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A Standardized Reviewer's Guide for Clinical Integrated Analysis Data

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ABSTRACT

The Integrated Summary of Safety (ISS) and Integrated Summary of Efficacy (ISE) are vital components of a successful submission for regulatory review in the pharmaceutical and biotechnology industry. The submission package includes integrated Data Reviewer's Guide (DRG) along with integrated database(s) (ISS and/or ISE) that allow reviewers to better understand traceability of the data, pooling strategy, analysis considerations, subject-specific significant information, and conformance findings.

The PHUSE Analysis Data Reviewer's Guide (ADRG) applies to a single study. Sponsors have been adopting this template and making amendments when creating a reviewer's guide for an integrated analysis data submission. PHUSE recognized the need for a new, standardized template and completion guidelines for an integrated analysis data reviewer's guide. The integrated analysis data reviewer's guide (iADRG) template was developed by the PHUSE project team considering integration strategies, challenges, and regulatory recommendations. This paper shares integration approaches that were considered and provides structure for context of the integrated analysis data to assist the regulatory reviewer.

DISCLAIMER

All views expressed in this paper are those of the authors and are not necessarily those of PHUSE, CDISC or the authors' companies: ADC Therapeutics, Merck, and Alexion AstraZeneca Rare Disease. A step-by-step approach to standardization and a consistent process to build an integrated data reviewer's guide presented in this paper should not be interpreted as a standard and/or information required by regulatory authorities.

INTRODUCTION

Pharmaceutical and biotechnologies are working to get their products quickly to market and are looking for ways to streamline this process. Regulatory agencies are also looking for consistencies from companies to improve the ease and efficiency of their reviews. Standardization of data and documentation have come from several industry groups including both CDISC and PHUSE. CDISC has provided data standards for submissions of clinical and non-clinical data while PHUSE has provided documentation accompanying data. For the clinical study analysis data, PHUSE with FDA developed the Analysis Data Reviewer's Guide (ADRG) to assist regulatory agencies to understand the analysis data details for a single study. However, there is no standard documentation to detail the pooled safety and efficacy data to regulatory agencies. Companies provide this information in different formats thereby creating a need for standardization. The PHUSE Optimizing the Use of Data Standards (ODS) Working Group has taken on this challenge to share a best practice for presenting pooled analysis data.

ACRONYMS

Acronym	Translation
ADaM	Analysis Data Model
ADaM IG	Analysis Data Model Implementation Guide
ADRG	Analysis Data Reviewer's Guide
ANDA	Abbreviated New Drug Application
BLA	Biologics License Application
CDISC	Clinical Data Interchange Standards Consortium
cSDRG	Clinical Study Data Reviewer's guide
FDA	US Food and Drug Administration
iADRG	Integrated Analysis Data Reviewer's Guide
icSDRG	Integrated Clinical Study Data Reviewer's Guide
iSAP	Integrated Statistical Analysis Plan
ISE	Integrated Summary of Efficacy
ISI	Integrated Summary of Immunogenicity
ISS	Integrated Summary of Safety
NDA	New Drug Application
ODS	Optimizing the Use of Data Standards
PHUSE	Pharmaceuticals User Software Exchange
PK/PD	PharmacoKinetics/PharmacoDynamics Data
PMDA	Pharmaceutical and Medical Devices Agency (Japanese Regulatory Agency)
SDTM	Study Data Tabulation Model
SDTM IG	Study Data Tabulation Model Implementation Guide

OVERVIEW

Pharmaceutical and biotechnology companies have adopted the CDISC data format as required by the FDA for individual studies used for NDA, ANDA, and certain BLA submissions as of Dec 17, 2016. Sponsors are providing integrated analysis data to support their regulatory submissions; however, sponsors have different ways of presenting the integrated analysis data and the associated documentation. There is an opportunity to standardize the reviewer's guide so that there is a consistency in presenting the analysis information important for a reviewer.

As pharmaceutical and biotechnology companies plan for regulatory submissions, they need to provide pooled analysis data, for both safety and efficacy. First, they must compile the appropriate studies that will support their submission for the target indication and then standardize and integrate this data. This data may be coming from multiple sources in multiple formats, which may require the recoding and/or harmonizing to incorporate data exchange and terminology standards. As there is no standardization for pooled analysis data, different companies have different approaches to combine data and provide information and clarification about this data to regulatory agencies. The industry needs to have standardized documentation to support regulatory submission to multiple agencies.

The PHUSE ODS Working Group has developed an Integrated Analysis Data Reviewer's Guide (iADRG) template incorporating information from the ADRG and gathering input from FDA and PMDA to create a document specific to the details of data integration. The Integrated Analysis Data Reviewer's Guide (iADRG) provides regulatory reviewers with additional context for integrated analysis datasets received as part of a regulatory submission. The iADRG is intended to describe analysis data submitted for integrated data summaries (e.g., ISS, ISE, etc.).

INTEGRATION APPROACHES

The integration approaches outlined below were considered in building the integrated Analysis Data Reviewer's Guide and shown in Figures 1.0 and 2.0.

a. **ADaM -> integrated ADaM**: This is the common approach followed where the individual study ADaM datasets pooled into integrated analysis datasets.

b. **ADaM +/- Legacy ADaM -> integrated ADaM**: This is also one of the common approaches where the individual study ADaM datasets are pooled with individual study legacy ADaM datasets (ADaM format but is no longer accepted by regulatory agency). The legacy ADaM data is up versioned to the ADaM version accepted by the agency and to the latest dictionary versions.

c. **ADaM +/- Legacy ADaM +/- Legacy analysis -> integrated ADaM**:
In this approach study ADaM datasets are pooled with legacy ADaM and analysis datasets from individual studies. The legacy analysis datasets are converted to ADaM format and legacy ADaM data are up versioned to the ADaM version accepted by the agency. Both legacy analysis and legacy ADaM dictionaries should be harmonized.

d. **Integrated SDTM -> integrated ADaM**: Integrated SDTM to integrated ADaM. This approach is not a conventional approach. Since some of the sponsors are still creating integrated SDTM to use for integrated analysis, this approach should be considered.

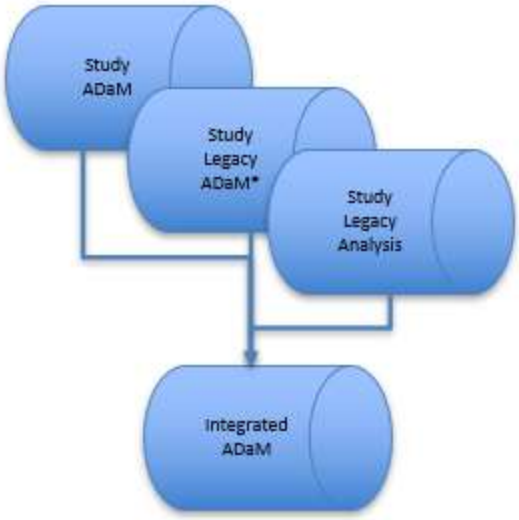

Figure 1.0 Analysis Datasets Used in Integration

*ADaM no longer supported per the Data Standards Catalog

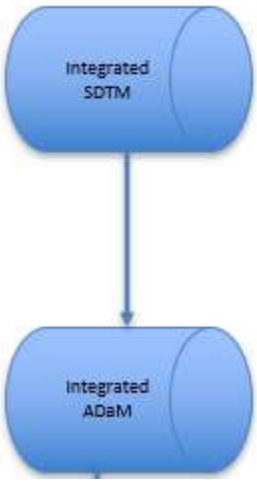

Figure 2.0 Non-conventional Approach for Analysis Integration

CONSIDERATIONS FOR CONSTRUCTION OF THE IADRG TEMPLATE

The iADRG addresses several key challenges of integration including the sources of the data, integration methods, and information that affects integrated datasets. The iADRG template is adopted from the individual study ADRG template and modified to accommodate integration analysis data related information. For most of the iADRG sections, the structure and purpose are consistent with the individual study ADRG template.

Special considerations in building the integrated template include Additional Content of Interest sections. This gives users an option to add information and to present tabular structures as necessary.

The iADRG assumes that the analysis datasets adhere to the ADaM standard to the extent possible. The

Legacy Data Conversion Plan and Report Appendix is needed in the event a sponsor has converted any non-standard source data during integration.

The significant elements of the iADRG are presented and outlined below.

- Source Data Used for Integrated Analysis Dataset Creation
- Traceability Flow Diagram
- Description of Protocols Used in the Integrated Dataset
- Integrated Analysis Strategy and Design in Relation to Analysis Concepts
- Analysis Considerations Related to Integrated Analysis Datasets
- Integrated Analysis Data Creation and Processing Issues
- Integrated Analysis Datasets Descriptions
- Data Conformance Summary
- Submission of Programs

SOURCE DATA USED FOR INTEGRATED ANALYSIS DATASET CREATION

This section provides a summary of the source data for each study used for integrated analysis datasets. In this section, a new table (Table 1.0) was introduced for ease of reading, providing the source data information and traceability for each study. Users would list the study identifier and/or protocol number, data standard used for that study (i.e., SDTM, ADaM, Legacy Tabulation, or Legacy Analysis data), cutoff date or database lock (DBL) date and study status (Continuing/Ongoing).

Study Identifier and protocol number are included in separate columns as these numbers could be different for some sponsors. For an ongoing study or one that has an ongoing follow-up component, the data cutoff rules may be described as “additional content of interest” in this section.

Study Identifier (STUDYID)	**Protocol Number**	**Source Data Standard**	**Cutoff-Date or DBL-Date / Study Status**
		SDTM IG <version> Legacy Tabulation Legacy Analysis ADaM IG <version>	

Table 1.0 Source Data Information

TRACEABILITY FLOW DIAGRAM

This is a new section that was added to provide a traceability flow diagram and to describe the flow from the various sources of data to the integration outputs. Additional details as needed regarding the traceability can be included. A sample illustration of a traceability diagram is shown in Figure 3.0 where the individual study datasets are coming from ADaM IG v1.0 (Legacy ADaM) and ADaM IG v1.1. The diagram shows the up-versioning and normalization of the data to ADaM IG v1.1 before integration and followed by the integration outputs.

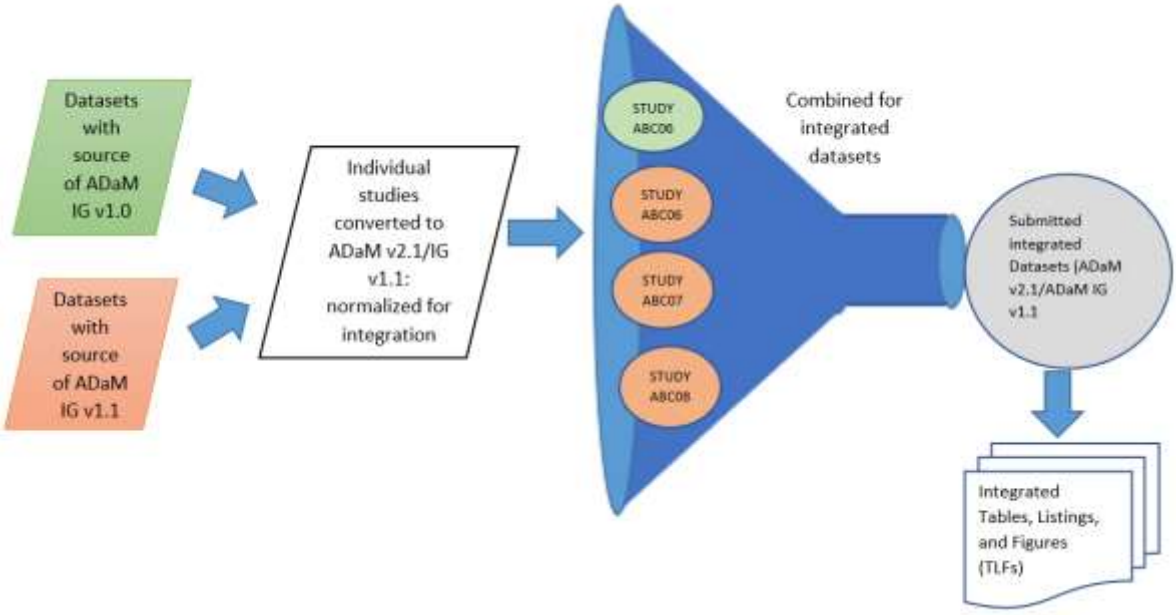

Figure 3.0. Traceability Flow Diagram

DESCRIPTION OF PROTOCOLS USED IN THE INTEGRATED DATASETS

This section provides information on protocol number and title, phase of the study, and treatment ARMs for each study in the integration. This information is captured in the table as shown below (Table 2.0), which has been added in the iADRG template.

The last two columns display planned treatment ARM(s) in the study and any planned treatment ARM(s) not used in the integration. This assists the reviewer in knowing which treatment ARMs are used in the integration and any that are not.

Authors can include or expand details about the study populations, primary endpoint(s), and dosing regimens/formulation in the Additional Content of Interest sub-section.

Protocol Number	Indication(s)/ Protocol Title	Phase	Treatment ARM(s)	Treatment ARM(s) not used
			<compound, placebo, and/or competitor>	<Not applicable>

Table 2.0 Protocol Information

INTEGRATED ANALYSIS STRATEGY AND DESIGN IN RELATION TO ANALYSIS CONCEPTS

This section is modified from the individual ADRG template to accommodate the integration analysis strategy. It is intended to elaborate on the complexities and concepts behind the integrated analyses, providing a road map to the integration plan and the design of the pooled datasets.

The ADaM model does not provide definition on integrated analysis variables and usage for a given analysis. For instance, no standard convention exists for 'phase' and 'period' terms across the industry and may not be consistent across the protocols. The standard ADaM variable definitions for treatment, analysis period, analysis phase, etc. used for integration are harmonized so that variables and values have the same meaning across all studies. This is a key element in promoting an understanding of how each protocol design relates to key analysis concepts used in ADaM and drives consistency across all the studies considered for integration.

It is strongly recommended to include references to an integrated statistical analysis plan, if available.

ANALYSIS CONSIDERATIONS RELATED TO INTEGRATED ANALYSIS DATASETS

This part of the iADRG is intended to document analysis considerations specific to the integrated analysis datasets creation, which includes the following areas of interest.

The "Core Variables" section lists common variables across the datasets, which are usually the variables from the ADSL dataset. In the integrated studies, it is expected to have a longer list of core variables than individual studies due to pooling flags, treatment periods, pooled treatment sequence, and pooled treatment group variables.

The "Treatment Variables" section is included for documenting the comparison of treatment variables ARM versus TRTxxP, and ACTARM versus TRTxxA. The use of planned and actual treatment or grouping variables is recommended to document in-detail with or without a table whether used for safety or efficacy or both. Also, it could be possible to have crossover or extension studies where the treatment sequence variables (TRTSEQP, TRTSEQPN, TRTSEQA, TRTSEQAN) are created during integrated datasets creation. Planned pooled treatment or sequence variables (TRxxPGy, TRxxAGy, TSSEQPGy, TSSEQAGy) information is to be document if derived. As the ADaM IG does not fully support integrations, the sponsor may create additional variables. Hence, for the user flexibility, the "Additional Content of Interest" section has been added.

The "Subject Issues that Require Special Analysis Rules" section in the ADRG is now updated to "Subject or Protocol Considerations that Require Special Integrated Analysis Rules" in the iADRG. Information related to special analysis rules across multiple datasets should be documented in this section. Examples include the rationale for subjects excluded from analysis datasets, handling rules if enrolled in multiple studies, and the difference in baseline derivations across multiple datasets. If any special analysis rule applies to only one dataset, it is recommended to document in its own dataset section. The iADRG also introduced a question prompt to indicate whether any recoding was performed to integrate individual studies.

The "Use of Visit Windowing, Unscheduled Visits, and Record Selection" section is included to document details about visit windowing on the planned and unscheduled visits. A question regarding record selection was added to document if record selection was used for analysis purposes. For example, multiple visits used for the same visit window or baseline selection can be explained.

Information about "Imputation/Derivation Methods" can be documented if common imputation and/or derivation rules, such as DATEFL, DTYPE, were used across multiple datasets.

INTEGRATED ANALYSIS DATA CREATION AND PROCESSING

Integrated analysis datasets may have data dependencies, require intermediate datasets, or require being split for submission. The integrated analysis dataset creation and processing requirements are similar to the requirements for individual studies analysis datasets. This section in the ADRG required minimal modifications for the iADRG. Data dependencies are generally displayed in a flow chart; however, a tabular format is recommended when the data dependencies are minimal.

The “Additional Content of Interest” sub-section was added to document any additional information to assist the reviewer.

INTEGRATED ANALYSIS DATASETS DESCRIPTIONS

This section contains 2 sub sections- 1) Overview and 2) Integrated Analysis Datasets.

1) Overview: Provides a summary to the integrated analysis datasets as documented in an integrated SAP and objectives in the integrated SAP. This section was modified from the individual ADRG to support the integrated data reviewer’s guide.

2) Integrated Analysis Dataset: This section contains an inventory table to provide the class, purpose, structure of each dataset and whether the dataset is pooled from all studies.

   The table columns are modified from the individual ADRG to accommodate the integration purpose and the below table (Table 3.0) shows the comparison between the ADRG and iADRG

The columns efficacy and safety combined to one column as integration is applicable for either Efficacy or Safety or Immunogenicity summary. PK/PD and Primary Objective columns are removed as they are not applicable for ISS/ISE. All studies contribute column was added to indicate whether all studies contribute or not to that dataset.

The analysis dataset description section remained unchanged from the ADRG template.

Individual ADRG inventory table:

Dataset Name Dataset Label	Class	Efficacy	Safety	Baseline or other subject characteristics	PK/PD	Primary Objective	Structure

Integrated ADRG inventory table:

New

Dataset Name Dataset Label	Class	Efficacy(E)/ Safety(S)/ Immunogenicity (I)	Baseline or other subject characteristics	All studies contribute	Structure
ADSL Subject-Level Analysis Dataset	ADSL		X	X	One observation per subject
		<E/S/I>			

Table 3.0 Comparison of iADRG and ADRG for analysis datasets

DATA CONFORMANCE SUMMARY

For standard ADaM datasets, ADaM CDISC conformance checks and FDA validation rules are applied. There are no conformance or validation rules specified for integrated datasets. The current industry practice is to use the same ADaM conformance checks and validation rules that are applied to individual study datasets.

The iADRG issues summary table (Table 4.0) has been updated to include Rule ID per recommendation from PMDA.

New

Dataset	Rule ID	Diagnostic Message	Severity	Count	Explanation

Table 4.0: Issues Summary

SUBMISSION OF PROGRAMS

This section covers integrated ADaM programs, integrated analysis output programs, and macro programs in tabular format and the documentation remains the same as the ADRG. As there are no guidelines from regulatory agencies specific to integrated studies, sponsors are using individual study program submission guidelines. However, it is always recommended to discuss with the specific regulatory division review team.

CONCLUSION

This paper describes the considerations used in building the iADRG template. This includes best practices to consistently document the information on the integration details, and nuances and non-conformances of the pooled study data used to provide integrated safety and efficacy analyses. With input from both FDA and PMDA, industry sponsors adoption of this analysis data reviewer's guide will provide consistent documentation and clarity of the integrated analysis data for regulatory agency reviewers.

REFERENCES

1. U.S. Department of Health and Human Services Food and Drug Administration, Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER). “Study Data Technical Conformance Guide”. FDA website. March 2022. Available at: https://www.fda.gov/industry/fda-data-standards-advisory-board/study-data-standards-resources
2. US. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER) Oncology Center of Excellence (OCE). “Providing Regulatory Submissions in Electronic Format — Standardized Study Data Guidance for Industry, Electronic Submissions Revision 2”. FDA website. June 2021 Available at: https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber
3. PHUSE Optimizing the Use of Data Standards Working Group. July 2019. ADRG Packages V1.2 18-Jul-2019 Available at: https://phuse.global/Deliverables/1
4. PHUSE Optimizing the Use of Data Standards Working Group. May 2022. iADRG Template, completion guidelines, example1 and example2 (iADRG Public Review link- https://advance.phuse.global/display/WEL/Hot+Topics).

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RECOMMENDED READING

- Analysis Data Reviewer's Guide Completion Guidelines, Version 1.2[3]
- Integrated Analysis Data Reviewer's Guide Completion Guidelines, Version 1.0[4]
- iADRG example 1[4]
- iADRG example 2_with_LDCP[4]

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