04 months, range: 0.03-11.7 months) was not considered clinically meaningful.

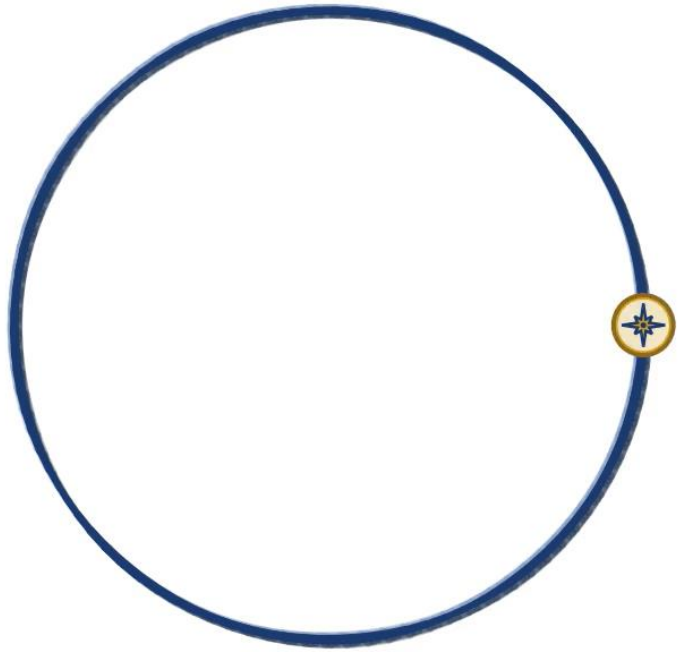
c. Prognostic heterogeneity issues affecting interpretability of the efficacy outcomes

d. Potential confounders from treatment interventions

Concomitant treatment interventions, including reduction in immunosuppression and proximity of rituximab therapy to study entry, affected the interpretability of the efficacy results.

BLA 125745, Jan 9, 2026 (ref. 1)

Different Views



Top-down view

CRL Example #2: Clinical Pharmacology/Bridging

CLINICAL PHARMACOLOGY

11. You have not provided sufficient data to demonstrate comparability between the proposed commercial product (DP) and the clinical DP used in your clinical studies. Analytical data alone will not be sufficient, and a clinical bridging study will be required to demonstrate comparability between the two formulations.

CLINICAL PHARMACOLOGY

Due to the deficiencies identified in bioanalytical method validation and bioanalysis for insulin aspart quantitation as indicated on the FDA Form 483 issued on (b) (4), the pharmacokinetic (PK) data from Study are considered unreliable and, therefore, cannot support the demonstration of no clinically meaningful differences between and US-licensed . The deficiencies include an invalid method ((b) (4)) due to inadequate validation for (b) (4) . These issues were not adequately resolved and considered not amenable to correction. We recommend that you conduct a new PK study using a validated bioanalytical method and appropriate bioanalysis to support the assessment of biosimilarity between and US-licensed .

BLA 761401, Apr 10, 2026 (ref. 1)
BLA 761403, Feb 26, 2026 (ref. 1)

CRL Example #2: Clinical Pharmacology/Bridging

CLINICAL PHARMACOLOGY

1. The results from the pivotal bioequivalence study (Study XS003-11) and population PK (POP-PK) study (Study XS003-16) indicate that XS003 (b) (4) capsules have approximately 25% lower systemic exposure compared to [redacted] 200 mg under fasting conditions in both single-dose and steady-state evaluations. This reduced exposure may result in diminished clinical efficacy for the following patient populations for whom [redacted] 200 mg is a recommended dosage:

CLINICAL/CLINICAL PHARMACOLOGY

The Agency finds that the scientific bridge between oxybate ER OS and the listed drugs (LDs), Xyrem and Xywav, is inadequate for the (b) (4) [redacted] Although the systemic exposures of the (b) (4) [redacted] of the proposed product are within the range of those observed for the LDs (Xyrem and Xywav), the shape of pharmacokinetic (PK) profiles is different from the LDs, as they are approved as twice-nightly regimens for the treatment of cataplexy or EDS in adults with narcolepsy. The exposure-response (E-R) analysis submitted by the Applicant relied on aggregated exposures (e.g., AUCinf, Cmax, and dose), assuming that the shape of PK profile has no effect on clinical response. However, this analysis itself does not demonstrate that differences in PK shape will not lead to different clinical outcomes. You have not submitted adequate and well-controlled clinical studies that support (b) (4) [redacted] of the LDs for (b) (4) [redacted]. In the absence of an adequate and well-controlled efficacy and safety study, the E-R analysis alone is insufficient to justify that the PK shape difference would not impact the efficacy or the safety of oxybate ER OS for (b) (4) [redacted]. Therefore, the proposed product, oxybate ER OS, cannot rely solely on the Agency's previous findings of effectiveness of the LDs for the treatment of cataplexy and EDS in narcolepsy.

NDA 217644, Jun 4, 2026 (ref. 1)

NDA 220138, Jun 15, 2026 (ref. 1)

CRL Example #3: Study Design, Conduct & Analysis Integrity

B. [redacted]-456

[redacted]-456 was a randomized, double-blind, placebo-controlled trial in subjects with Autonomous Cortisol Secretion (ACS) and Cushing's Syndrome, associated with uncontrolled systolic hypertension and/or DM/IGT. However, the trial did not meet its primary efficacy endpoint, defined as the mean change in 24-hour average systolic blood pressure (SBP) based on 24-hour ABPM, from baseline to Week 22 in subjects with systolic hypertension at baseline. In the (b) (4) subjects with ACS and Cushing's Syndrome and with hypertension at baseline ([redacted] in each arm), the mean change in 24-hour SBP from baseline was -5.8 mmHg in the [redacted] arm and -5 mmHg in the placebo arm, resulting in a between-arm difference ([redacted] vs. placebo) of -0.85 mmHg (95% CI: -6.7, 4.9; p-value 0.77).

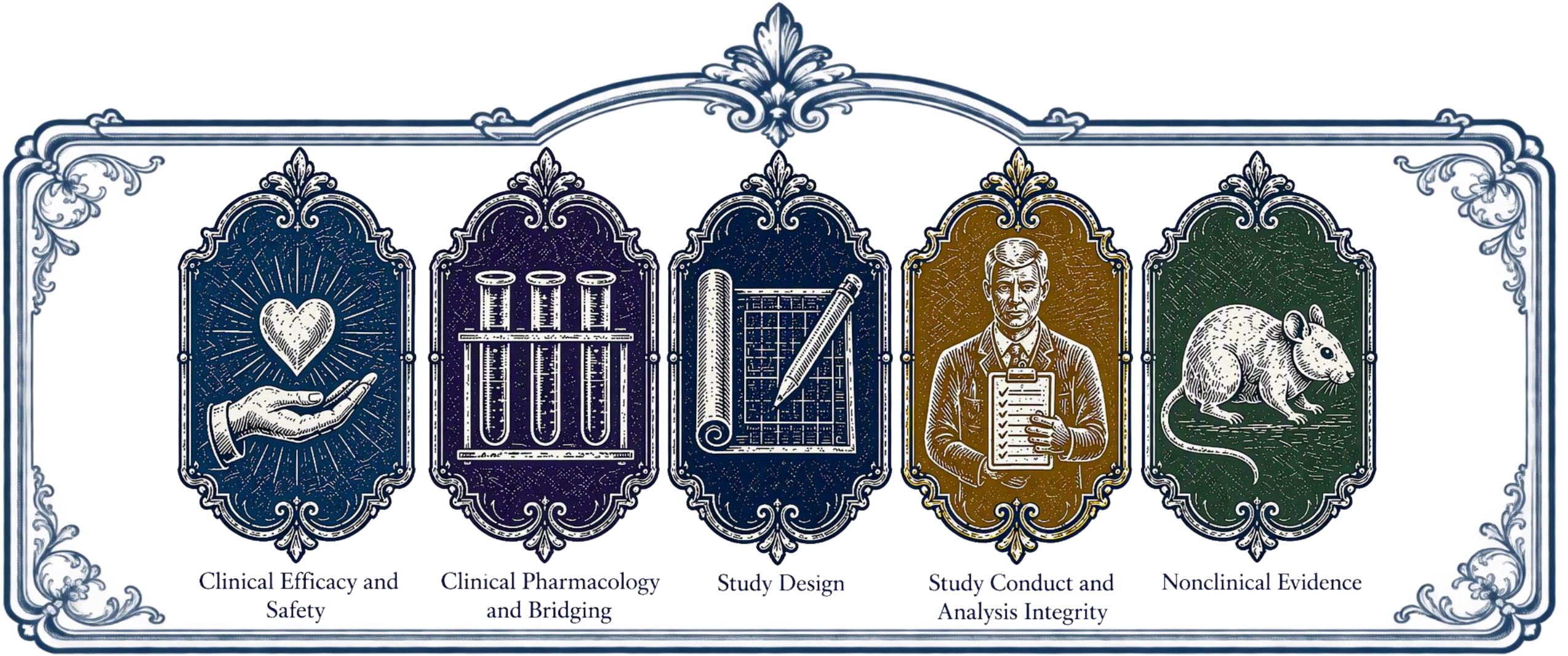
NDA 219398, Jan 28, 2026 (ref. 1)

CRL Example #3: Study Design, Conduct & Analysis Integrity

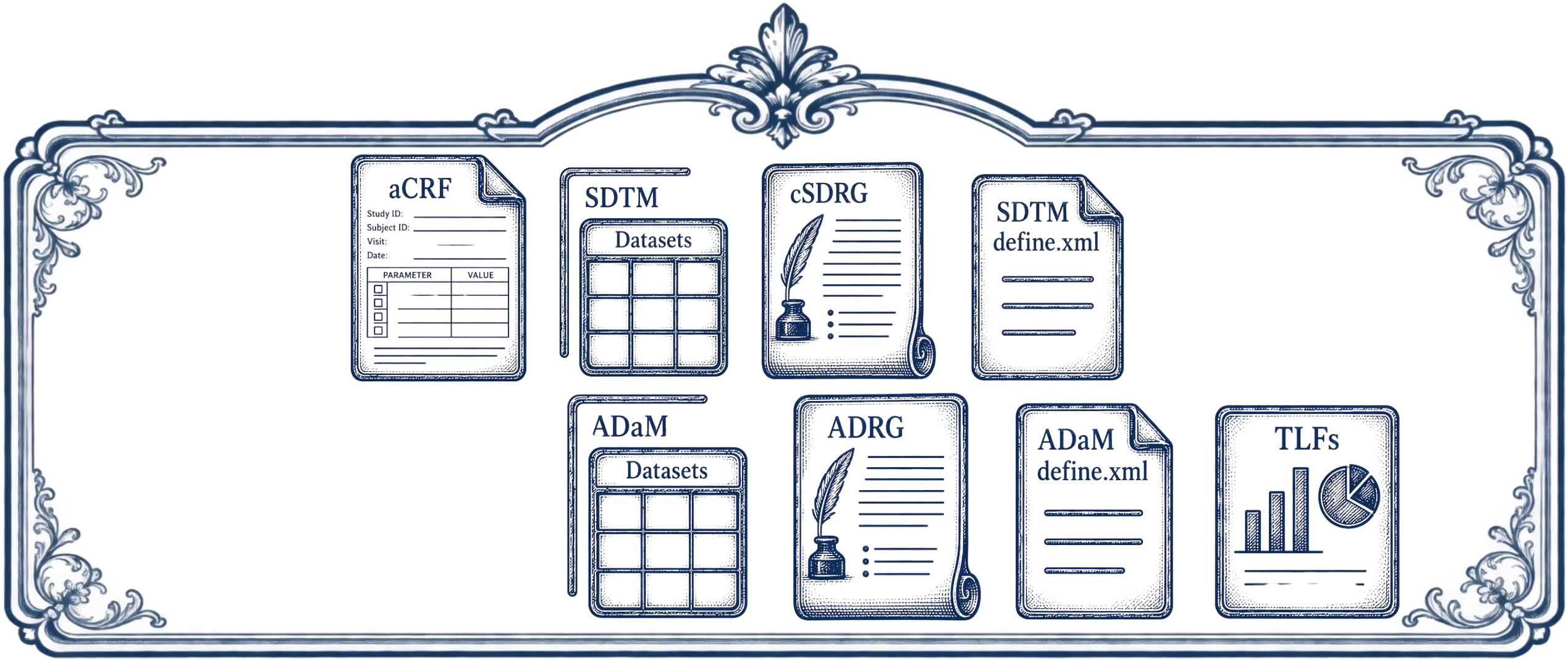
While [redacted]-455 met its primary endpoint, the analysis was conducted in a highly enriched population. Of the [redacted] (b) (4) subjects enrolled, 102 subjects had hypertension at baseline, of which 40 (39%) subjects discontinued the trial during the open-label phase and only 46 (45%) subjects entered the randomized withdrawal phase. As such, the observed treatment effect in the randomized withdrawal phase likely overestimates the treatment effect of [redacted] in the intended population. We acknowledge that in the 22-week open-label period, in which all subjects were treated with [redacted] the mean (SD) change from baseline in systolic blood pressure at the end of the open-label phase was -5.2 (10.4) mm Hg (with missing data imputed using a return-to-baseline approach). However, we find this treatment estimate to be unreliable given the large amount of missing data. In addition, there was no control group with which to interpret the change in blood pressure.

NDA 219398, Jan 28, 2026 (ref. 1)

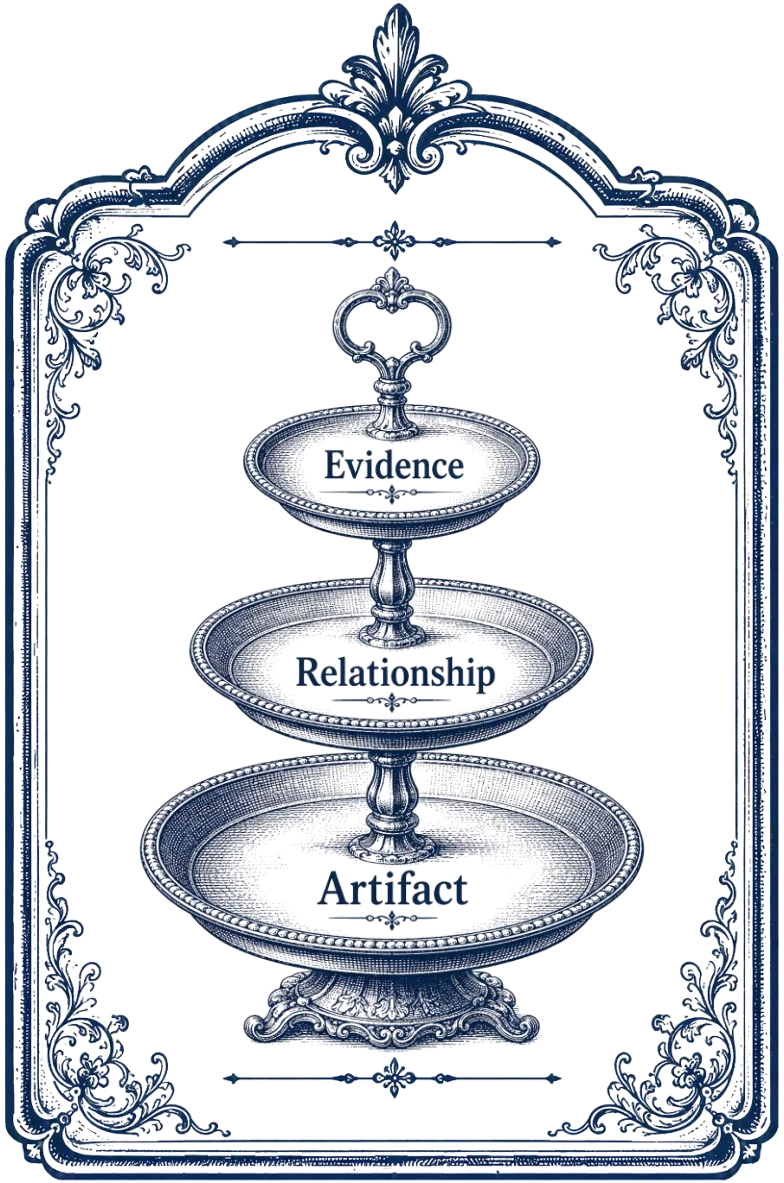
“Closing” the Loop



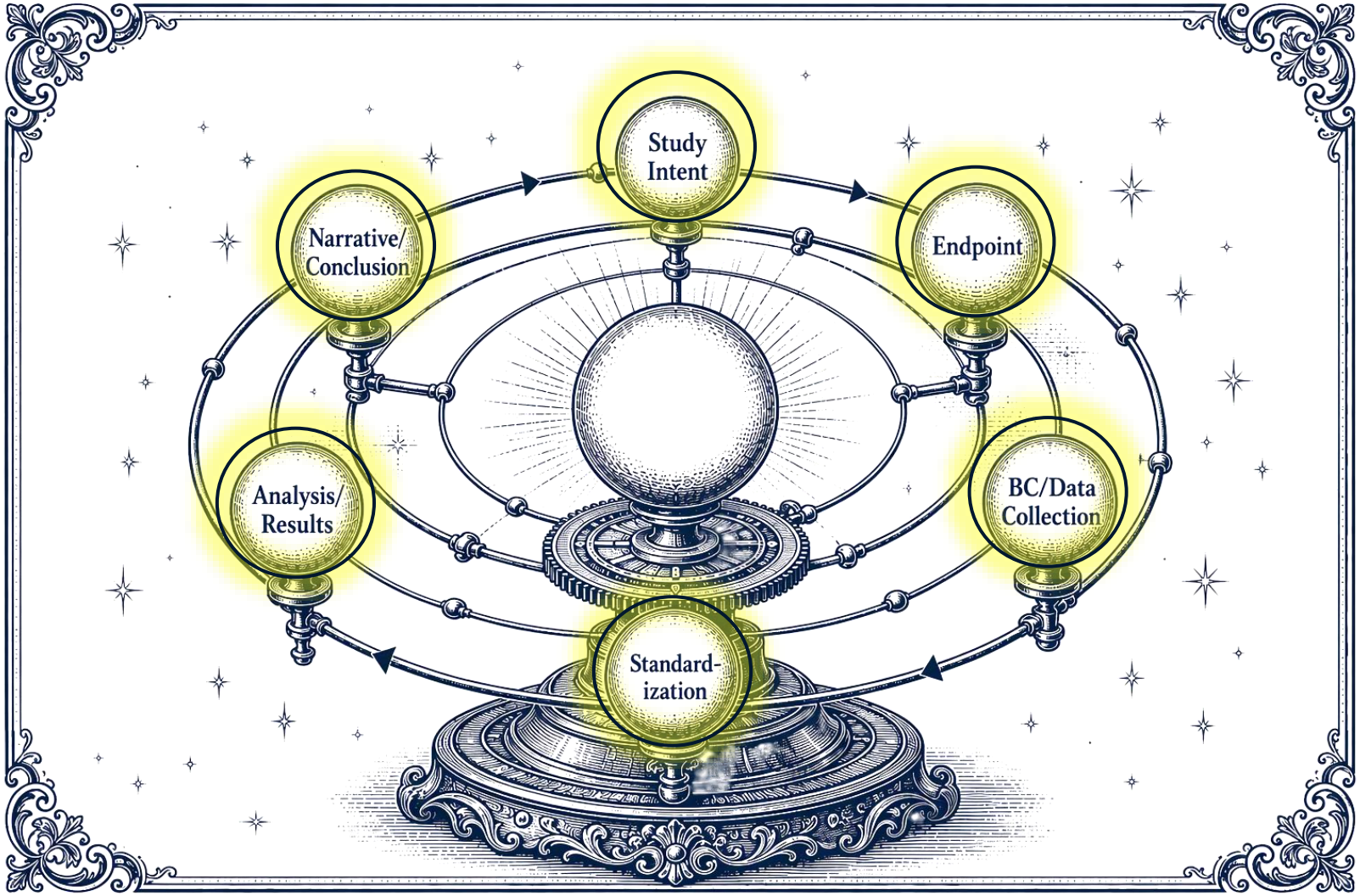
Pieces


aCRF
Study ID:
Subject ID:
Visit:
Date:
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cSDRG
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ADaM
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TLFs

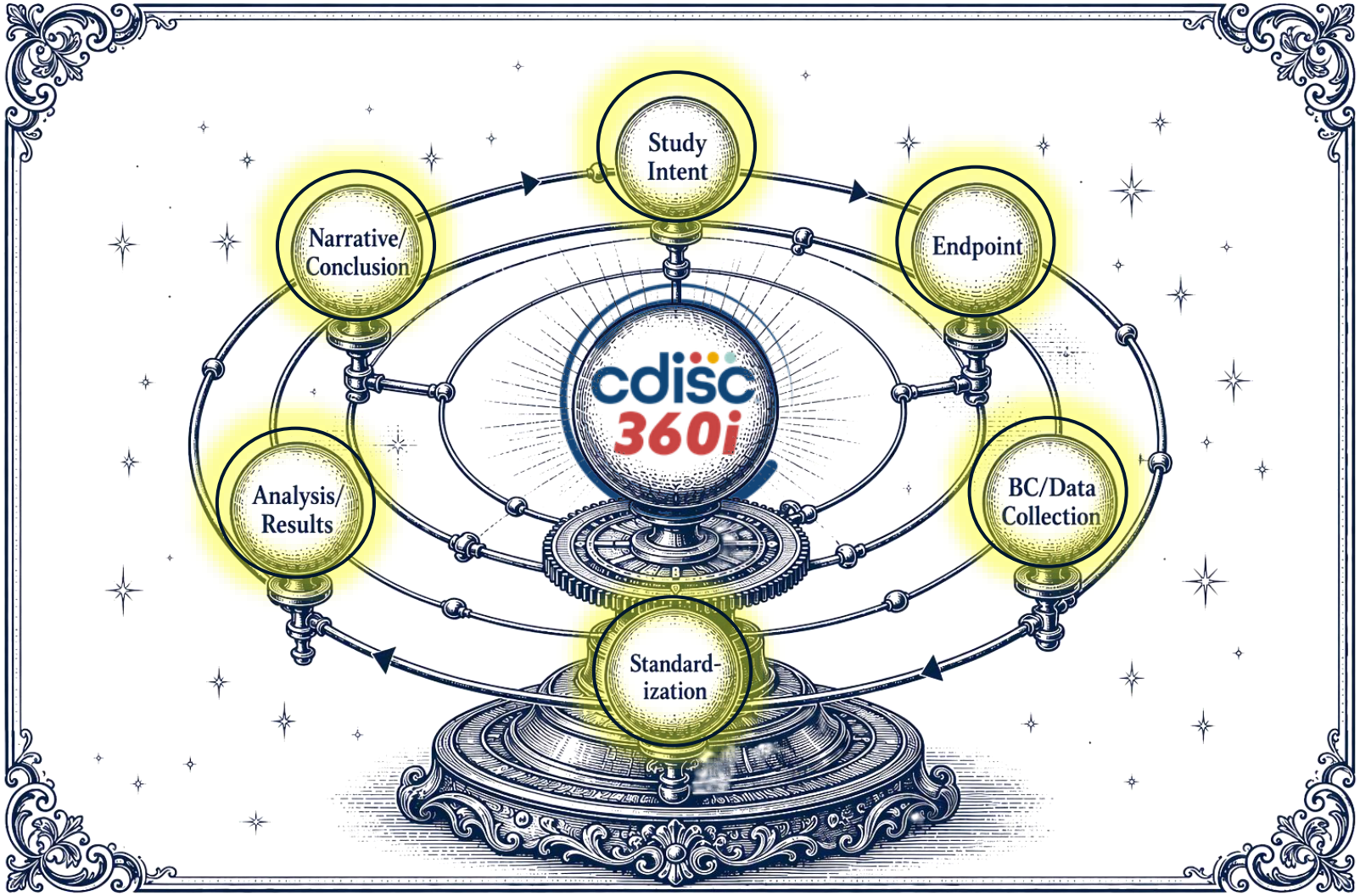
Change the Unit of the Question



Follow the Evidence



CDISC 360i: A Foundation for the Connections



What Connections Let Us Test

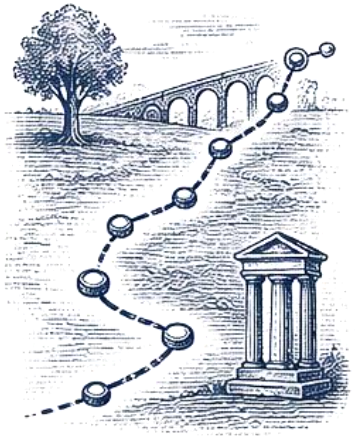
1



CONFORMANCE

Are defined requirements met?

2



TRACEABILITY

Can the concept be followed through the lifecycle?

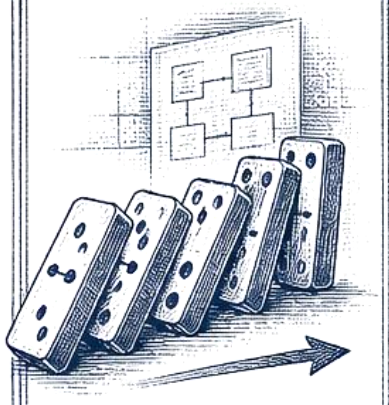
3



CONSISTENCY

Do related artifacts tell the same story?

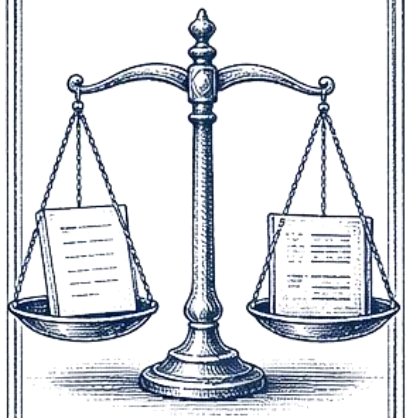
4



CHANGE IMPACT

Which downstream representations may be affected?

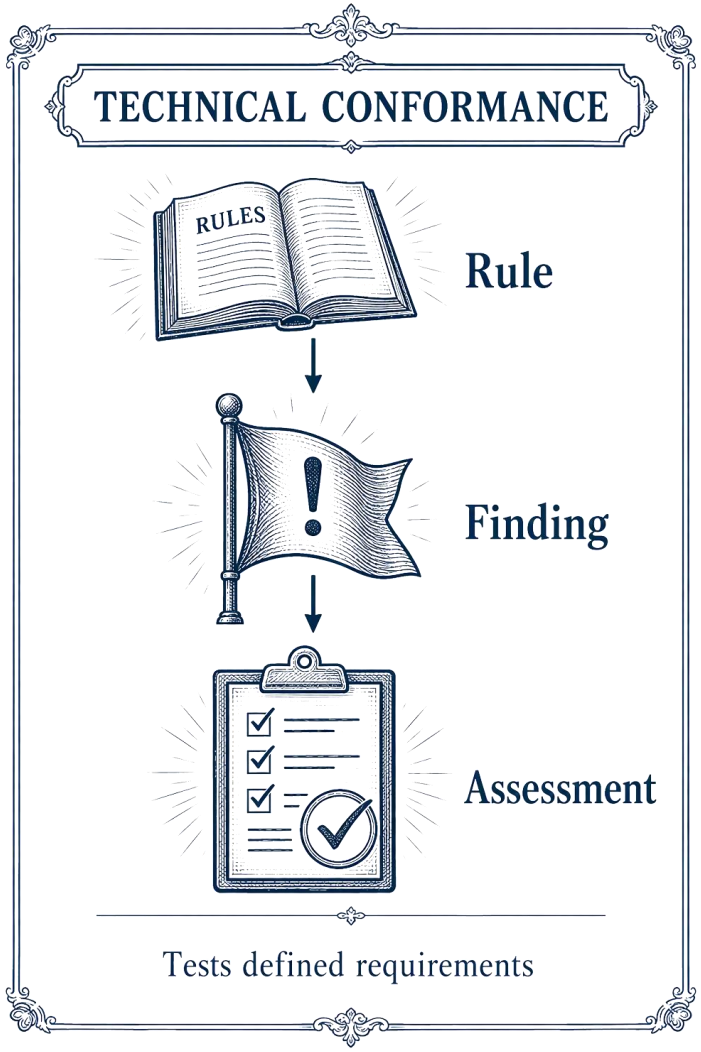
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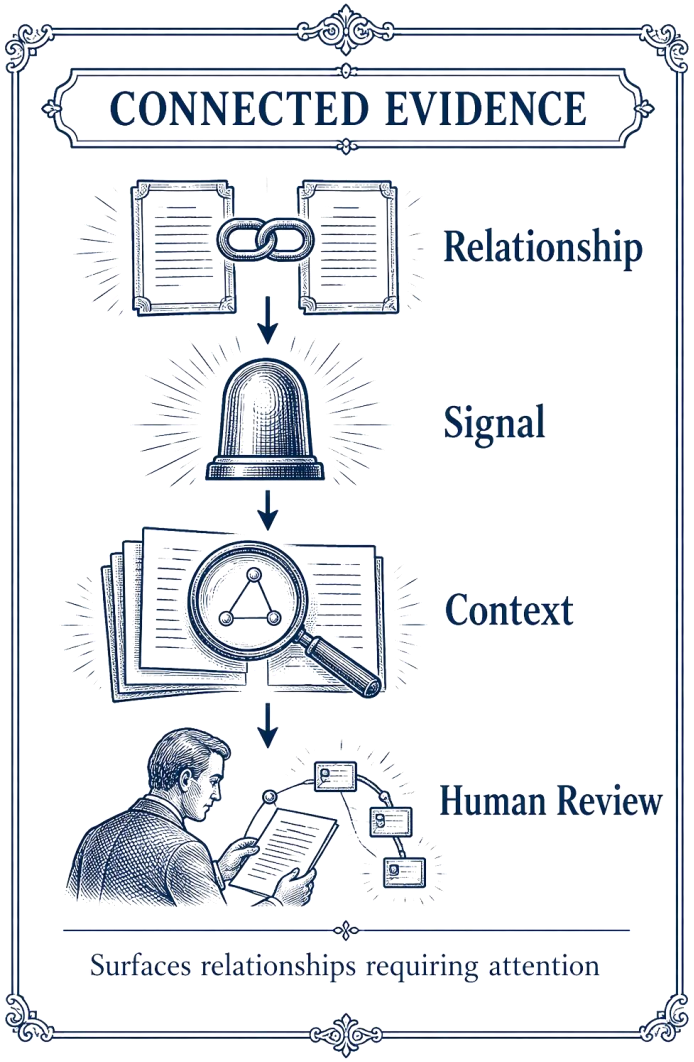


RECONCILIATION

Can differences be identified and explained?

Better Questions, Not More Flags

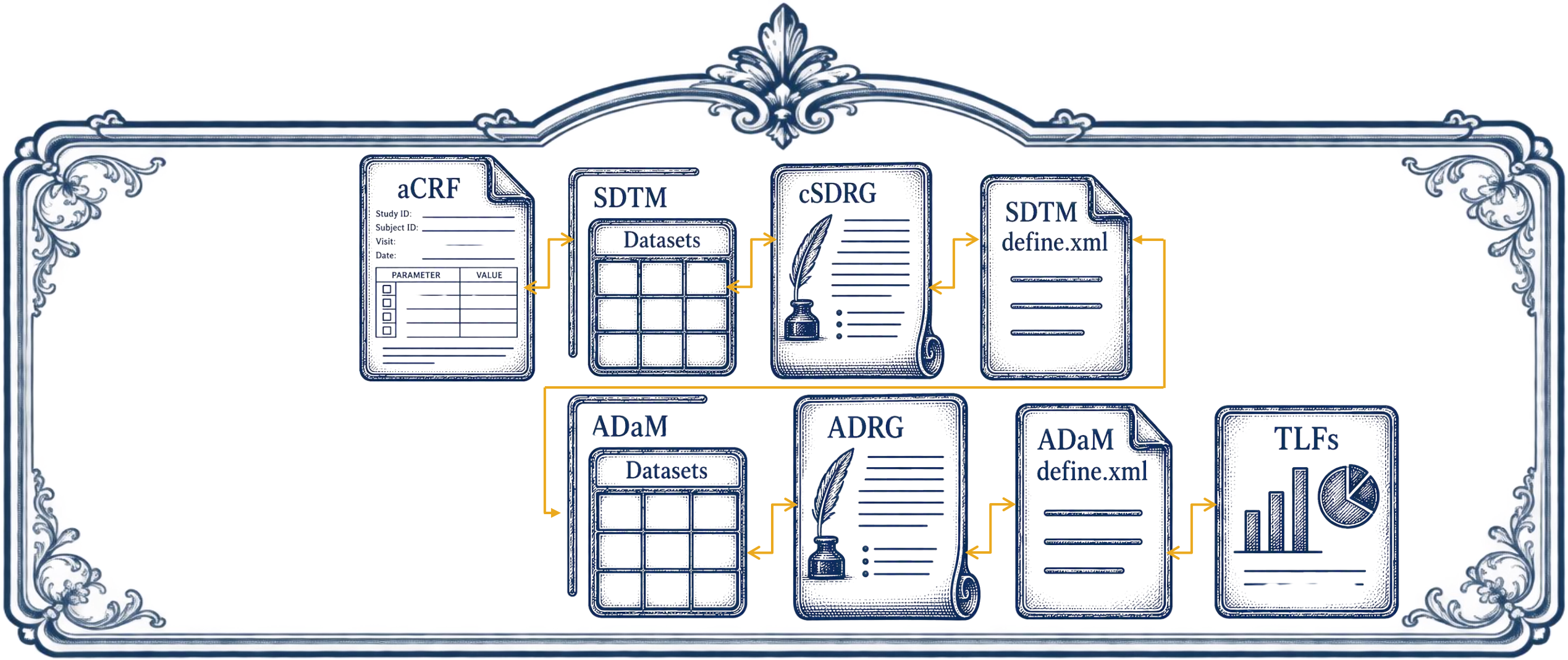




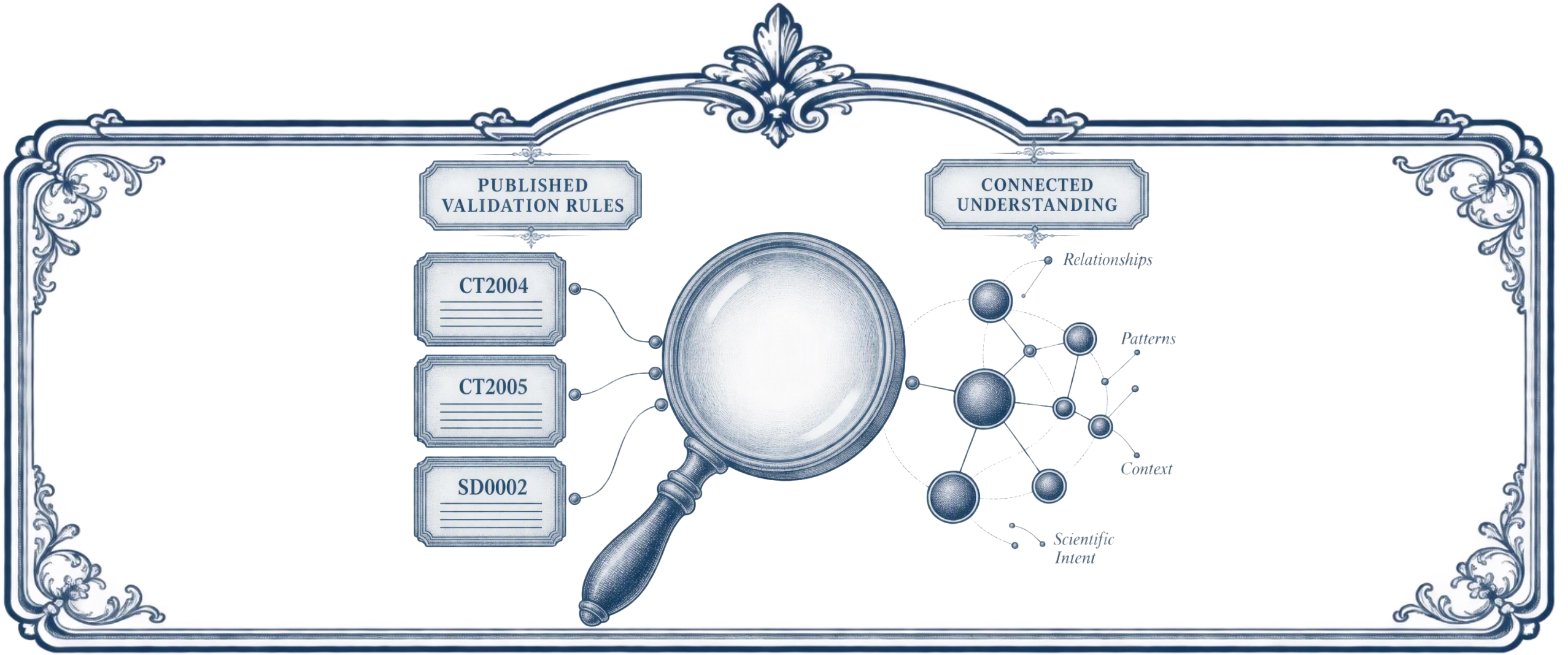
The Prestige



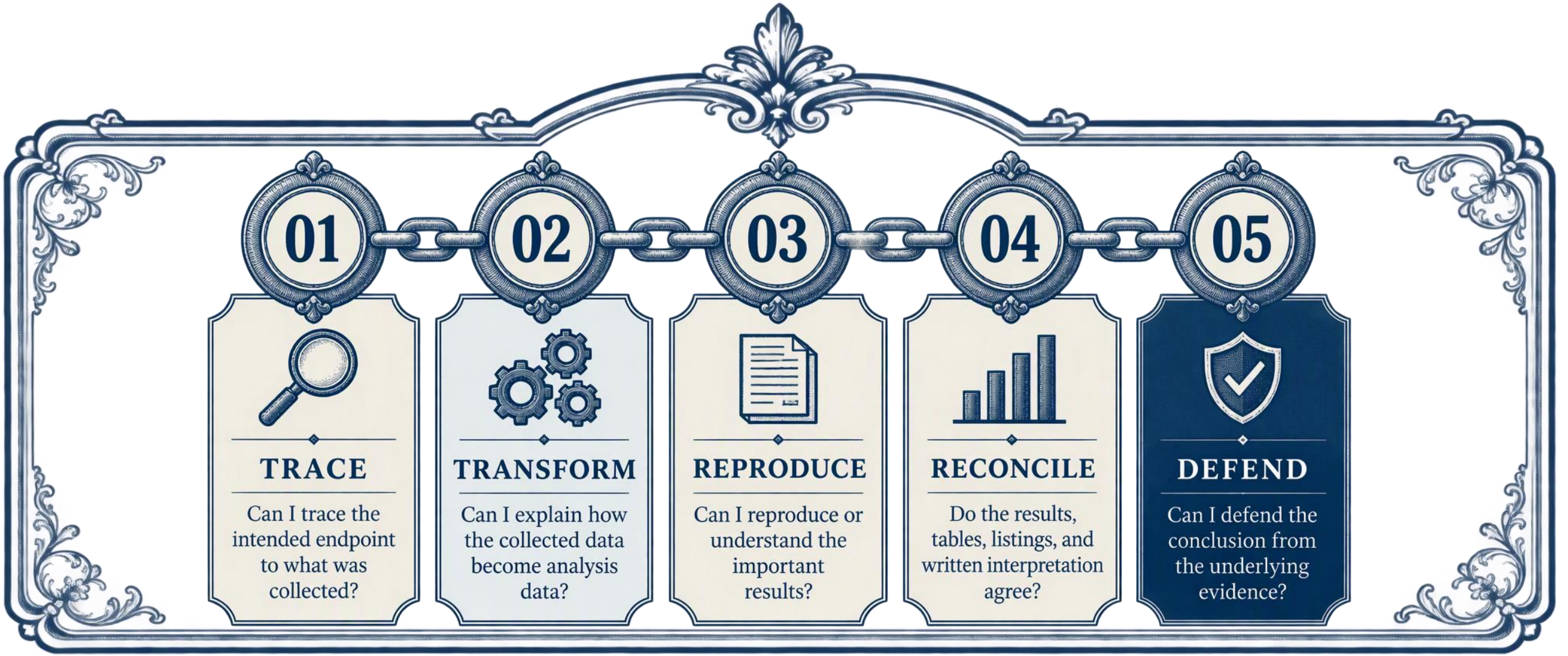
Coherence vs. Defensibility



Where Judgment Begins



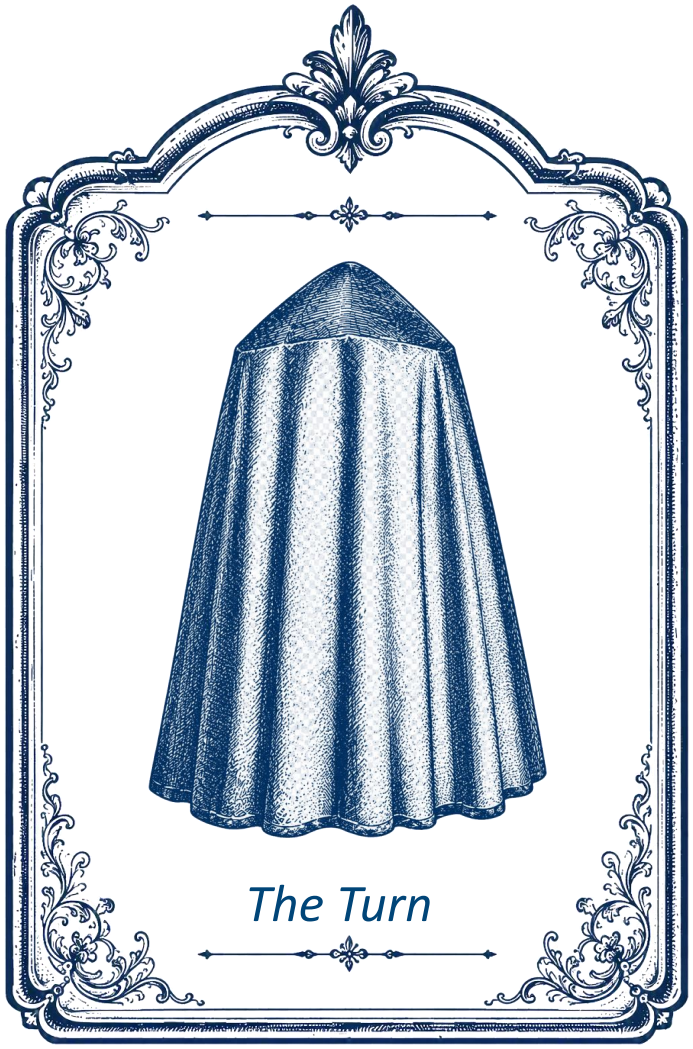
Five Questions for the Evidence Chain



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Revisiting the Magic Trick







Don’t Stop Validating. Start Asking More.



Connected evidence helps us understand, explain, and defend our submissions before the reviewer asks us to.

Special Thanks

- Michael Beers, Director Consultative Services

References

1. U.S. Food and Drug Administration. Complete Response Letters Database. openFDA. Accessed September 30, 2026. https://open.fda.gov/crltable
2. U.S. Department of Health and Human Services, Food and Drug Administration. *Proactive Disclosure of Complete Response Letters*, RIN 0910-AJ16, Unified Agenda of Regulatory and Deregulatory Actions, Fall 2026. Proposed rule stage. https://www.reginfo.gov/public/do/eAgendaViewRule?pubId=202510&RIN=0910-AJ16
3. U.S. Food and Drug Administration. (2025, July 10). *FDA embraces radical transparency by publishing complete response letters* [Press release]. https://www.fda.gov/news-events/press-announcements/fda-embraces-radical-transparency-publishing-complete-response-letters

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