

PHUSE US CONNECT 2025

Regulatory Submissions – Exciting, Challenging or Both

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Date: 19-March-2025



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Authors Biography



Ganesh Gupta is an Associate Director in Statistical Programming at Ephicity Consulting Group, bringing 18 years of experience in clinical data analysis and regulatory submissions. He has successfully led teams through complex projects in Immunology, fostering collaboration and innovation to improve workflows and achieve organizational goals. Outside of work, he is passionate about continuous learning, staying updated with industry trends, and contributing to his organization and the broader community. He believes in creating a positive impact through his work and relationships.

Randi McFarland, MS, is an Associate Director of Statistical Programming at the Ephicity Consulting Group overseeing Oncology and other projects. She has over 25 years of experience including management of statistical programming teams and project management. Randi led statistical programming teams for several successful FDA and EMA Oncology submissions. She has been an active member of the PHUSE Optimizing the Use of Data Standards (ODS) Working Group since 2019 developing the iADRG and icSDRG templates.

 Introduction

 Working With Data Management

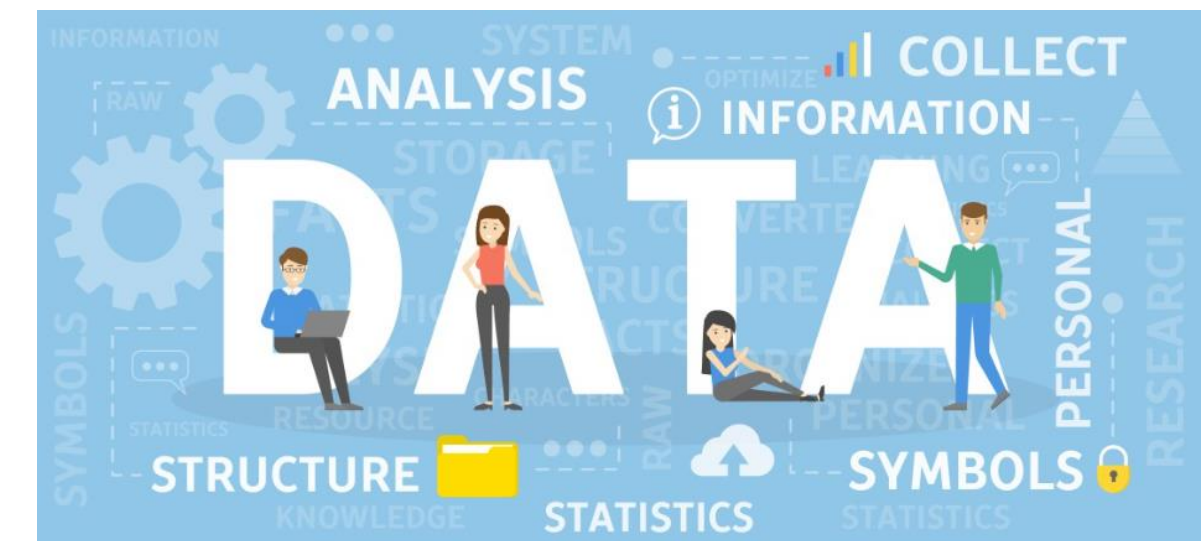
 Integration Planning and Development

 Documentation

 Best Practices

Introduction

- Clinical trials aim for regulatory approval for medical use.
- Success depends on quality data processing and analysis.
- Statistical programming ensures accurate and reliable data submissions.
- Collaboration between programmers, statisticians, and data managers is essential.



Working With Data Management

- Roles of Data Managers
 - Ensure accurate data collection, review, and cleaning
 - Resolve issues like missing or questionable data
- Key Challenges
 - Chronological mismatches in visit dates and data
 - Data integrity issues (e.g., incorrect event start and end dates)



- Example 1 of Data Challenges

Table of Patient 201 with Invalid Dates for Visits

Visit	Collection Date	Pain Rating
1	2/22/2022	10
2	7/22/2022	3
3	4/23/2022	8
4	5/24/2022	7
5	3/23/2022	10

- Incorrect sorting can misrepresent treatment impact.
- Programmers must ensure visits and dates match chronologically.

- Example 2 of Data Challenges

Table of Adverse Events with Invalid Dates

Subject	Adverse Event (AETERM)	Event Start Date	Event End Date
30010-001	Headache	30AUG2023	17JUN2023
30501-003	Nausea	05NOV2022	04NOV2022
20221-005	Hypertension	10FEB2023	01JAN2023
20252-002	COVID-19	16MAY2024	13MAY2024

- End date before start date affects analysis accuracy
- Data managers must review and correct these errors

Working With Data Management

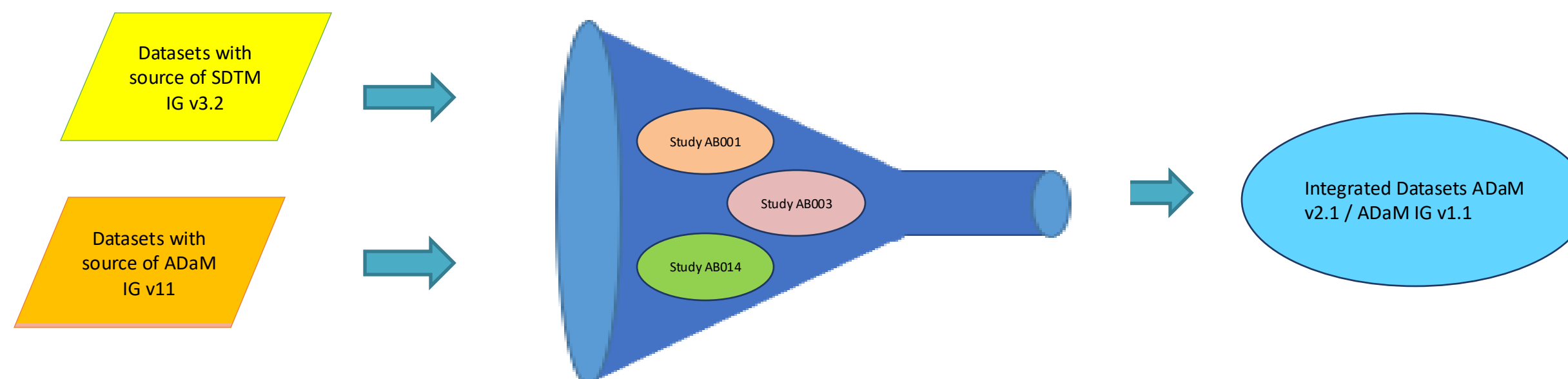
- Strategies for Effective Collaboration

- Begin collaboration early in the project
- Conduct frequent communication and data reviews
- Provide feedback to ensure data meets analysis requirements
- Detect and resolve data issues early to prevent submission delays
- Overall clear communication and early planning between teams ensure accurate, reliable, and timely data submissions.



- Purpose of Data Integration

- Combine data from multiple studies or sources to enable analysis as per the integrated Statistical Analysis Plan (iSAP).
- Address complexities in data collection, coding standards, and dictionaries to ensure consistency.
- Ensure successful harmonization to produce accurate and consistent analyses.





- Planning Steps:
 - Create an Integrated Statistical Analysis Plan (iSAP):
 - Define analysis strategies and pooling methods
 - Specify primary endpoints (e.g., OS, PFS) and statistical models.
 - Develop Detailed Specifications:
 - Outline data pooling methods, grouping, and re-coding of variables.
 - Ensure consistency and accuracy across datasets.
 - Coordinate with Teams:
 - Collaborate with data managers and statisticians.
 - Plan data cuts and resolve discrepancies early.

Statistical Analysis Plan
Integrated Summary of Safety (ISS)

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- **Mock Tables and Naming Strategy**

- Mocks with unique identifiers simplify linking tables and figures (e.g., TE-01 for efficacy tables, FE-01 for figures).
- Use prefixes like "SE" or "SS" for Integrated Summary of Efficacy (ISE) and Safety (ISS).
- Assign mocks to specific ICH tables (e.g., 14.1.1, 14.2.1) to ensure clarity and avoid rework.

Table of Mock assignments for ISS and ISE

Program Name	ICH Table Number	Mock Table Number	Include in ISS	Include in ISE
tdemsum	14.1.1	SSTS-01	X	X*
tcharsum	14.1.2	SSTS-02	X	X*
taeall	14.3.1.1	SSTS-03	X	X*
taesoc	14.3.1.2	SSTS-04	X	
tlabhem	14.3.2.1	SSTS-07	X	
flabvis	14.3.2.2	SSFS-04	X	X*
teff01	14.2.1	SETE-01		X
feff01	14.2.1.1	SEFE-01		X

Integration Planning and Development

- Detailed Dataset Specifications:
 - With clear SAP and mock tables in place, the specification
 - Outlines methods for pooling, re-coding, and creating new variables
 - Specifies grouping variables and address known differences between studies
 - Maintains traceability between pooled data and original sources

- Addressing Integration Challenges
 1. Differences in baseline definitions or treatment lag times across studies
 - Solution: Create a table of algorithm differences to standardize or document variations.

Table of algorithm differences across studies and submissions

Algorithms	Data	Study 1	Study 2	Study 3	ISS
Baseline	Vital sign measurements	Last value prior to visit 1	Day 1 value	Last visit of run-in period	Last visit prior to Day 1
Baseline	ECG measurements	Average of last Triplicate prior to visit 1	Day 1 value	Last visit of run-in period	Last visit prior to Day 1
Treatment Lag time	On-treatment Adverse Events	7 days post last dose	14 days post last dose	10 days post last dose	7 days post last dose

- Addressing Integration Challenges
 - 2. Adverse event terms coded differently in older MedDRA versions.
 - Solution: Up-version to the latest dictionary for harmonized analysis.

Table of MedDRA coding differences when up-versioning

Adverse Event (AETERM)	Preferred Term (MedDRA v24.1)	Preferred Term (MedDRA v27.0)
Eyelid Papilloma	Blepharal Papilloma	Papilloma
Left Knee Pain	Osteoarthritis	Arthralgia
Malaise With Vaccination	Vaccination Complication	Immunisation Reaction
Tachycardia Post Covid-19 Infection	Post-acute Covid-19 Syndrome	COVID-19

Integration Planning and Development

- Strategies for successful integration
 - Document and update differences for consistent data integration.
 - Ensure traceability to original sources for reliability.
 - Validate pooling and algorithms through statistical review.



- Challenges

- Documentation Standards

- The Technical Conformance Guide (TCG)
 - » Data Standards Catalog and more
 - CDISC SDTM and ADaM Implementation Guides (IGs)
 - Study Data Standardization Plan (SDSP)
 - PHUSE cSDRG, ADRG, iADRG templates



Analysis Data Model Implementation Guide
Version 1.2 (Final)



Study Data Tabulation Model
Implementation Guide: Human Clinical Trials
Version 3.4 (Final)

Electronic Common Technical Document (eCTD) v4.0 TECHNICAL CONFORMANCE GUIDE

Technical Specifications Document

This Document is incorporated by reference into the following
Guidance Document(s):

*Guidance for Industry Providing Regulatory Submissions in Electronic Format — Certain Human
Pharmaceutical Product Applications and Related Submissions Using the
eCTD Specifications*

For questions regarding this technical specifications document, contact CDER at
esub@fda.hhs.gov or CBER at esubprep@fda.hhs.gov

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)



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Documentation



FDA Data Standards Catalog

FDA Data Standards Catalog v10.4													
Full description of column headings in Instr.& Column Descriptions tab. Rows with data models are in bold with blue fill. Dependant properties (i.e., IG, technical document) for each model are listed beneath. Sorting may obscure													
Use	Standard	Exchange Format	SDO	Property	Related Properties	FDA Center(s)	Date Support Begins	Date Support Ends	Date Requirement Begins	Date Requirement Ends	Statutory, Regulatory, or Guidance Authority	Statutory, Regulatory, or	Information Sources
Clinical study datasets	ADaM	XPT	CDISC	ADaMv2.1		CDER, CBER	Ongoing		12/17/2016 [1]		Standardized Study Data		CDISC.org - ADaM
Clinical study datasets	ADaM	XPT	CDISC	ADaMIGv1.0		CDER, CBER	Ongoing	03/15/2019 [1] [12]	12/17/2016 [1]	03/15/2019 [1] [12]			
Clinical study datasets	ADaM	XPT	CDISC	ADaMIGv1.1		CDER, CBER	10/2/2017						
Clinical study datasets	ADaM	XPT	CDISC	ADaMIGv1.2		CDER, CBER							
Clinical study datasets	ADaM	XPT	CDISC	ADaMIGv1.3		CDER, CBER	07/18/2022						
Clinical study datasets	SDTM	XPT	CDISC	SDTMv1.1		CDER, CBER	Ongoing	01/28/2015 [12]					
Clinical study datasets	SDTM	XPT	CDISC	SDTMIGv1.1		CDER, CBER	Ongoing	01/28/2015 [12]					

<Sponsor>: <Name of Product>: <Indication>: <IND> SDSP

4.3 Pooled Studies

Data Pool Identifier	Data Pool (List of Studies)	Pool Status	Pool Description	Exchange Standards	Terminology Standards
		CURRENT	ISS <any additional information, such as certain domains>	ANALYSIS LEGACY	Sponsor Defined Terminology
		PLANNED	ISE <any additional information, such as certain domains>	ADaM v<version>/ ADaM IG <version>	CDISC SDTM Terminology <date> <TBD>
				ADaM define.xml <version>	MedDRA (Adverse Events/ Medical History/ <other>)
				ADaM vTBD/ ADaM IG TBD	Initial <version> Final <version> Initial TBD Final TBD
				ADaM define.xml TBD	TABULATIONS LEGACY
				SDTM v<version>/ SDTM IG <version>	WHO-DD (Medications) <version> <TBD>
				SDTM define.xml <version>	LOINC (Lab Test Term) <version> <TBD>
				SDTM vTBD/ SDTM IG TBD	SNOMED CT (Indication)
				SDTM define.xml TBD	

PHUSE Study Data Standardization Plan (SDSP)
<https://phuse.global/Deliverables>



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Documentation



- PHUSE Data Reviewer’s Guides

Study <Protocol Number>

Analysis Data Reviewer’s Guide

Analysis Data Reviewer’s Guide

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2.2 Protocol Design in Relation to ADaM Concepts.....

3. Analysis Considerations Related to Multiple Analysis Datasets.....

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3.2 Treatment Variables.....

3.3 Subject Issues that Require Special Analysis Rules

3.4 Use of Visit Windowing, Unscheduled Visits, and Record Selection.....

3.5 Imputation/Derivation Methods.....

4. Analysis Data Creation and Processing Issues

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4.2 Data Dependencies

4.3 Intermediate Datasets.....

Study <Protocol Number>

Clinical Study Data Reviewer’s Guide

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2.3.2 TE – Trial Elements

2.3.3 TV – Trial Visits.....

2.3.4 TI – Trial Inclusion/Exclusion Criteria

2.3.5 TS – Trial Summary.....

3. Subject Data Description.....

3.1 Overview

3.2 Traceability Flow Diagram:

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3.4 SDTM Subject Domains

3.4.1 AE – Adverse Events

3.4.2 DS – Disposition

3.4.3 EX – Exposure.....

3.4.4 Dataset – Dataset Label.....

4. Data Conformance Summary

4.1 Conformance Inputs

4.2

Integrated
Analysis Data Reviewer’s Guide

<Sponsor Name>

<Compound Name>

<Type of Integration>

<iADRG Version x.x>

iADRG Template Version yyyy-mm-dd

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- Strategies

- Clear, complete and organized submission documentation

- Examples:

- standalone programming codes
 - data reviewer's guides and SDSP
 - define.xml (ADaM and SDTM)
 - Pinnacle 21 (P21)
 - other documents as appropriate
 - analysis methods
 - »Ex. different study algorithms for same analysis data points.

Best Practices

Submission Planning is Key

- Early in the statistical programming process
 - Regular project team meetings
 - Clearly defined data cuts and data cleanliness (DM)
 - Clearly defined populations and analyses, SAP and mocks (Stats)
 - Raw and SDTM data availability to start programming analyses (DM)

Submission Planning is Key

- Plan data integrations from different sources through data review
 - Plan dictionary or CDISC upversioning if needed
- Organize and minimize duplication of documentation and programming
- Refer to industry guidance documents for correctness and completeness



THANK YOU

References



- ¹ Study Data Technical Conformance Guide - Technical Specifications Document (Oct 2024)
[[Study Data Technical Conformance Guide_v5.9_Oct 2024](#)]
- ² Data Standards Catalog (April 2024)
[<http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm>]
- ³ Providing Regulatory Submissions in Electronic Format — Standardized Study Data (June 2021)
[<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf>]
- ⁴ Clinical Data Interchange Standards Consortium (CDISC): SDTM and ADaM Standards and Implementation Guides [<https://www.cdisc.org/standards>]
- ⁵ PHUSE Submission templates including BIMO, Data reviewer's Guides and Study data Standardization Plan (SDSP) [<https://advance.phuse.global/display/WEL/Deliverables>]
- ⁶ PMDA Technical Conformance Guide (April 2024)
[<https://www.pmda.go.jp/files/000267935.pdf>]

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