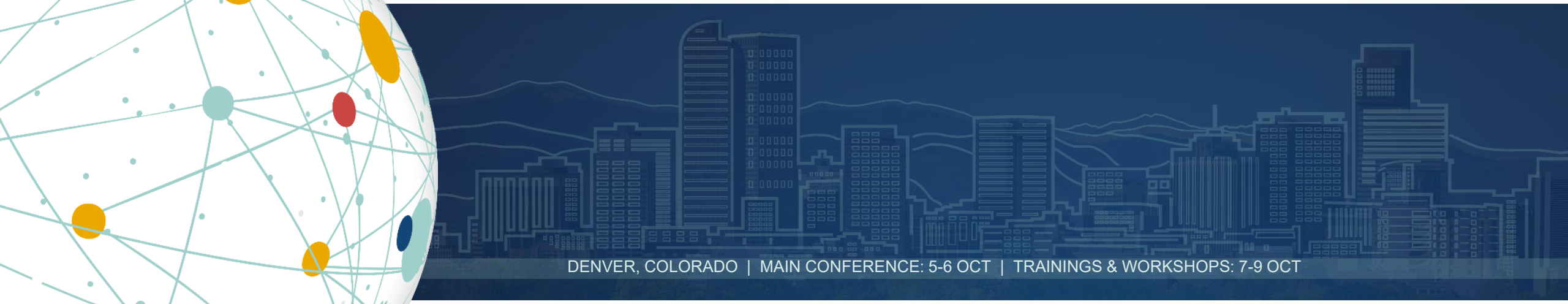


cdisc® 2026 US Interchange

THE FUTURE IS CONNECTED: STANDARDS AND AI POWERING DIGITAL TRANSFORMATION



Architectural Divergence Across Three Hemophilia Studies
A Standards-Driven Framework for Rare Disease Multi-Study Programs

Prasanna Kakade | Manager Statistical Programming | Ephicacy Consulting Group
Achin Wadhwa | Associate Principal Scientist II | Ephicacy Consulting Group

Agenda

01 The challenge

02 Hemophilia program

03 Divergences

04 Seven-pillar framework

05 Results and key takeaways

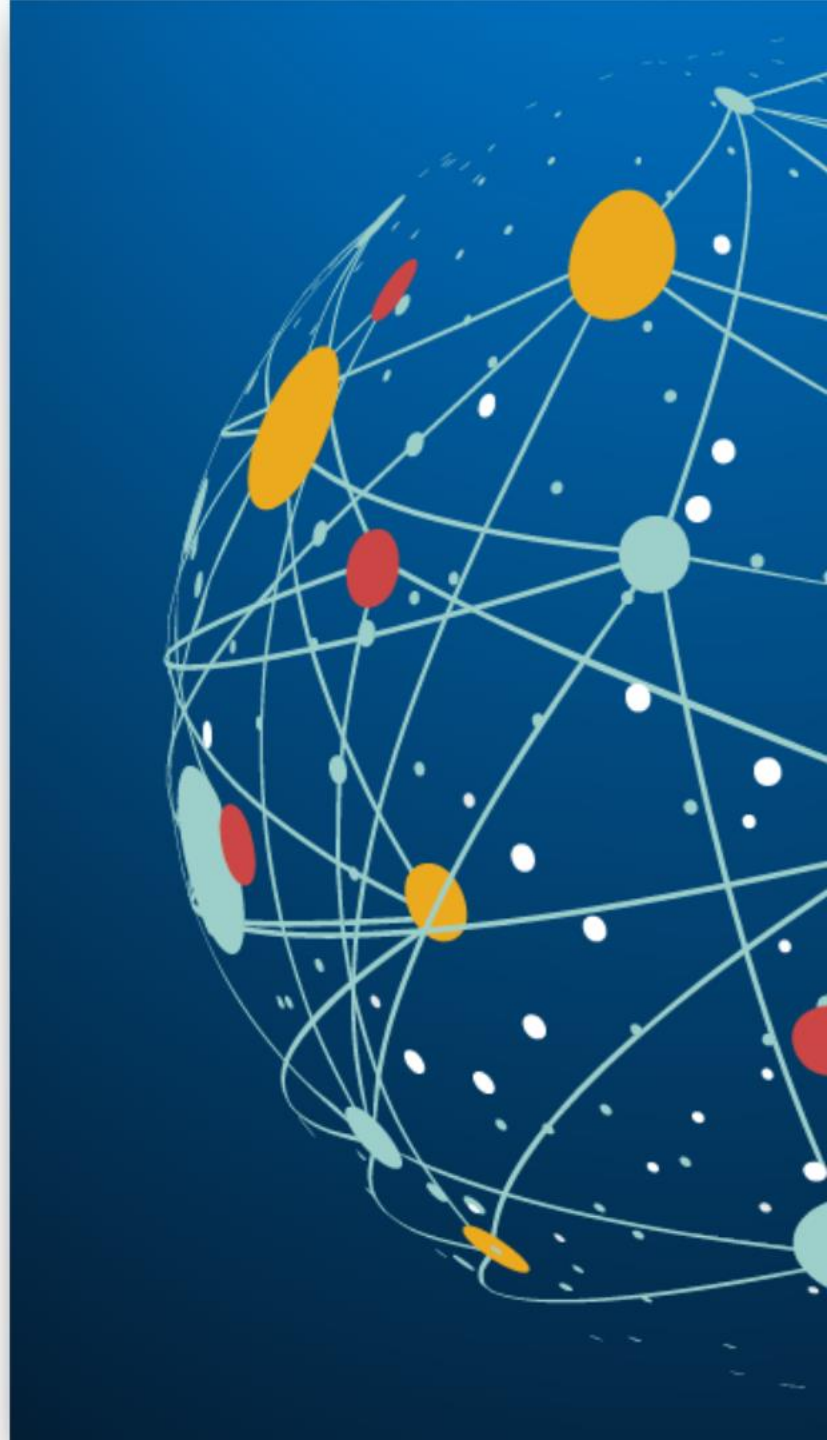
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The Challenge

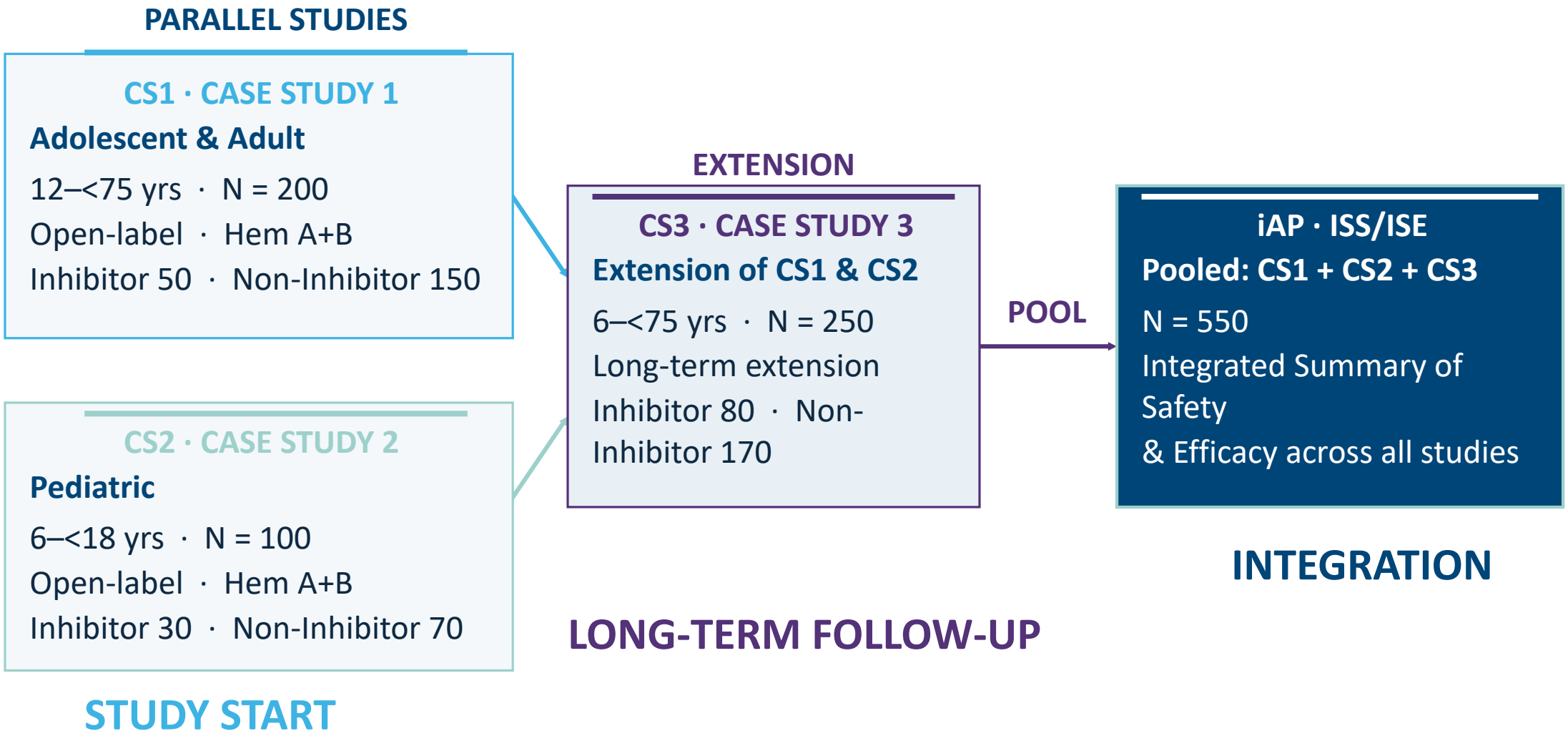
Why multi-study rare disease programs fail at the seams
— not in the datasets

The Governance Gap

- A drug program may span a Phase 3 adolescent/adult study, a parallel pediatric study, and a multi-year extension - each with its own SAP, CRF design, and vendor team.
- CDISC standards applied to each study in isolation do not guarantee the program produces harmonized, poolable, reviewable outputs.
- The governance gap is where rare disease programs fail:
  - Not in individual dataset quality -
  - but in the architecture connecting datasets across studies, derivations across SAP versions, and outputs across submission packages.
- Closing it requires prospective architectural decisions at the program level - not remediation at the submission level.



02 Hemophilia Program: Four Related Submissions



03 Architectural Divergences: Six Root Causes

- **Endpoint Nonuniformity**
  - ABR Algorithm: Bleed-counting rules, observation windows, and treated/untreated thresholds diverged across studies.
- **Dosing Schema Differences**
  - Age-stratified arms forced ADEX/ADPC dose-normalization to be re-derived per group.
- **Lab Schedule & Unit Heterogeneity**
  - Pediatric reference ranges, IU/dL vs % units, and visit windows broke CS1 flag logic.
- **Age & Demographic Derivations**
  - Derived vs protocol age mismatches required documented exceptions.
- **eDiary Workflow Architecture**
  - CS1 and CS2 used different eDiary versions and CRF reconciliation rules - separate code branches.
- **Cohort Transitions**
  - Inhibitor: Participants with dual stratum membership created recurring P21 findings in ADSL.

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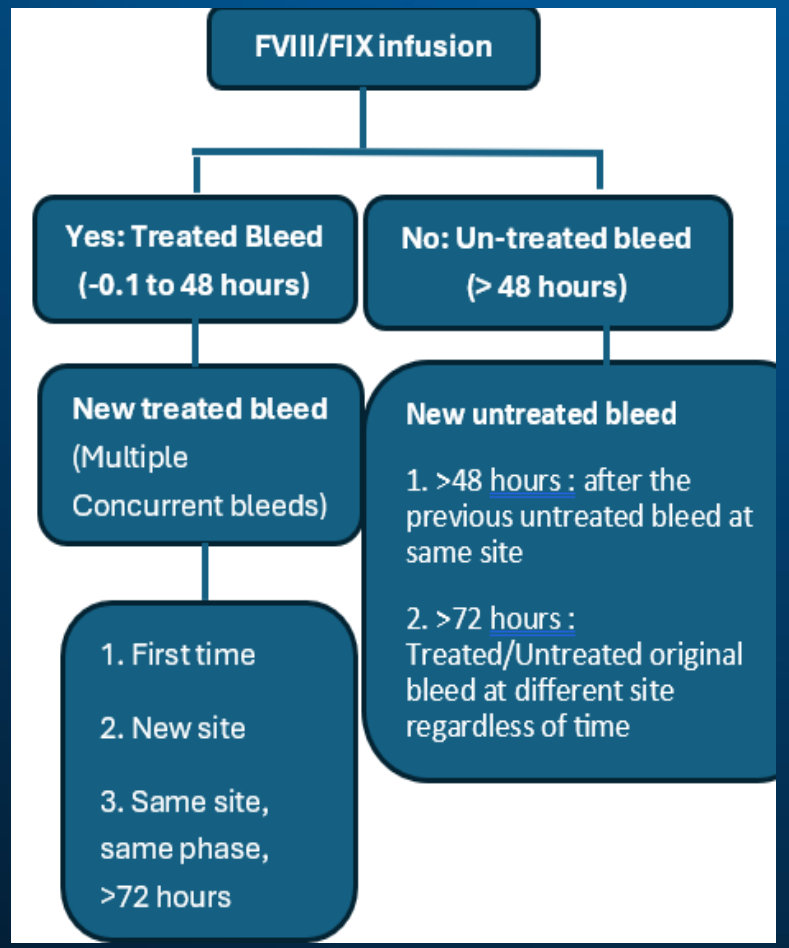
Spotlight: Endpoint Non-Uniformity

- ABR is the primary efficacy endpoint - yet a single formula concealed many diverging decision points.
- CS1: separate OP and ATP derivations; new treated bleed = new site, first-time, or same site >72h apart.
- CS2: by-age-group ABR (6–<12 vs 12–<18) and a new ADABRMON monthly structure absent from CS1.
- CS3: period-level derivations layering CS1/CS2 history; forced full efficacy dataset rederivation.
- iAP: harmonizing OP/HIS removal and the 12–17 bridging population across pediatric and adult logic.
- **A "treated bleed" in CS1 ≠ a "treated bleed" in CS2 - breaking cross-study comparability.**

Conceptually consistent…

ABR = (qualifying bleeds ÷ observation days) × 365.25

…divergent in implementation.



Why Architectural Divergence Matters

Regulatory	Non-reproducible derivations and conflicting population definitions violate the FDA Study Data Technical Conformance Guide - risking Complete Response Letters, added data requests, and review delays.
Scientific	A “treated bleed” defined differently in CS1 vs CS2 undermines the pooled ABR claim. With only ~500 patients, every misclassification weakens the primary endpoint's interpretability.
Operational	Re-deriving ADABR from scratch, rebuilding population flags, and multi-enroller records consumed programming capacity, compressing CSR timelines and leading to reactive QC.
Patient Safety	Inconsistent AE schemas, lab ranges, and exposure denominators make integrated safety summaries non-comparable - potentially obscuring signals in a small, high-risk rare-disease population.

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CSR-Level Consistency That May Lead to Failures

- Publishing CSR tables misaligned with standalone TLFs - derivation updates not propagated.
- Mock shell and output misalignment across CS1/CS2/CS3 for the same endpoint.
- Population flag inconsistencies - FAS/PP/Safety definitions diverged across study CSRs.
- Sensitivity analysis drift - same analysis, subtly different logic, violating ICH E9(R1).
- Agency-specific propagation gaps - EMEA updates missed when FDA TLFs were revised.

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distinct failure modes - all the visible face of upstream architectural debt.

04 The Seven-Pillar Framework

Converting governance from a remediation activity into a design discipline

The Seven-Pillar Framework at a Glance

Pillar	Governance Objective	Primary Failure Mode Prevented	Stage
1. CDASH CRF Architecture	Unified data collection across all studies from Day 1	eDiary version divergence; pediatric field gaps	Protocol Design 1
2. Metadata Governance	Single source of terminology & derivations	Controlled-terminology & spec–implementation drift	Program Initiation 2
3. Harmonized Derivations	Key endpoints (e.g. ABR) defined once, branched per study	Non-uniform ABR rules; ADABR incompatibility	Pre-SAP Finalization 3
4. SDTM/ADaM & P21	Continuous conformance validation at every milestone	Unsorted datasets; missing specs; non-independent QC	DBL → final → eSUB 5
5. ISS/ISE Readiness	Pooling keys & agency-split logic built into each study	Bridging rederivations; dual-USUBJID; agency divergence	ADaM design; pre-iAP 7
6. Change Control & Transition	Formal change governance & team-transition protocols	Statistician gaps; undocumented SAP deviations	Ongoing Lifetime (all stages)
7. CSR-Level Consistency	**First-class governance of TLFs, publishing tables & Define.xml**	**In-text misalignments; mock-shell & version drift**	**Pre-CSR lock; eSUB 6**

Framework Foundation: Pillars 1 & 2

Pillar 1 ·CDASH CRF Architecture

- **Single master CRF in CRF library with study-specific configuration overlays - not separate designs.**
- Align bleeding-episode fields and eDiary schema to one controlled-terminology set from Day 1.
- Anticipate age-stratified subpopulations: age-group flags and pediatric fields at design time.
- Define eDiary–CRF reconciliation rules in the protocol.
- ***Artifact: Master aCRF, eDiary field dictionary, reconciliation rulebook.***

Pillar 2 · Metadata Governance

- **A centralized repository as the single source of truth for terminology and derivations.**
- Every terminology or derivation change triggers formal cross-study impact assessment.
- SDTM domain metadata defined at program level before study initiation.
- Repository linked directly to the Define.xml generation pipeline for traceability.
- ***Artifact: Program Metadata Repository, with a cross-study branch map and automatic impact lists.***

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Derivation & Conformance: Pillars 3 & 4

Pillar 3 · Harmonized Derivations

- **Define the ABR algorithm once at program level - counting rules, windows, concurrency.**
- Document age-group variations as branches within one spec, not separate SAP appendices.
- Common ADABR / ADABRMON structures at inception; study differences as parameters.
- Program-level ABR spec signed off before any individual study SAP is finalized.
- ***Artifact: Master Endpoint (ABR) Derivation Spec - numbered rules plus a reference implementation and test cases.***

Pillar 4 · SDTM/ADaM & P21

- **Run P21 validation at every milestone - DBL, interim, final - not only at eSUB.**
- Sort all datasets on key variables from initial delivery as a standards requirement.
- Enforce independent (non-identical) PROD and QC programs with formal sign-off.
- Approve dataset specifications before programming begins, not retroactively.
- ***Artifact: Conformance Milestone Gate & P21 Findings Register, feeding the ADRG conformance summary.***

Integration & Control: Pillars 5 & 6

Pillar 5 · ISS/ISE Readiness

- **Design every key dataset with consistent pooling keys (STUDYID, USUBJID, flags).**
- Define the bridging population and dual-USUBJID rules in the iAP design at inception.
- Encode agency-specific splits (e.g., EMEA <12 exclusion) as design parameters.
- Conduct a pre-iAP harmonization review when the last study closes.
- ***Artifact: Integration Design Document (IDD) - pooling keys, subject-identity map, agency-split matrix.***

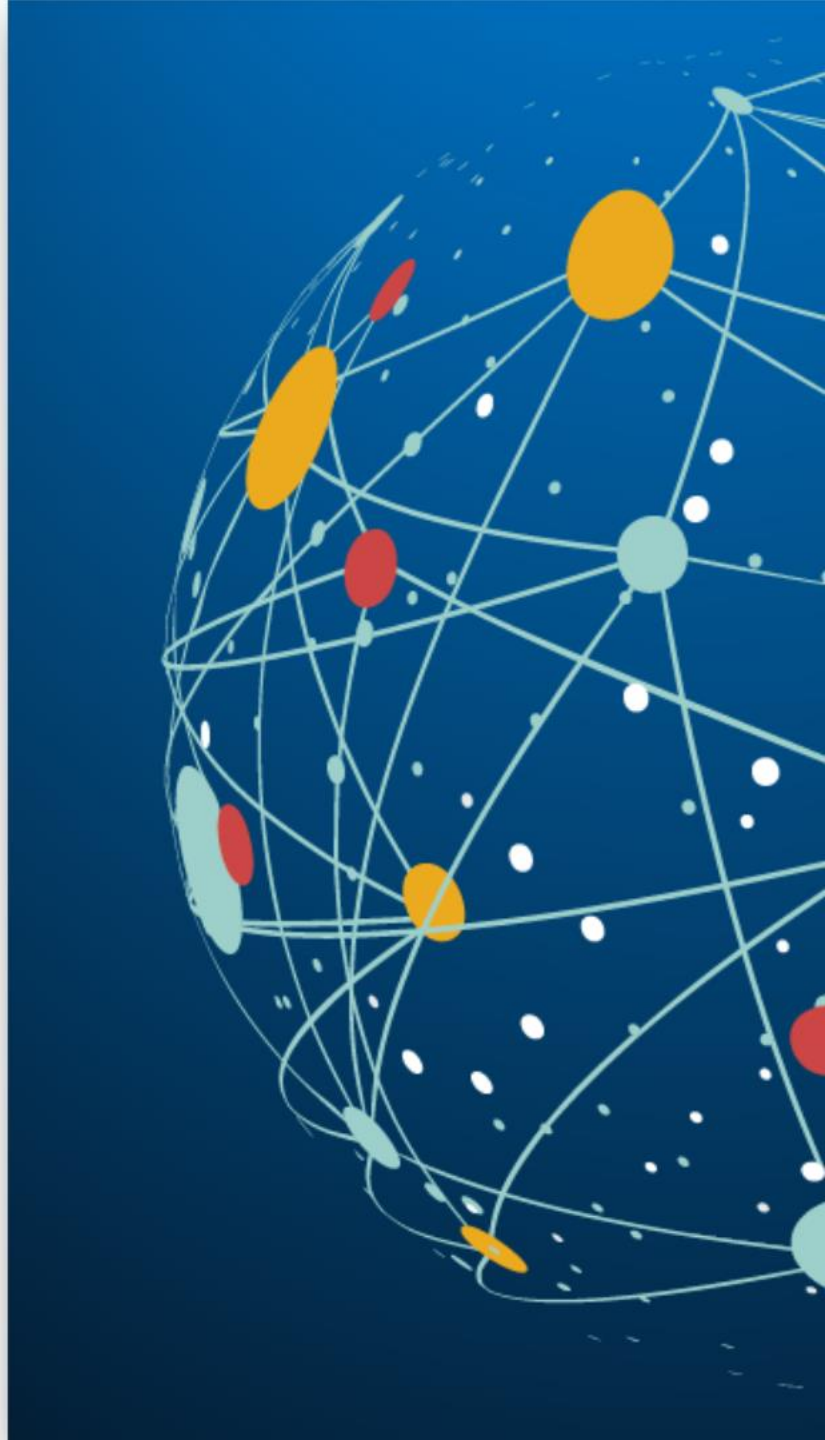
Pillar 6 · Change Control

- **Maintain a living derivation decision log with rationale and cross-study impact.**
- Require structured knowledge transfer at every statistician / vendor transition.
- Map timeline dependencies so study deliverables feed iAP without overlap rework.
- Run a post-CSR, pre-iAP lessons-learned review to close spec gaps.
- ***Artifact: Derivation Decision Log & Transition Dossier - a defined offboarding gate at every handoff.***

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Pillar 7: CSR-Level Consistency Governance

- **The unique seventh pillar: CSR consistency as a first-class deliverable, not an emergent property of correct TLFs.**
- Publication table reconciliation protocol - every value validated against TLF and ADaM before CSR lock.
- Version-controlled mock-shell repository with cross-study impact assessment on every change.
- Program-level population flag specification - one master document; study ADSLs trace back to it.
- Estimand-aligned sensitivity analysis library mapped to ICH E9(R1).
- Agency-specific TLF parameter architecture - one master program, agency as a switch.
- Define.xml / ADRG freeze protocol and a TLF version-traceability manifest in the ADRG.
- ***Artifact: CSR Consistency Dashboard & TLF Delivery Manifest, tracking every table to its ADaM and CSR source.***



Making It Real: Enabling Technology & Automation

Metadata-Driven Automation

- **A metadata repository (MDR) operationalizes Pillars 1–3 - one governed source of truth for terminology, mappings, and derivations.**
  - Version control and impact analysis show the downstream effect of any change before it ships.
  - CDISC 360i (2025) points the industry toward standards-driven automation from design through results.
  - AI/ML now assists metadata curation, lineage, and up-versioning - connective tissue under Pillars 2 and 6.

Conformance & Modern Transport

- **Continuous P21 (Pinnacle 21) validation enforces Pillar 4 at every milestone - not a one-time eSUB scramble.**
  - Define.xml generated from the MDR keeps documentation and datasets in lock-step (Pillars 2 and 7).
  - Dataset-JSON - now validated for FDA submission - modernizes transport and traceability beyond legacy XPT.
  - The CDISC Rare Diseases TAUG (NORD-funded) is the baseline; the seven pillars are the governance layer on top.

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The Payoff

Measurable returns across regulatory, scientific, and operational dimensions

Expected Results: Returns on the Investment

- **Regulatory**
  - P21 findings near-zero at eSUB; reproducibility met via the TLF manifest; clean agency-specific variants; shorter review cycles.
- **Scientific**
  - A harmonized endpoint (ABR) carries consistent meaning – reductions become comparable estimates of one phenomenon; valid pooled ISS/ISE. Example if we have ABR reduction differences in the different studies we will strive for consistent results.
- **Operational**
  - The single largest hidden cost - rework - is eliminated; QC deployed prospectively; iAP timelines predictable.
- **Long-Term Value**
  - Easier post-approval commitments and RWE integration; preserved institutional knowledge; a data asset for the rare disease community.

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Conclusion: Key Takeaways

01 Architectural divergence is predictable - the consequence of treating study-level conformance as sufficient when program-level consistency is the real requirement.

02 CDISC standards provide the vocabulary; they do not auto-produce harmonized outputs across a program.

03 CSR-level consistency is the most consequential and least-discussed dimension of the governance gap.

04 The seven-pillar framework converts governance from remediation into a design discipline - implementable from program inception, with a concrete artifact per pillar.

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Thank You!

