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Improving Risk-Based QA in Outsourced Studies Using Cross-Domain ADaM Derivation Comparisons

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ABSTRACT

In outsourced clinical trials, sponsor oversight often relies on a risk-based quality assurance (RBQA) model rather than full independent reprogramming of ADaM datasets. While RBQA effectively verifies derivation accuracy *within* individual ADaM domains, it does not ensure that conceptually related derivations are implemented *across* multiple datasets align with each other. This implicit assumption of cross-domain consistency represents a blind spot that can compromise analytical coherence, especially for time-to-event (TTE) endpoints, composite outcomes, and derivations dependent on shared clinical concepts such as treatment exposure, event dates, and censoring logic.

This paper presents a structured framework for cross-domain ADaM derivation checking designed to complement RBQA without expanding scope into full reprogramming. Using real-world patterns observed in outsourced studies, we illustrate typical cross-domain misalignments and present example tables, SAS code snippets, and process recommendations. Case studies show how simple output-based comparisons can detect inconsistencies otherwise invisible to Pinnacle 21, vendor QC, and domain-level review. Incorporating cross-domain checks into RBQA strengthens sponsor oversight, improves inspection readiness, and enhances confidence in final analyses.

INTRODUCTION

Over the past decade, the pharmaceutical industry has shifted toward outsourced programming models, where vendors create ADaM datasets, perform internal QC, and generate clinical outputs. Sponsors, in turn, use Risk-based QA (RBQA) frameworks to validate critical components without duplicating all programming effort. This approach is efficient focusing sponsor attention on high-risk endpoints, critical variables, and essential analytic pathways.

However, RBQA commonly means validating ADaM domains **independently**, relying on:

- ADaM specifications
- Vendor QC reports
- Pinnacle 21 compliance checks
- Targeted sponsor review of key variables

Risk-based QA for outsourced studies emphasizes traceability, specification compliance, and internal validity within a dataset or domain, avoiding duplicate programming. Many clinical analyses, however, depend on similar derivations repeated across multiple ADaM domains and parameters. When programming ownership is distributed, small implementation differences can arise that remain invisible to domain-centric checks yet degrade analytical coherence across endpoints.

Why Cross-Domain Issues Arise

Cross-domain inconsistencies occur due to:

1. **Parallel programming streams**
    - Different programmers build ADSL, ADEX, ADTTE, ADAE, ADVS, ADBDS.
    - Derivations are implemented separately even when logically identical.
2. **Specification ambiguity**
    - Specifications rarely state:
      "Ensure ADSL.TRTSDT matches ADEX.EXSTDTC (earliest)."
3. **SDTM limitations**
    - Partial dates
    - Missing sequences
    - Domain-specific cleaning
4. **Endpoint-specific business rules**
    - Composite endpoints use multiple input domains
    - Events filtered differently across domains

Because RBQA focuses on domain-level correctness, issues often surface late in analysis—during TFL generation or clinical/statistical review—leading to rework, timeline risk, and audit exposure.

This paper addresses this gap by proposing a practical cross-domain QA framework.

METHODS

To build a practical, scalable cross-domain QA approach, we classify cross-domain derivations into four categories—treatment exposure derivations, event derivations, censoring derivations, and analysis windows and visit alignment—and illustrate these concepts through six representative examples included in this paper.

For each category, we provide:

- a **Rationale** to explain why the derivation is cross-domain–dependent,
- a **cross-domain comparison check**, illustrated through a structured Comparison Table,
- a brief **Why This Matters** explanation describing the analytical impact, and
- **SAS code examples**, where applicable.

A simplified visual depiction of the cross-domain QA process is provided in **Appendix A** as one example workflow. The main paper focuses on the derivation categories and examples rather than prescribing a specific operational sequence

RESULTS

Below we show six example categories.

EXAMPLE 1 — Treatment Start/End Date Alignment

Rationale

Treatment start date appears in:

- ADSL (TRTSDT, TRTSDTM)
- ADEX (EXSTDTC)
- ADTTE (origin of time scale)
- Derived exposure summaries

All analyses relying on treatment timing depend on these dates matching.

Cross Domain Comparison Check

Subject	ADSL.TRTSDT	ADEX.EXSTDTC (min)	ADTTE Origin Start	Result
1001	2023-01-05	2023-01-04	2023-01-05	❌ Misaligned
1002	2023-02-10	2023-02-10	2023-02-10	✓ Aligned
1003	2023-03-08	2023-03-09	2023-03-09	

Why this Matters: Common Root Causes

- ADSL uses imputation for partial EX dates; ADEX uses raw SDTM values.
- ADEX contains screening doses that should be excluded.
- ADTTE uses treatment start defined by protocol, not exposure.

SAS Code Example

```sql
proc sql;
  create table trt_align as
  select a.usubjid,
         a.trtsdt as adsl_trtsdt,
         min(b.exstdtc) as adex_trtsdt format=date9.,
         case
           when calculated adsl_trtsdt = calculated adex_trtsdt
           then "Aligned"
           else "Mismatch"
         end as result
  from adsl a
  left join adex b
    on a.usubjid=b.usubjid
  group by a.usubjid;
quit;
```

EXAMPLE 2 — Event Date Alignment (ADTTE vs ADAE/ADVS)

Rationale

Time-to-event endpoints (e.g., time to first AE, time to first progression) rely on consistent event dates derived across domains.

Cross Domain Comparison Check

Subject	ADTTE.EVNTDT	ADAE.AESTDTC	ADVS Date	Result
1023	2023-06-15	2023-06-14	—	❌ 1-day mismatch
1044	2023-08-01	—	2023-08-01	✓ Match
1052	2023-09-12	2023-09-12	2023-09-13	

Why this Matters: Common Root Causes

- ADAE filtered incorrectly for qualifying events.
- ADTTE applied additional criteria (e.g., must occur after start of treatment).
- Visits used to identify events occur on different days (AE vs VS).

SAS Code Example

```sql
proc sql;
  create table event_compare as
  select a.usubjid,
         a.evntdt,
         b.aestdtc,
         case
           when a.evntdt = b.aestdtc then "Match"
           else "Mismatch"
         end as result
  from adtte a
  left join adae b
    on a.usubjid=b.usubjid
   and b.qualifying_event_flag="Y";
quit;
```

EXAMPLE 3 — Censoring Logic Alignment

Rationale

Censoring dates should reflect **last evidence of being event-free**.
These dates come from multiple ADaM domains.

Cross Domain Comparison Check: Censoring Alignment Across Domains

USUBJID	ADTTE.CNSRDT	Last AE	Last VS	ADSL.LSTALDT	QC Result
2001	2024-01-10	2024-01-14	2024-01-13	2024-01-14	❌ Too Early
2002	2024-02-05	—	2024-02-05	2024-02-05	✓ Correct
2003	2024-03-01	2024-02-28	2024-03-01		

Why this Matters: Common Root Causes

- Censoring defines each subject's time-at-risk, and even small discrepancies can shift survival curves and median estimates.
- Early censoring inflates event-free time, making treatment look more effective than it truly is.
- Late censoring understates risk, potentially masking true differences between treatment arms.

- Censoring relies on multiple domains (ADSL, ADAE, ADVS, ADEX), so misalignment often goes undetected in single-domain QC.
- Incorrect censoring classifications directly impact hazard ratios and interpretation of time-to-event analyses.
- Regulatory reviewers evaluate censoring logic closely, making cross-domain alignment essential for traceability and inspection readiness.

SAS Code Example

```
data cnsr_check;
  merge adtte(keep=usubjid cnsrdt)
        adsl (keep=usubjid lstaldt)
        ae_max (rename=(max_ae=last_ae))
        vs_max (rename=(max_vs=last_vs));
  by usubjid;

  max_date = max(last_ae, last_vs, lstaldt);

  if cnsrdt = max_date then result="Correct";
  else result="Incorrect";
run;
```

EXAMPLE 4 — Analysis Window Boundaries

Rationale

Analysis windows guide visit classification and scheduled assessments.

Cross Domain Comparison Check: Window Boundary Check

VISIT	ADVS Window	ADEX Window	Result
Week 12	77–91 days	75–89 days	❌ mismatched
Week 24	168–182	168–182	✓ match

Why this Matters: Common Root Causes

- Shifts in window rules change baseline definitions, longitudinal analyses, and responder rates.

EXAMPLE 5 — Baseline Flag (ABLFL) Cross-Domain Consistency

Rationale

Baseline selection in ADRE depends on **ADSL.RANDDT** and **RE-derived dates (FEV.REDTC / ADFEV.ADT)**.
If the randomization date in ADSL does not align with date variables used in ADRE, the wrong baseline record may be flagged with **ABLFL = 'Y'**, causing incorrect BASE, CHG, and PCHG calculations.

Cross Domain Comparison Check: Baseline Check

USUBJID	ADSL.RANDDT	ADFEV Baseline ADT	Expected Baseline ADT	Result
1001	2023-03-05	2023-03-01	2023-03-04	❌ incorrect baseline
1002	2023-04-10	2023-04-09	2023-04-09	✓ correct
1003	2023-02-20	2023-02-18	— (no RE before RANDDT)	❌ missing baseline

Why this Matters: Common Root Causes

- Incorrect baseline flags cascade into **incorrect BASE, CHG, and PCHG values**.
- Subjects may be assigned baseline values from the wrong day or wrong measurement type.
- Downstream analysis flags (e.g., ANL01FL) may select the wrong record for modeling.
- This error often cannot be detected within ADFEV alone — it requires **cross-domain comparison with ADSL and RE**.

Example 6— SCS Event Date Alignment Between ADSL and ADTTE

Rationale

The TTSCSOT endpoint in ADTTE—*Time to First Systemic Corticosteroid (SCS) Use up to Week 52*—pulls its event date from ADSL.FSCSDT(first systemic corticosteroid use date), uses ADSL.RANDDT as the time-to-event origin, and applies a Week 52 analysis window derived from ADSL.EOSDT and SDTM.SV.SVENDTC. Because ADTTE relies on these ADSL and SDTM variables to determine both the event date (ADT) and censoring (CNSR), any inconsistency or window misalignment between domains can incorrectly classify an event or censoring date, directly affecting time-to-event calculations.

Cross Domain Comparison Check — ADSL vs ADTTE SCS Event Consistency

(Uses ADSL.RANDDT, ADSL.FSCSDT, ADSL.EOSDT, SV.SVENDTC, and ADTTE derivation rules.)

USUBJID	RANDDT	FSCSNPDT	Expected ENDDT	ADTTE.ADT	ADTTE.CNSR	Result
3001	2023-01-05	2023-03-02	2024-01-04	2023-03-02	0	✓ Match
3002	2023-02-10	2023-02-01	2024-02-09	2024-02-09	1	❌ Should censor (event before RANDDT)
3003	2023-01-15	2024-02-01	2023-08-10	2024-02-01	0	❌ Event after Week 52 window
3004	2023-03-01	—	2024-02-29	2024-02-29	1	✓ Correctly censored

Why this Matters: Common Root Causes

Misalignment between ADSL (where the SCS event originates) and ADTTE (where the event is analyzed) can lead to:

- events counted when they should be censored,
- events censored when they should be counted,
- incorrect ADT (event date),
- incorrect CNSR classification, and
- shifts in time-to-event distributions and hazard ratios.

Because this endpoint is often used for assessing rescue medication usage in NP treatment studies, ensuring cross-domain consistency is critical for accurate interpretation and regulatory submission.

DISCUSSION

Cross-domain derivation checks are not a replacement for RBQA but a **critical complement**. They:

- Identify inconsistencies invisible to domain-level review
- Capture analytical misalignment early
- Improve trust in derived endpoints
- Strengthen submission narratives regarding traceability

LIMITATIONS

- Requires thoughtful selection of derivation categories

- Requires coordination with vendors
- Output-based checks cannot detect *incorrect but consistent* logic

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CONCLUSION

Cross-domain ADaM derivation checks significantly enhance RBQA by potentially inconsistencies that might have otherwise been overlooked. They improve analytical coherence, strengthen sponsor oversight, reduce timeline risk, and support inspection readiness. A structured, output-based approach offers high value with minimal burden.

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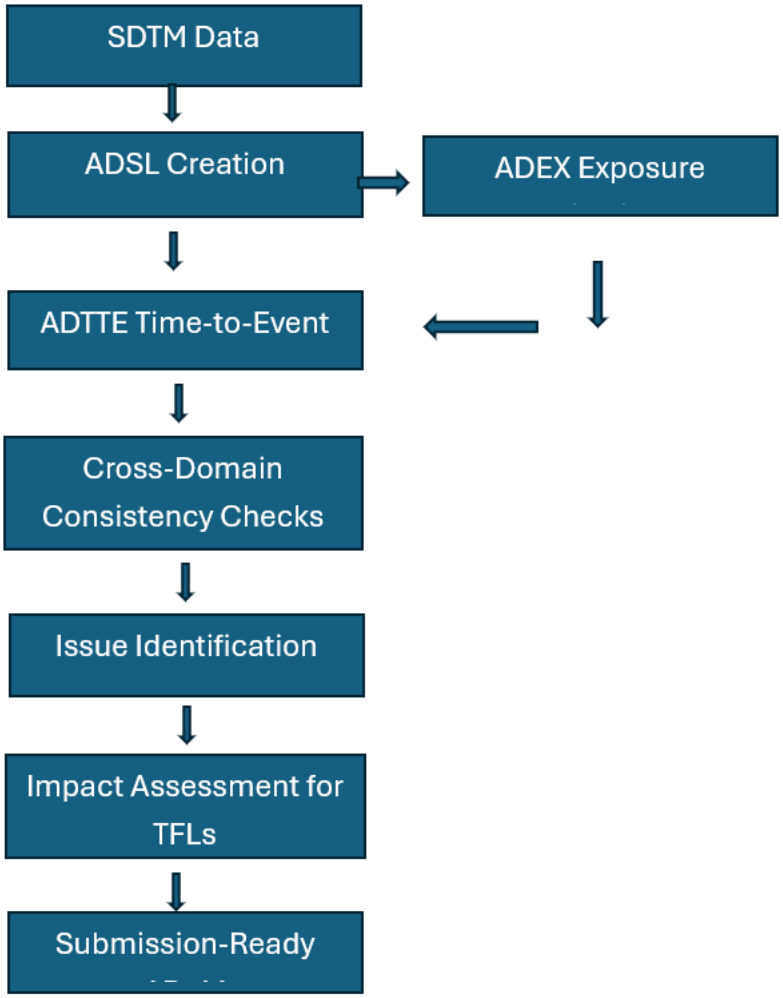
APPENDIX A — Example Cross-Domain QA Workflow (Illustrative Only)

The figure below provides one example of how cross-domain ADaM consistency checks can fit into an overall quality-assurance workflow. This visual representation is not intended to prescribe a specific operational process; instead, it offers a simplified view of how SDTM, ADSL, ADEX, ADTTE, and cross-domain comparisons may flow in practice.

Figure A1. Example Cross-Domain QA Workflow


SDTM Data
ADSL Creation
ADEX Exposure
ADTTE Time-to-Event
Cross-Domain Consistency Checks
Issue Identification
Impact Assessment for TFLs
Submission-Ready