

Introduction



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Lily Cheng is a Biostatistical Programming leader with nearly a decade of experience spanning both sponsor and CRO environments. Lily has led integrated analyses for multiple global Phase 3 studies, contributing to drug approvals across oncology, immunology, hematology, and rare diseases. She works closely with statisticians and clinical teams to deliver results needed for investigational product's overall efficacy and safety profiles, which are crucial for supporting FDA, EMA, and/or PMDA regulatory submissions.



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Dr. Qiong Wei is a Subject Matter Expert (SME) with years of hands-on experience in SAS programming for analysis, reporting, and preparing electronic submission package across Phase I/II/III clinical trials. She has supported the preparation of CDISC-Compliant data and submission of Phase I–III clinical study data (SDTM, ADaM, ISS, ISE) across diverse therapeutic areas to regulatory agencies such as the FDA and PMDA

Data Harmonization for ISS and ISE: a Practical Checklist for Integration Success

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By Lily Cheng, Qiong Wei, Ji Qi, Biopier LLC, a Veramed Company

The Veramed logo is displayed in a large, bold, dark teal font. The word "Veramed" is written in a sans-serif typeface, with the "V" being particularly prominent. The background of the slide features a light green to teal gradient, and a large, stylized white graphic of the letters "M" or "W" is visible in the upper right corner.

What are ISS & ISE?

Integrated Summary of Safety (ISS)

Combines safety data from multiple clinical studies to evaluate drug safety across diverse populations. Includes patients exposed to the investigational drug.

Integrated Summary of Efficacy (ISE)

Combines efficacy data and endpoints across studies to demonstrate treatment effectiveness. Critical for NDAs and BLAs.

The Integration Challenge

Studies conducted over different time periods by different vendors with varying protocols, SAPs, and programming conventions

Different Standards

Varying SDTM/ADaM versions across studies require alignment to a single target version

Coding Dictionaries

MedDRA and WHODrug versions must be harmonized to ensure consistent adverse event and medication coding

Visit Schedules

Inconsistent visit windows, naming conventions, and numbering schemes need standardized mapping

Derivation Logic

Different baseline definitions and analysis flag derivations require rederivation at integrated level

Work closely with sponsor to streamline required analyses

Practical Checklist Overview



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Dataset Implementation Guide Alignment

Dataset IG Alignment: Key Steps



Select Studies & Pivotal Reference

Choose which studies to include and identify pivotal study as baseline standard. Selection of a pivotal study establishes baseline standards for integration and helps manage complexity.

Collect Implementation Guides

Gather all SDTM/ADaM IGs from included studies. Note domains for integrated analyses: ADSL (subject-level), ADAE (adverse events), ADCM (concomitant medications), ADLB (laboratory), ADVS (vital signs), and efficacy-specific domains

Determine Integration Approach

Work with sponsor to decide: Integrated SDTM + ADaM or ADaM only? Mixture of legacy, SDTM, and ADaM datasets needed? Method must be clearly documented.

Example: IG Version Harmonization



Study	SDTM IG	ADaM IG
Study A	v3.1.2	v1.0
Study B	v3.2	v1.1
Study C (Pivotal)	v3.4	v1.2

Solution: Harmonize Studies A and B to match Study C's IG v3.4 / v1.2
All data must be upgraded to the target implementation guide version



Integrated Analysis Data Reviewer's Guide Completion Guidelines, section 1.4

This section is used to describe the type(s) of data sources used to create the integrated analysis datasets.

Study Identifier (STUDYID)	Protocol Number	Source Data Standard	Cutoff-Date or DBL-Date/Study Status
ABC-101	ABC-101	SDTM 1.7/IG 3.3 ADaM 2.1/IG 1.1	2022-01-26/ Completed
ABC-102	ABC-102	SDTM 2.0/IG 3.3 ADaM 2.1/IG 1.2	2024-03-02/ Completed
ABC-103	ABC-103	SDTM 2.0/IG 3.3 ADaM 2.1/IG 1.2	2025-12-12/ Ongoing

The table in this section should list each study included in the integration, along with the data standard used for that study (i.e. SDTM, Legacy Tabulation, Legacy Analysis or ADaM data).

Include one row for each study included in the integration.



Variable Specification Reconciliation

Evaluate variable specs: names, types, lengths, labels, controlled terminology

Use integrated SAP to determine:

- Required populations, analysis groups, and endpoints
- Which studies apply similar derivations
- When new variables or parameters need creation

If no comparable derivations exist across studies:

New variables will need to be created in the integrated dataset and documented in the integrated specification and Analysis Data Reviewer's Guide

Example: Treatment Dose Harmonization



Study	Dose Levels
Study A	100, 200, 300, 400, 500, 600, 700, 800 mg
Study B	300, 600, 900 mg
Study C	600 mg

Integrated Variable Creation per SAP:

Create integrated dose categories:

- < 300 mg
- 300 mg - ≤ 600 mg
- > 600 mg

Example: Causality Terminology



Study	Causality Terms
Study A	Unlikely, Definite
Study B	Not related, Unlikely, Possibly, Related
Study C	Not Suspected, Suspected

CDISC Analysis Convention - Standardize to Two Categories:

'Not Related': Unlikely, Not related, Not Suspected

'Related': Definite, Possibly, Related, Suspected



Coding Dictionaries

Dictionary Version Harmonization



MedDRA

Medical Dictionary for Regulatory Activities – codes adverse events. All AEs must be coded to a single MedDRA version in ISS.

WHODrug Global

Codes medications in clinical trials. All medications must be coded to a single WHODrug version.

Example: MedDRA version harmonization

Study A: v20.1

Study B: v22.0

Study C: v26.1

ISS requires: v28.0

Action Items:

1. Identify versions used
2. Consult sponsor on target
3. Up-version all studies
4. Document in iADRG



Variable Attributes & Metadata

Variable Harmonization Areas



Labels & Lengths

- Max 8 chars for names
- Max 40 chars for labels
- Max 200 chars for values
- CDISC-compliant labels
- For character values, accommodate longest value

Format Standardization

- Date formats (ISO 8601)
- Display formats
- Unified imputation rules, if applicable
- Consistent representation

Case Standardization

- Character variable casing
- Treatment values
- Controlled terminology
- Numeric vs char type
- Semantic consistency

Example: Treatment Value Case Standardization



Study	TRTP (Planned Treatment) Values
Study A	DRUG A 100 MG, PLACEBO
Study B	Drug A 100 mg, Placebo
Study C	Drug A 100 mg, PLB

Standardized Solution:

TRTP = 'Drug A 100 mg', 'Placebo' (character)
TRTPN: 1 = Drug A 100 mg, 2 = Placebo (numeric)



Integrated Analysis Data Reviewer's Guide Completion Guidelines, section 3.2

This section provides information specific to the comparison of the values of treatment variables and the use of planned and actual treatment variables in the integrated analyses. This is a comparison of variables *within* the integrated datasets.

The following questions must be answered. Italicised text is included for guidance. Additional information may be added below these required questions as needed.

ARM versus TRTxP
<<The purpose of this section is to describe/contrast values of ARM vs TRTxP.>>

Are the values of ARM equivalent in meaning to the values of TRTxP? <Yes/No>
*If yes, state 'Yes' here.
If no, state 'No' and insert additional text or a mapping table or a figure here.*

STUDYID	ARM	TRT01P	TRT02P	TRT03P
ABC-101	DRUG A 100 MG - PLACEBO	DRUG A 100 MG	PLACEBO	
ABC-102	Drug A 100 mg	Drug A 100 mg		
ABC-101, ABC-102	DRUG A 100 MG - PLACEBO	DRUG A 100 MG	PLACEBO	DRUG A 100 MG



Visit Mapping & Timing Variables

Visit Mapping Considerations

Essential for time-based analyses. Different studies use different schedules, naming, and numbering.

Visit Window Alignment

Define consistent visit windows across studies with different schedules. Create integrated visit structure that accommodates all study designs while maintaining analytical comparability. Follow SAP guidance and collaborate with sponsor.

Study Day & Analysis Day Calculation

Use integrated first dose date (earliest exposure across all studies). Study day = days from first dose. Adjust for rollover subjects. ADY may differ if SAP defines different reference date. Remember: Day 1 = first dose, Day -1 = prior, No Day 0 per CDISC.

Multi-Study Timing: Rollover Subjects

Rollover subjects who continue from Study A into Study B:

- Continue with integrated visit numbering (don't restart at Baseline or Day 1)
- Baseline remains defined from first enrolled study
- Integrated first dose date = earliest exposure date
- Use STUDYID to track enrollment, STUDID01/02 to record origin

Example: Subject 001 Integrated First Dose

Study	First Dose	Integrated TRTSDT
Study A	12JAN2009	12JAN2009
Study B	14FEB2012	12JAN2009



Analysis Flag Derivation Logic

Analysis Flag Harmonization



ABLFL – Baseline Flag

- Identifies baseline assessment
- Definitions may vary across studies
- Rederive using integrated baseline definition
- Critical for rollover subjects
- Single standardized definition required

ANLxxFL – Analysis Flags

- Identify specific record subsets
- On-treatment periods
- Evaluable populations
- Time windows
- Clinical criteria

AVALCATx – Value Categories

- Group continuous into ranges
- Support categorical analyses
- Clinically meaningful groupings
- Align with TFL requirements
- Standardize across studies

Analysis Flags: Critical Considerations

Variables with same names across studies may have different meanings - careful review required!

No guarantee that variables with same name contain same meaning across studies

CDISC ADaM variables (ANLxxFL, AVALCATy) may be defined differently per study:

- Baseline definitions vary: last non-missing before dose, predefined visit, average of multiple
- Analysis flags identify different subsets: on-treatment, time windows, evaluable populations
- Value categories group data differently across studies

Solution: Detailed review required to determine appropriate flags for integration

- Rederive flags using integrated definitions per SAP
- Align with TFL requirements
- Document in ADaM specifications and Analysis Data Reviewer's Guide



Unique Subject
Identifier
Coordination

USUBJID Standardization



Challenge: Subjects in Multiple Studies

Maintaining consistent USUBJID across studies is essential to prevent subject-level conflicts while preserving traceability. Different USUBJID structures can create conflicts. CDISC recommends STUDYID–SITEID–SUBJID, but variations occur.

Study	Original USUBJID
Study A	VWFA123-11-345678
Study B	ABC123-11-345678

Solution: Standardize to Study B structure; retain original as OUSUBJID for full traceability

Parameter & Unit Reconciliation

Parameter & Unit Harmonization

Critical for laboratory, vital signs, and measurement domains. Variability arises from different methods, codes, and units.

PARAMCD/PARAM Mapping

- Ensure strict 1:1 relationship
- Map different codes for same test
- Watch for PARCAT1 inconsistencies
- Document all mappings
- Confirm with sponsor

Example: ALB vs ALBC → PARAMCD='ALB'
HCG: PARCAT1 = 'Pregnancy' vs 'Urinalysis'

Unit Conversion

- Standardize to single unit
- Use validated conversion factors
- Retain original + converted (AVAL)
- Keep SDTM variables (--ORRES, --STRESN)
- Document in specifications

Example: Creatinine
mcmol/L → mg/dL ($\div 88.42$)

Submission Requirements

Required Submission Components

FDA and PMDA require ISS/ISE data per current eCTD requirements

Integrated ADaM Datasets

CDISC-compliant, conform to Study Data Technical Conformance Guide

Define-XML

Complete metadata per specification, validated with P21

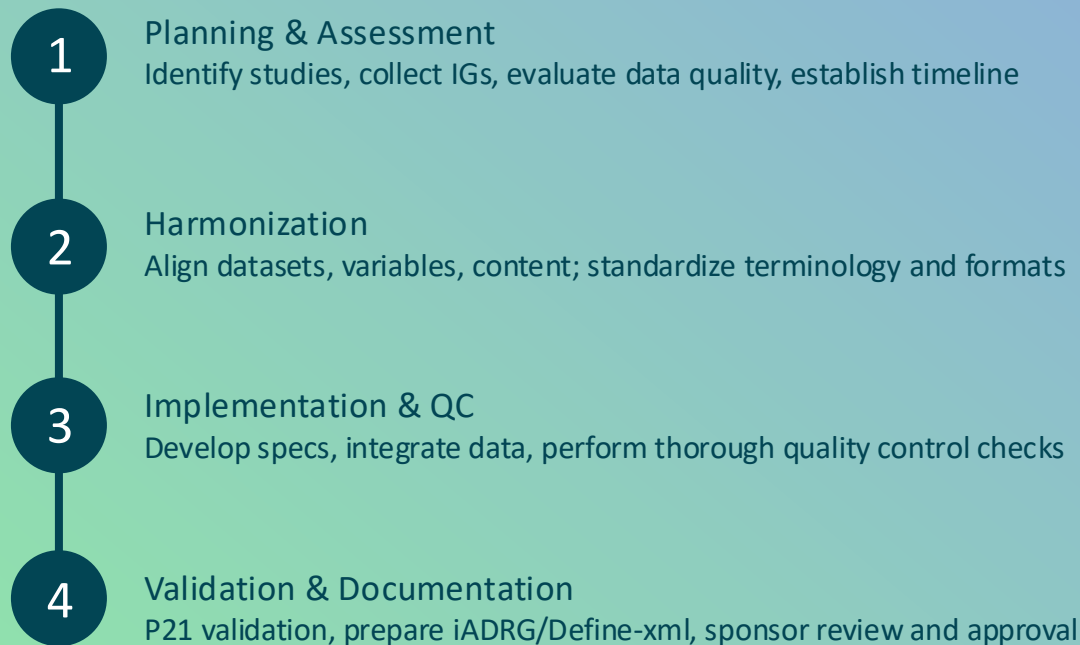
iADRG (Integrated ADRG)

Document all harmonization decisions, mappings, unresolved P21 issues

P21 Validation

Resolve all feasible errors/warnings, document justifications

Implementation Workflow





Questions?

Thank you for your attention

Use the practical checklist in your next ISS/ISE integration project.

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