



Kishore Pothuri is Executive Director of Biometrics, Clinical Data Services, and Operations at Vita Global Sciences. With 15 years of experience across CROs, medical device companies and multiple FSP partnerships with major sponsor organizations, Kishore is a seasoned leader and subject matter expert in SDTM, CDISC standards, clinical data management and life sciences operations.

Kishore has presented at PHUSE, PharmaSUG and other industry conferences, sharing insights into data standards, innovation and best practices. He has been Co-Chair for the Software Demonstration Stream at the PHUSE US Connect, Co-Chair for the PHUSE SDE Boston 2025, and is the Chair for the PHUSE SDE Texas 2026.

Kishore is a member of the Forbes Technology Council (2025), where he contributes thought leadership on technology adoption and transformation within life sciences.

He is deeply passionate about advancing the life sciences industry through meaningful collaboration, developing and harmonizing global data standards, and building high-performing teams who drive quality, efficiency and innovation.

Kishore strongly believes in fostering partnerships across organizations, enabling data-driven decision-making, and contributing to a more connected and standards-aligned clinical ecosystem.



Ajay Gunda serves as a Manager at Vita Global Sciences, where he leads Biometrics and Clinical Data Services. With more than 13 years of experience in Contract Research Organizations (CROs) and Functional Service Provider (FSP) partnerships with sponsor companies, he has built a strong reputation as an expert in the life sciences industry. A recognized Subject Matter Expert in CDISC standards, including SDTM and ADaM, Ajay's expertise and impactful contributions have established him as a go to person and made a significant impact within the company.



Vita Global Sciences

FROM RESEARCH TO REALITY

SA10

From Legacy to ISS/ISE: Real-World Lessons in Module 5 Submissions

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Session Objectives



Why ISS and ISE increase Module 5 complexity

ISS/ISE require pooling across studies with different designs and standards, increasing reconciliation, re-derivation, and traceability burden in Module 5.



Common real-world FDA submission pitfalls

Pooled datasets are often submitted without clear provenance or consistent population definitions, making analyses hard to reproduce.



FDA-aligned strategies to reduce filing and review risk

Standardize pooling rules and derivations early and provide explicit, reviewer-friendly metadata and navigation.

Why Module 5 Matters

- **Most Data-Intensive & Reviewer-Facing**
 - Full clinical evidence package (CSR, SDTM, ADaM, TLFs, metadata)
 - Reviewers actively interrogate datasets — not just read summaries
- **Drives Reviewer Efficiency & Confidence**
 - Clear traceability: CSR → SDTM → ADaM → TLF
 - Logical organization builds trust in submission quality
- **Organization Affects Filing Risk**
 - Dataset placement & link integrity matter
 - Poor structure → IRs, filing delays, potential RTF concerns

What Is in Module 5

- **Clinical Study Reports**

- Detailed narratives describing individual study design, conduct, and results.

- **SDTM & ADaM Datasets**

- Structured data supporting regulatory review, validation, and reproducible analysis.

- **TLFs & Metadata**

- Tables, Listings, Figures, define.xml, ADRG, and cSDRG guiding reviewer traceability.

High-Level Module 5 Structure

Standard Regulatory Hierarchy

The high-level folder structure is defined by regulatory guidance and must be followed consistently.

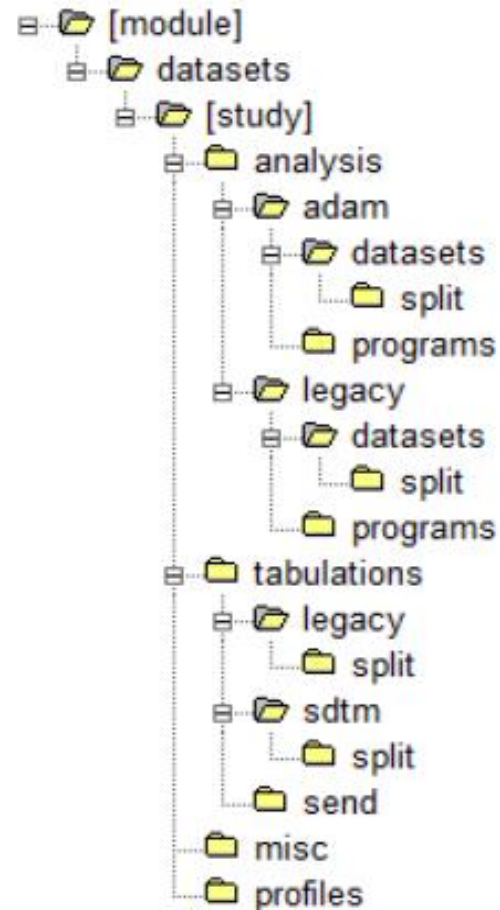
Sponsor Flexibility

Within that structure, sponsors retain flexibility to organize datasets, metadata, and outputs logically.

Reviewer Usability First

Clear navigation and traceability matter more than creative layouts or unconventional organization.

High-Level Module 5 Structure



Why ISS and ISE Are Different

1 Multi-Study Pooling

- Integrated analyses combine data across multiple trials, often conducted years apart.



2 Structural & Standards Variability

- Different CDISC versions, dictionary releases, and study designs introduce alignment challenges.



3 Study-Level Logic Does Not Scale

- Derivations, visit definitions, and population flags that worked at the study level rarely translate directly to pooled analyses.

Legacy Studies and Remediation

1 Legacy Standards Require Remediation

- Older SDTM and ADaM versions often must be updated to align with current CDISC expectations and integration needs.



2 Non-Standard Variables Create Inconsistency

- Custom or study-specific variables complicate pooling and reduce comparability across studies.



3 Metadata Falls Out of Sync

- define.xml, ADRG, and reviewer guides frequently lag behind remediated datasets, creating traceability gaps.

Integrated Analysis Complexity

1 Harmonize Analysis Populations

- Ensure consistent definitions of safety, efficacy, and analysis flags across all pooled studies.



2 Align Treatment Variables & Timing

- Standardize treatment assignments, exposure timing, and derivation rules before integration.



3 Standardize Endpoints & Visits

- Reconcile visit schedules, windowing rules, and endpoint derivations to support valid pooled results.

Regulatory Perspective

[1] Strong Emphasis on Traceability & Filing Readiness

- Datasets, metadata, and outputs must be logically connected and submission-ready at filing.
Reviewers expect seamless navigation from CSR → SDTM → ADaM → TLF without structural confusion.



[2] Low Tolerance for Ambiguity or Broken Links

- Unclear dataset placement, inconsistent naming, or hyperlink errors quickly reduce confidence.
Even minor technical gaps can signal broader quality concerns during filing review.



[3] Clear Separation of Integrated Content

- ISS and ISE datasets must be distinctly organized apart from study-level content.
Blurring study-level and pooled analyses complicates reviewer understanding and increases early questions.

Why Organization Matters

1 Increases Risk of Filing Delays

- Structural inconsistencies, misplaced datasets, or incomplete metadata can slow filing assessment.
Even if not triggering an RTF, these issues may delay acceptance and require clarification before review proceeds.



2 Leads to Early FDA Information Requests

- Unclear integration logic or traceability gaps prompt reviewers to seek clarification.
Early IRs increase workload, compress timelines, and create avoidable review friction.



3 Negatively Affects Reviewer Confidence

- Repeated navigation challenges or inconsistencies influence overall perception of submission control.
Reduced confidence can shape the tone and efficiency of the entire review cycle.

Case Example Overview

Five Phase 2 and
Phase 3 studies
pooled

Approximately
ten years of
clinical data

Multiple SDTM
versions and
MedDRA releases

- m5
 - datasets
 - ABC-001
 - ABC-002
 - ABC-003
 - ABC-004
 - ABC-005
 - ISE
 - ISS
 - analysis
 - adam
 - datasets
 - split
 - programs
 - figures
 - listings
 - tables
 - legacy
 - misc
 - profiles
 - tabulations
 - legacy
 - sdtm
 - split
 - tfls
 - figures
 - listings
 - tables

Common ISS Issues



INCONSISTENT DERIVATION OF
SAFETY POPULATION FLAGS



TREATMENT VARIABLES NOT
HARMONIZED ACROSS STUDIES



REUSE OF STUDY-LEVEL DEFINE.XML
FOR POOLED DATASETS

Common ISE Issues

Non-comparable visit definitions across studies

Baseline derivations differed across trials

Endpoints shared names but used different logic

Recommended ISS/ISE Organization



Clear separation from study-level Module 5 content



Dedicated integrated datasets for ISS and ISE



Dedicated metadata and reviewer documentation

Visit Harmonization

1

Use AWTARGET to
define target visits

2

Use AWRANGE to
define acceptable
windows

3

Use AWTDIFF to
quantify deviation
from target

Metadata Alignment

1 define.xml Must Reflect Final Datasets

- Variable attributes, derivations, and controlled terminology must match the actual remediated and pooled datasets.

Even small mismatches can create traceability confusion during FDA review.



2 ADRG Explains Pooling Logic

- The ADRG should clearly describe harmonization rules, integration decisions, and deviations from standards.

Reviewers rely heavily on this document to understand how ISS/ISE analyses were constructed.



3 cSDRG Documents SDTM Decisions

- Structural compliance choices and remediation details must be transparently described.

This ensures reviewers understand both legacy constraints and submission-level updates.

Common Pitfalls

1 Metadata Not Updated After Remediation

- Datasets are corrected, but define.xml and reviewer guides remain outdated.

This creates inconsistencies that are immediately visible to reviewers.



2 Broken Traceability to TLFs

- ADaM derivations do not clearly map to reported outputs.

Reviewers may request clarification if they cannot reproduce reported results efficiently.



3 Undocumented Dictionary Variations

- Multiple MedDRA or WHO versions are used without clear explanation.

This increases uncertainty around pooled safety or efficacy conclusions.

Risk Mitigation

1 Conduct Early Mock Module 5 Builds

- Simulate final folder structure before submission-critical timelines.
This exposes navigation, placement, and linkage issues early.



2 Maintain End-to-End Traceability

- Map CSR → SDTM → ADaM → TLF → define.xml.
Clear traceability reduces reviewer friction and information requests.



3 Ensure Early Cross-Functional Alignment

- Programming, biostatistics, and regulatory must align on integration strategy.
Late-stage structural changes significantly increase rework risk.

Regulatory Impact

1 Refusal-to-File (RTF) Risk Signals

- Unclear dataset placement or broken hyperlinks may signal submission unreadiness.

While rarely the sole cause, structural deficiencies can contribute to filing concerns.



2 Early Information Requests (IRs)

- Poor navigation or unclear integration logic leads to clarification questions.

This increases workload for both sponsor and agency.



3 Reduced Reviewer Confidence

- Repeated inconsistencies affect perception of submission control.

Confidence influences overall review efficiency and tone of engagement.

Key Takeaways

1 Treat ISS/ISE as Standalone Deliverables

- Plan them as independent submission components, not extensions of study-level analyses.
Dedicated datasets and metadata reduce integration ambiguity.



2 Standardize Before Pooling

- Harmonize populations, treatment logic, visits, and endpoints upfront.
Retrospective alignment increases complexity and risk.



3 Plan Datasets & Metadata Together

- Integration strategy and documentation must evolve simultaneously.
Misalignment between data and metadata is a frequent review trigger.



4 Think Like an FDA Reviewer

- Walk through Module 5 as a reviewer would - navigation first, validation second.
Technical compliance alone does not guarantee reviewer usability.

Thank You

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