

# Integrated Analysis Data Reviewer's Guide Completion Guidelines

Version 1.0

**Disclaimer:** Any examples provided in this document should not be considered best practice for data pooling. Any questions from the sponsor should be directed to the agency review division.

## Revision History

Version	Date	Summary
1.0	2023-09-01	Initial published version.

# Integrated Analysis Data Reviewer's Guide Completion Guidelines

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## Integrated Analysis Data Reviewer's Guide Completion Guidelines Overview

### Integrated Analysis Data Reviewer's Guide Purpose

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 (Integrated Summary of Safety (ISS), Integrated Summary of Efficacy (ISE), etc.). The iADRG purposefully duplicates limited information found in other submission documentation (e.g. the study protocols, integrated statistical analysis plan, Define-XML) to provide regulatory reviewers with a single point of orientation to the integrated analysis datasets. The submission of a reviewer's guide does not obviate the requirement to submit a complete and informative Define-XML document to accompany the integrated analysis datasets.

Where some of the information is duplicated, it is advised to avoid redundancy between the iADRG and the Define-XML. A white paper<sup>1</sup> has been published that discusses this topic and is available on the PHUSE site for reference.

### iADRG Overview

The iADRG has seven required sections:

1. Introduction
2. Description of Protocols Used in the Integrated Datasets
3. Analysis Considerations Related to Integrated Analysis Datasets
4. Integrated Analysis Data Creation and Processing Issues
5. Integrated Analysis Dataset Descriptions
6. Data Conformance Summary
7. Submission of Programs

The iADRG also has two optional sections:

- Appendix (for other documentation that would be helpful to a reviewer)
- Legacy Data Conversion Plan and Report Appendix

The Introduction provides an overview and an inventory of standards used in the integration, and describes the source data used to create the integrated analysis datasets. The Description of Protocols Used in the Integrated Datasets section provides a brief orientation to the studies and describes how planned treatment and timing variables relate to the analysis plans. The Analysis Considerations Related to Integrated Analysis Datasets section provides an overview of topics relevant to multiple datasets such as a description of core variables appearing on most datasets, subject or protocol considerations requiring special analysis rules, windowing rules and imputation/derivation methods. The Integrated Analysis Data Creation and Processing Issues section describes split datasets, data dependencies and intermediate datasets. The Integrated Analysis Dataset Descriptions section provides an overview of the integrated

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<sup>1</sup> <https://phuse.s3.eu-central-1.amazonaws.com/Deliverables/Optimizing+the+Use+of+Data+Standards/Best+Practices+for+Documenting+Datasets+Metadata-Define-XML+Versus+Reviewers+Guide.pdf>

analysis datasets with additional detail beyond that found in the Define-XML where warranted. The Data Conformance Summary describes how ADaM conformance was assessed and summarises conformance findings. The Submission of Programs section itemises the programs that are included in the submission. An optional Appendix section may be included if needed to document any additional information that would be helpful to a reviewer. The iADRG assumes that the analysis datasets adhere to the ADaM standard to the largest 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.

### **iADRG Completion Guidelines Purpose**

The purpose of this document is to provide sponsors with a clear, concise set of instructions that facilitates the consistent development of the iADRG from the Integrated Analysis Data Reviewer's Guide Template. In addition to the iADRG Completion Guidelines, iADRG examples are available as a reference.

### **Organisation of This Document**

This document has three sections: iADRG Purpose and Overview, iADRG Template Completion Instructions and iADRG Finalisation Instructions. The section number in the iADRG Template Completion Instructions corresponds directly to the iADRG Template. The iADRG Finalisation Instructions describe how to format the document for submission after completing the iADRG Template.

## iADRG Template Completion Instructions

This section provides companion instructions for the iADRG Template. The section numbering corresponds directly to the iADRG Template. **Note: Certain iADRG sections include a series of questions intended to aid regulatory reviewers. Provide complete answers to all questions. Do not delete the sections (unless they are optional) or questions from the final document.**

### Cover Page

Update the cover page with sponsor name, compound name and type of integration (ISS, ISE or ISI). This template is not developed for integrated PKPD submission. However, it can be used at the sponsor's discretion. There should be one reviewer's guide for each integrated summary data package. The template version date should **not** be updated (this is the version of the source template used to create the iADRG). It is at the sponsor's discretion to include the iADRG document version in addition to the iADRG Template version.

## 1. Introduction

### 1.1 Purpose

This required section states the purpose of the iADRG. Refer to the iADRG Template for standard text. Do not change the text except to remove the last sentence if not applicable, or, when applicable, keep the sentence but remove the brackets.

### 1.2 Acronyms

This section documents any sponsor-specific or non-industry-standard acronyms used in the iADRG. Sponsors may choose to list industry-standard acronyms.

*Example:*

Acronym	Definition
SAP	Statistical Analysis Plan
DBL	Database Lock
NA	Not Applicable
....	....

*End of Example*

### 1.3 Data Standards and Dictionary Inventory for Integrated Datasets

This required section documents the ADaM and Define-XML versions used for the integrated datasets. Source SDTM versions, if applicable, are documented in section 1.4.

Include the versions of SDTM controlled terminology and ADaM controlled terminology used in the integrated datasets.

Document the versions of any TAUGs (Therapeutic Area User Guides) used, if applicable.

Document the versions of the Medications Dictionary and the Medical Events Dictionary. Any additional information regarding recoding or upversioning of dictionaries performed when integrating could be documented in section 3.3.

Versions of standard published questionnaires, scoring algorithms or other published standards used for integrated analysis should be mentioned in the 'Other Standards' row.

**Do not delete any rows.** If any information is not applicable, note as 'NA' in the second column.

Note: Version(s) of conformance checks are documented in section 6.

### Additional Content of Interest

Include any standards or dictionary-related additional information in this section. Could also include **rationale** for use of specific controlled terminology, MedDRA dictionary versions, WHODD dictionary versions, TAUGs and any other standards documented in the last row of the table. If applicable, document here all character sets used in the data other than ASCII.

**Example:**

Standard or Dictionary	Versions Used
SDTM Controlled Terminology	SDTM CT 2020-12-18
ADaM	ADaM Model Document v2.1 ADaM Implementation Guide v1.1 ADaM Occurrence Data Structure v1.0 ADaM Basic Data Structure for Time to Event Analysis v1.0
ADaM Controlled Terminology	ADaM CT 2020-11-06
Data Definitions	Define-XML v2.0
TAUG	Asthma Therapeutic Area User Guide v1.0
Medications Dictionary	WHODrug Global B3 Sep2020
Medical Events Dictionary	MedDRA v22.0
Other Standards	NCI Common Toxicity Criteria (CTCAE) v4.03

## 1.4 Source Data Used for Integrated Analysis Dataset Creation

This section is used to describe the type(s) of data sources used to create the integrated analysis datasets. While the most common sources for integrated analysis datasets are individual study SDTM, individual study ADaM or integrated SDTM datasets, it is recognised that there may be other source data types, or a combination of data sources, used to create the integrated analysis datasets. The purpose of this section is to provide a high-level introduction to the types of data used for integrated analysis dataset creation.

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), sorted by Study Identifier. SDTM and ADaM data sources should include the IG version number. Include one row for each study included in the integration.

Study Identifier (STUDYID)	Protocol Number	Source Data Standard	Cutoff-Date or DBL-Date/ Study Status
		SDTM Model/IG <version> Legacy Tabulation Legacy Analysis ADaM Model/IG <version>	YYYY-MM-DD/ Completed Ongoing
...			

The Study Identifier column should display the value of the STUDYID variable used in each study (should match the value in the source datasets). Protocol Number may be different from what was used in the STUDYID variable; if identical, then list the same value in both columns.

In the last column, Cutoff-Date or DBL-Date should be displayed in ISO 8601 format and Study Status should be either 'Completed' or 'Ongoing'. Both date and status should be provided.

If the integrated analysis datasets are created from integrated SDTM, then state 'iSDTM' in the Study Identifier column and note the SDTM Model/IG version used for the source-integrated SDTM data. Protocol Number and Cutoff-Date or DBL-Date/Study Status should be 'NA' (see Example 3 below). The details of the SDTM integration should be provided in an icSDRG (Integrated Clinical Study Data Reviewer's Guide).

In cases where legacy integrated data is converted to SDTM and/or to ADaM, or any source study was converted from a legacy format during integration, then include a reference to the Legacy Data Conversion Plan and Report Appendix. If an ADaM model/IG is no longer supported in the Data Standards Catalog, a conversion to the supported model/IG should be described in the Legacy Data Conversion Plan and Report Appendix.

**Additional content of interest** may include but is not limited to the following:

- ✓ In the case of a study which is ongoing or has an ongoing follow-up component, the data cutoff rules may be described.



- ✓ If any intermediate or reference datasets were used which are not CDISC-compliant, summarise in this section and note where they are included in the eCTD folder structure (e.g. misc folder under m5/datasets/study folder).
- ✓ If there are any special cases of data supplied, they should be described here. For example, in some cases sponsors may create customised lookup tables to classify certain data, such as adverse events of special interest.

If there is no additional content of interest, then include a statement such as 'There is no additional content' or 'Not applicable'. ***Do not delete this section.***

The following are examples of the type of information that might be included in this section.

***Example 1:***

Study Identifier (STUDYID)	Protocol Number	Source Data Standard	Cutoff-Date or DBL-Date/Study Status
ABC-1001	ABC-1001	SDTM 1.1/IG 3.1.1	2015-03-10/Completed
ABC-1002	ABC-1002	SDTM 1.2/IG 3.1.2	2016-01-20/Completed
ABC-1003	ABC-1003	SDTM 1.3/IG 3.2	2019-05-09/Completed
ABC-1004	ABC-1004	SDTM 1.3/IG 3.2	2021-02-01/Ongoing

**Additional Content of Interest**

- Studies ABC-1001 and ABC-1002 were upversioned to SDTMIG 3.2 for integration. Details of the conversion can be found in the Legacy Data Conversion Plan and Report Appendix.
- Interim data was used for study ABC-1004 following six months' participation for the first 1,000 subjects. All data available at the time of the data cutoff is included in the integrated datasets.

***Example 2:***

Study Identifier (STUDYID)	Protocol Number	Source Data Standard	Cutoff-Date or DBL-Date/Study Status
ABC-1001	ABC-1001	ADaM 2.1/IG 1.1	2015-03-10/Completed
ABC-1002	ABC-1002	ADaM 2.1/IG 1.1	2016-01-20/Completed
ABC-1003	ABC-1003	ADaM 2.1/IG 1.1	2019-05-09/Ongoing

**Additional Content of Interest**

- Study ABC-1003 had an interim data cutoff taken on 9 May 2019, which included all data entered as of that cut-off. Several adverse events did not have end dates entered at the time of the data cutoff and are assumed to be ongoing as of that date.
- A dataset containing the MedDRA preferred terms pertaining to pre-identified adverse events of special interest (AESIs) was used to flag qualifying events in the integrated adverse events analysis dataset (ADAE). The aesi.xpt file can be found in the m5/datasets/iss/misc folder.

***Example 3:***

Study Identifier (STUDYID)	Protocol Number	Source Data Standard	Cutoff-Date or DBL-Date/Study Status
iSDTM	NA	SDTM 1.3/IG 3.2	NA

The integrated analysis datasets were generated from integrated SDTM datasets. See the icSDRG for details of the SDTM integration.

### Additional Content of Interest

Not applicable.

### End of Examples

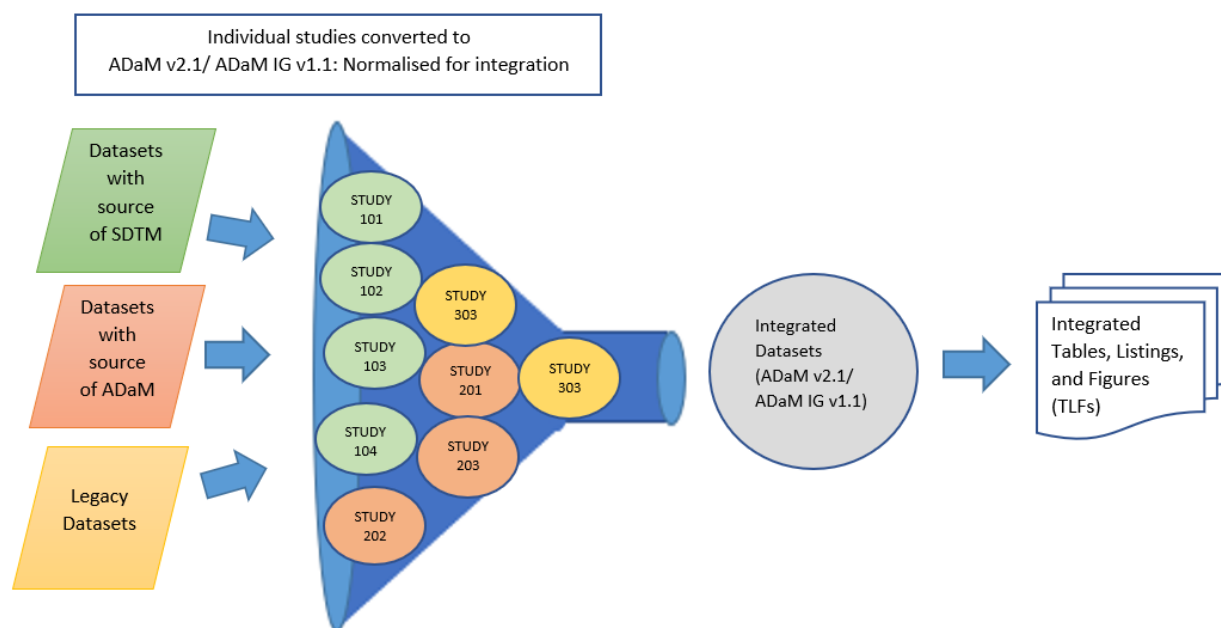
## 1.5 Traceability Flow Diagram

This section provides a flow diagram showing the integrated ADaM datasets creation and traceability back to the various sources of data and any conversion that was performed for the integration. Colours may be used in the diagram to differentiate the studies or data flows.

**Do not delete this section.**

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### Example:



### End of Example

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## 2. Description of Protocols Used in the Integrated Datasets

### 2.1 Protocol Number and Title

This section provides a summary of each protocol included in the integration. The table should be completed with information for each study.

Protocol Number should reflect the individual study protocol number.

In the Indication(s)/Protocol Title column, provide ALL the indications of the protocol along with the title. If the protocol title reflects the indication(s), then sponsors are NOT required to provide the indication(s). If the protocol title is long, sponsors may opt to provide the shortened version. If any protocol(s) has/have multiple indications and not all the indications were included in certain integrated dataset(s), it is recommended to provide the details in section 5.2.x.

If the protocol title doesn't include all the indications, then document the list of indications in the additional content of interest. The Treatment ARM(s) column should reflect the planned treatments for each study. Include one row for each protocol included in the integration.

Protocol Number	Indication(s)/Protocol Title	Phase	Treatment ARM(s)
			<compound, placebo, and/or competitor.>
...			

**Additional content of interest** may include additional details about (but is not limited to):

- ✓ Any treatments from one or more protocols which were not included in the integration
- ✓ Any of the indications of a protocol not included in the integration
- ✓ Study populations
- ✓ Primary endpoints
- ✓ Dosing regimens/formulation

## 2.2 Integrated Analysis Strategy and Design in Relation to ADaM Concepts

This section describes how ADaM analysis variables were harmonised such that variables and values have the same meaning across all studies. For example, variables such as planned treatment assignments (TRTxxP, TRTSEQP), analysis phase (APHASE), analysis period (APERIOD), subperiod (ASPER) and cycle (ACYCLE) are defined in ADSL and other analysis datasets and help define how a particular observation relates to treatment and timing across all protocols. The way these variables are harmonised across the studies aids the understanding of how each protocol design relates to key analysis concepts used in ADaM. Note that the ADaM model does not regulate how these variables are defined and used to produce a given analysis. Because the terms 'phase' and 'period' are not used in a standard fashion across the industry and may not be consistent across protocols, it is useful to describe how the standard ADaM variables relate to key analysis concepts. These variables can be described textually. Sponsors may include references to an integrated statistical analysis plan, if available.

The examples below are for illustrative purposes only:

**Example 1:**

This integrated dataset includes the following study designs:

Studies 1 and 2 (Study Design #1): A two-arm randomised double blind to an open-label study.

Study 3 (Study Design #2): An open-label study

Study 4 (Study Design #3): A randomised double blind three-period cross-over study

APERIOD is used to describe all the periods that are included across the studies. In this integration, we have three blinded periods and an open-label period. The first study design has one double-blind period and an open-label period. The second study design has one open-label period while the third study design has three double-blind periods. The following table describes how these periods will be contained in the variable APERIOD.

	Study Design		
	Study Design #1	Study Design #2	Study Design #3
	STUDY01, STUDY02	STUDY03	STUDY04
APERIOD=1	Treatment in double blind phase	-	1st treatment in double-blind phase
APERIOD=2	-	-	2nd treatment in double-blind phase
APERIOD=3	-	-	3rd treatment in double-blind phase
APERIOD=4	Treatment in open-label phase	Treatment in open-label phase	-

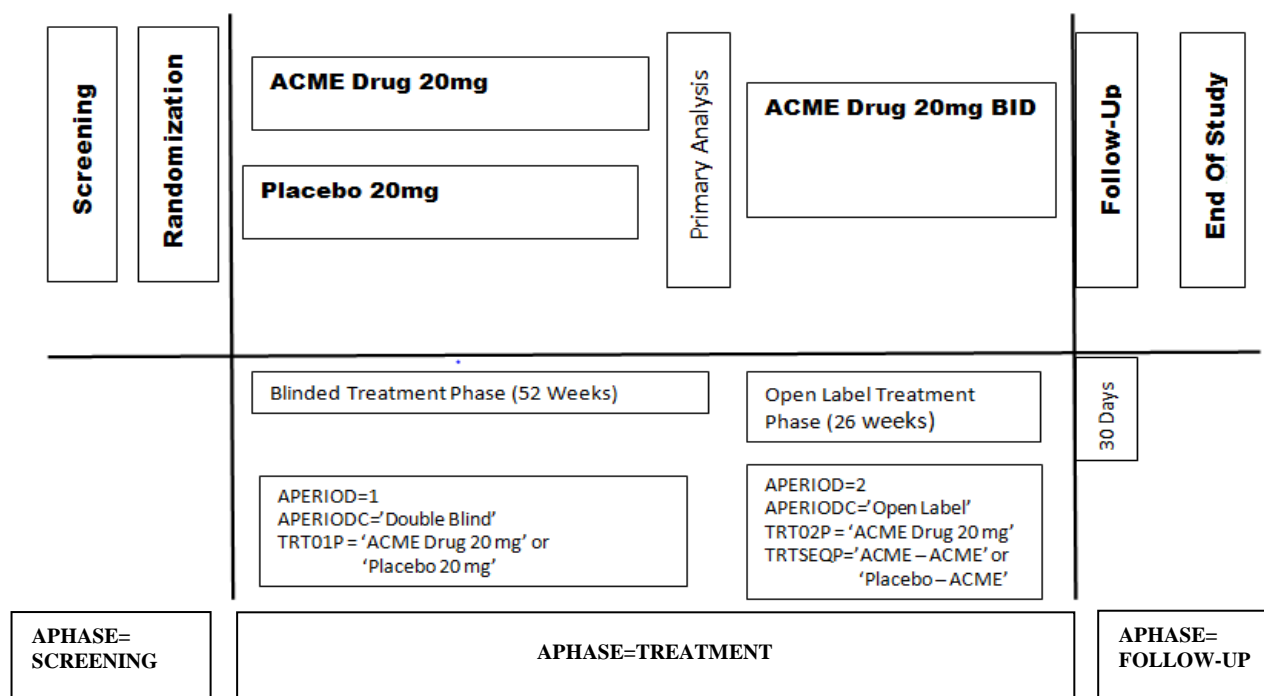
**Example 2:**

Treatment variables TRT01P/TRT01A represent the treatment to which a subject was randomised/actually received during the first double-blind period. TRT02P/TRT02A represents the second double-blind period. TRT03P/TRT03A represents the third double-blind period, and TRT04P/TRT04A represents the open-label phase. The table below shows how the individual study treatments were assigned to the integrated treatment arms.

Arm	Possible Treatment Assignments
TRT01P	ACME Drug 20 mg or ACME Drug 40 mg or Placebo 20 mg, Control Drug 20 mg
TRT02P	ACME Drug 20 mg or Placebo 20 mg, Control Drug 20 mg
TRT03P	ACME Drug 20 mg or Placebo 20 mg, Control Drug 20 mg
TRT04P	ACME Drug 20 mg

**Example 3:**

The variable TRTSEQP provides a description of the sequence of planned treatments from informed consent to the end of the study. Records collected prior to randomisation and/or treatment are assigned APHASE= 'SCREENING'. All records collected during double-blind or open label have APHASE= 'TREATMENT' and records collected after treatment has been completed have APHASE= 'FOLLOW-UP'.



### 3. Analysis Considerations Related to Integrated Analysis Datasets

#### 3.1 Core Variables

Core variables are those that are represented across all integrated analysis datasets. If any of the core variables are not included in any of the datasets, it is recommended they be documented in section 5.2.x.

The designation of 'core' is given to variables that are useful for all integrated analyses (such as common population flags) or have been identified as key subgroup variables (such as age group, sex, race, treatment arm, weight, body mass index, metaboliser status, renal status) and/or serves as an important reference variable (such as STUDYID or treatment start date). A table with each core variable name and a brief description is required.

Since both USUBJID and STUDYID are required by the ADaM model, then at a minimum, this table would contain these two variables.

*Example:*

Variable Name	Variable Description
STUDYID	Study identifier
USUBJID	Unique subject identifier
SITEID	Unique site identifier for the investigator site
COUNTRY	Country code using ISO
TRT01P	Planned treatment for Period 01
TRT01PN	Planned treatment for Period 01 (N)
SEX	Sex
AGEGRP1	Age group (<65 and >=65)
RACE	Race
ITTFL	Intent to treat population flag
SAFFL	Safety population flag
HBA1CBL	Baseline value of HbA1C, which is used as a covariate in all efficacy analyses

*End of Example*

#### 3.2 Treatment Variables

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 (not a comparison of source values to the integrated/harmonised values, which should be addressed in section 2.2).

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 TRTxxP

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

Are the values of ARM equivalent in meaning to the values of TRTxxP? <Yes/No>

*If yes, state 'Yes' here.*

*If no, state 'No' and insert additional text or a mapping table or a figure here.*

#### **Example 1:**

No – see below for treatment descriptions used in ARM and TRT01P. The ARM values are carried over from the individual studies. TRT01P reflects the harmonised treatment descriptions for the integrated analysis. (See section 2.2 for more details.)

STUDYID	ARM	TRT01P
STUDY01, STUDY02	ACME Low Dose	ACME Drug 10 mg
STUDY01	ACME Mid Dose	ACME Drug 20 mg
STUDY01, STUDY02	ACME High Dose	ACME Drug 30 mg
STUDY02	Placebo	Placebo

#### **Example 2:**

No – because some of the studies involved cross over treatments, the planned treatments for periods 1 and 2 (TRT01P, TRT02P) indicate the treatments given during each treatment period whereas the ARM values indicate the entire sequence of planned treatments. Note that studies STUDY01, STUDY02, STUDY03 were single treatment period studies, so ARM will match TRT01P in these studies.

STUDYID	ARM	TRT01P	TRT02P
STUDY01, STUDY02	Treatment 1	Treatment 1	-
STUDY01, STUDY02	Treatment 2	Treatment 2	-
STUDY01, STUDY02	Placebo	Placebo	-

STUDYID	ARM	TRT01P	TRT02P
STUDY03	Treatment 1 – Treatment 2	Treatment 1	Treatment 2
STUDY03	Treatment 2 – Treatment 1	Treatment 2	Treatment 1

***End of Examples*****ACTARM versus TRTxxA**

<<The purpose of this section is to describe/contrast values of ACTARM vs TRTxxA.>>

If TRTxxA is used, then are the values of ACTARM equivalent in meaning to the values of TRTxxA? <Yes/No>

*If yes, state 'Yes' here.*

*If no, state 'No' and insert additional text or a mapping table or a figure here.*

*If TRTxxA was not used, then state 'No TRTxxA variables were used in the analysis' here.*

***Example:***

No – see below.

STUDYID	ACTARM	TRT01A
ABC06, ABC07, ABC08	Treatment A	Active 200 mg
ABC08	Treatment B	Active 500 mg
ABC07	Treatment C	Placebo

***End of Example*****Use of Treatment Variables in Integrated Analysis**

<<The purpose of this section is to describe the use of planned and actual treatment variables in the integrated analysis>>

Are both planned and actual treatment variables used in integrated analysis?

*If no, state 'No' here and indicate which treatment variables are used.*

*If yes, explain at a higher level (e.g. across safety, efficacy) planned versus actual treatment for each type of analysis.*

***Example 1:***

Yes, TRT01A was used for safety analyses and TRT01P was used for disposition tables.



**Example 2:**

Type of Analysis	Treatment Variable Used
Safety	TRT01A
Demographics and Baseline Characteristics	TRT01P

**End of Examples****Use of Treatment Grouping Variables in Integrated Analysis**

<<The purpose of this section is to describe the use of planned and actual treatment grouping variables in the integrated analysis >>

Are both planned and actual treatment grouping variables used in integrated analysis? <Yes/No>

If no, state 'No' here and note which set of treatment variables is used or state that no treatment grouping variables were used.

If yes, explain at a higher level (e.g. across safety, efficacy) planned versus actual treatment grouping for each type of analysis.

**Example:**

Type of Analysis	Treatment Grouping Variable Used
Safety	TR01AG1N/ TR01AG1
Demographics and Baseline Characteristics	TR01PG1N/ TR01PG1

**End of Example****Additional Content of Interest:**

Document any special considerations for treatment group assignment or additional information to assist the reviewer on treatment variables.

If no additional content of interest, then state 'No additional information' here.

*Example:***Additional Content of Interest**

Studies included in this integrated analysis are open-label single treatment studies and the actual treatment is the same as the planned treatment, thus only planned treatment TRT01P is used.

*End of Example*

### 3.3 Subject or Protocol Considerations that Require Special Integrated Analysis Rules

This section provides a description of any situation that occurred which affects the data integration across **multiple datasets**. Any protocol-specific issues or considerations should be addressed in the study-level reviewer's guides.

There is one required question which must be answered and should not be deleted:

Were any additional updates (e.g. codelists, value-level metadata, dictionaries) performed when integrating?

<Yes/No> (insert additional text here or a table or a figure)

*If no, state 'No' here.*

*If yes, explain the updates made during the integration for controlled terminology, the medical events dictionary (MedDRA), the WHODD dictionary, CTCAE criteria, and updates of values for variables at the study level that are inherited into the integrated datasets.*

*Provide details specific to impacted datasets in the dataset-level summary in section 5.2.x.*

**Additional Content of Interest** may include but is not limited to the following:

- ✓ Describe whether any subjects were excluded from integrated analysis datasets and the rationale for the exclusion.
- ✓ If any subjects were enrolled in multiple studies (for instance, an extension study), explain how this was handled for integrated analysis. If this occurs, note if the same USUBJID is or is not used across all records for a given subject.
- ✓ Provide any special considerations for protocols while integrating, such as:
  - Were there any protocol deviations that were handled differently in the integrated analysis? If yes, provide details.
  - Were any analysis rules modified in integrated analysis causing results to differ from the individual studies (or same rule resulting in different results in integrated data)?
- ✓ Differences between individual study datasets and integrated datasets which affect multiple integrated datasets, for example:
  - ✓ Baseline definitions
  - ✓ Study populations
  - ✓ Grouping core variables (such as age group)

- ✓ Any standardisation across studies such as CAT/TESTCD, particularly if the product was acquired from another company or co-developed and standards were not aligned (if applicable to multiple datasets; otherwise, document in section 5.2.x).

*Example:*

Impacted Dataset	STUDYID	Individual Study Definition	Description of Change
ADEG	ABC03, ABC04	Baseline value was the average of a triplicate	The highest value prior to study treatment from screening or any pre-dosing assessments
	ABC06, ABC07, ABC08, ABC09	Baseline value of the last ECG prior to study treatment	The highest value prior to study treatment from screening or any pre-dosing assessments

*End of Example*

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

This section provides an overview of how the observed visit records from source datasets were used in the analysis. The following questions should be answered Yes or No and should NOT be deleted. Provide additional details where indicated.

Was windowing used in one or more integrated analysis datasets? <Yes/No>

*If no, then state 'No' here.*

*If yes, then describe the definition of visit windows. If there are differences in definitions between integrated analysis datasets, then provide further details in section 5.2.x.*

Were unscheduled visits included in any integrated analysis datasets? <Yes/No>

*If no, then state 'No' here.*

*If yes, then document in section 5.2.x as appropriate.*

Were rules used for record selection in one or more integrated analysis datasets?

*<Yes/No> (insert additional text here)*

*If yes, be sure to describe how records were selected in the case where multiple visits are assigned to the same visit window, if applicable. Baseline record selection can be described here if one set of rules applies across multiple datasets.*

**Additional Content of Interest** may include but is not limited to the following:

Were there records which are included in one or more integrated analysis datasets that were never used for any analysis (after follow-up period, screening, etc.)? For example, the sponsor may keep all vital sign results but only select one set of results per visit window.

### 3.5 Imputation/Derivation Methods

This section provides an orientation to the use of record-level imputation or derivation and the use of associated ADaM variables.

If date imputation was performed during integration, were there rules that were used in multiple integrated analysis datasets?

*<Yes/No> (insert additional text here)*

*If yes, then either point the reviewer to the location of the description of these common rules in the specific section of the integrated SAP (for example, 'see section 9.3 in the SAP') or describe the rules here. Include in which integrated analysis datasets these common rules were applied.*

If common date (or other) imputations were not done but imputations were specific to individual analysis datasets, then refer the reviewer to the appropriate part(s) of section 5 for more information regarding specific analysis datasets where these imputations occurred.

**Additional Content of Interest** may include but is not limited to the following:

- ✓ Was DTYPE used in multiple integrated analysis datasets?  
If yes, describe the controlled terminology and associated definitions. Consider referencing integrated SAP if appropriate.
- ✓ Was BASETYPE used in multiple integrated analysis datasets?  
If yes, describe the use of BASETYPE and provide controlled terminology and definitions. Consider referencing integrated SAP if appropriate.
- ✓ Was ONTRTFL used in multiple integrated analysis datasets?  
If yes, describe the use of ONTRTFL and provide definitions. Consider referencing integrated SAP if appropriate.
- ✓ Was TRTEMFL used in multiple integrated analysis datasets?  
If yes, describe the use of TRTEMFL and provide definitions. Consider referencing integrated SAP if appropriate.
- ✓ Describe the algorithms followed to calculate timing variables used across integrated analysis datasets (e.g. ADY). These should align with the definitions in the Define-XML.
- ✓ Discuss any differences between iSDTM and iADaM (if applicable) in the definitions of derived variable concepts (e.g. baseline (xxBLFL versus ABLFL), actual study day (xxDY versus ADY)).
- ✓ Discuss any other flagging variables across analysis datasets, in particular those which are not used routinely or require additional information to aid interpretation.
- ✓ Discuss any imputed assessment values across analysis datasets (e.g. LOCF).

- ✓ Note if any imputations or derivations done in the integrated datasets were done differently from what was done in the individual studies. Describe the differences and impact.
- ✓ If all derivations were done within study-level datasets and no further derivations were done during integration, then the sponsor can refer the reviewer to the study-level reviewer's guides.
- ✓ Document any other variable conventions used by a sponsor that cannot be easily established in the Define-XML. Explain at a higher level the rationale for using certain standard or additional variables. The variables described should be those that are over and above the conventions specified in any of the CDISC ADaM documentation.

***Example:***

Study ABC1234 included one subject (USUBJID='ABC-7023') who had dosing errors in the first cycle of treatment. This subject was randomised to active treatment but actually received placebo for the first cycle. For this reason, all safety-related analysis datasets included the record-level treatment variables TRTA and TRTAN. In safety analysis tables, subjects are categorised by the actual treatment at the time of the observation. Tables that summarise data by cycle will show a change in subject count from cycle to cycle and are footnoted accordingly.

***End of Example***

## 4. Integrated Analysis Data Creation and Processing Issues

### 4.1 Split Datasets

This section is intended for use when the sponsor splits an analysis dataset for submission (e.g. a separate ADLBxx for a different category). It is required when an analysis data was split for submission but is otherwise optional. The sponsor should clearly describe the method by which the dataset(s) was split (e.g. by parameter) and notify reviewers of the need to reassemble the analysis dataset prior to any analysis. It is recommended to note the location of the split datasets within the eCTD folder structure.

If there are no split datasets, then state 'Not Applicable' or 'No split datasets'. Do not delete the section.

***Example:***

Source Dataset	Split Dataset	Split Value
ADLB	ADLB01	PARCAT1 = Chemistry
ADLB	ADLB02	PARCAT1 = Haematology

The laboratory analysis dataset (ADLB) was split due to size constraint. The split datasets are placed in a subdirectory 'split' under Module 5 (m5) of the eCTD folder structure. Reviewers who wish to execute the SAS programs provided for safety laboratory analysis (see Program Inventory in section 7) should first reassemble the two datasets into a single dataset named ADLB. The metadata describing laboratory results is described under dataset ADLB in the Define-XML.

***End of Example***

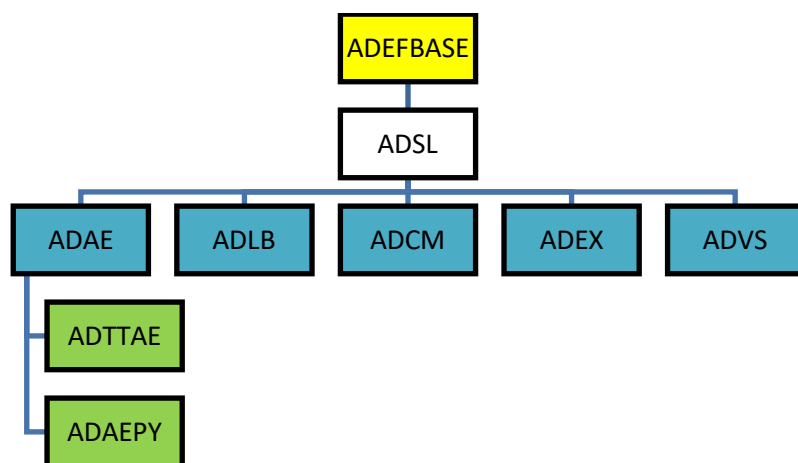
## 4.2 Data Dependencies

This section is used to describe any dependencies between integrated analysis datasets. A flowchart is recommended when there are dependencies between analysis datasets beyond a dependency on ADSL. In the case of very minimal analysis dataset dependencies, the user may opt for creating a table to explain the dataset dependencies as an alternative to a flow chart. Where no dependencies exist between analysis datasets beyond a dependency on ADSL, then a simple statement asserting that fact is recommended. Dataset dependencies involving the creation of intermediate analysis datasets should be noted here and further described in section 4.3 Intermediate Datasets, as appropriate. Similarly, reference datasets used should be noted here and further described in section 1.4. Include the dependency on intermediate datasets, non-ADaM and reference datasets in the data dependency diagram.

If there is no information for this section, **do not delete it**. The following are examples of the type of information that might be included in this section.

### Example 1

In this diagram, blue is used to indicate datasets that have dependency only on ADSL, green indicates dependency on other analysis datasets, and yellow indicates an intermediate dataset that was used for ADSL.



### Example 2:

Dataset	Input Datasets
ADTTE	ADAE, ADCE, ADSL

### Example 3:

There are no analysis dataset dependencies other than ADSL.

### End of Examples

### 4.3 Intermediate Datasets

This section is used to describe the existence of intermediate integrated analysis datasets and the resultant analysis datasets. Intermediate datasets may have been created during integration to handle cases when working with complex derivations and/or when a smaller dataset was created from the larger parent analysis dataset for reporting purposes and internal review. If applicable, describe any naming convention used for interim datasets. Anything that requires a clinical review to set a flag, such as protocol deviations to determine if the deviation is major or minor, may require an intermediate dataset.

It is recommended to note the location of the intermediate datasets within the eCTD folder structure.

If there is no information for this section, **do not delete it**.

The following are examples of the type of information that might be included in this section.

**Example 1:**

Intermediate Dataset	Output Dataset(s)
ADEX	ADEXCYCL, ADEXTOT

**Example 2:**

Dataset ADEX is not used in analyses but is supplied to provide traceability for ADEXCYCL and ADEXTOT and used for a listing. The source data were collected using a per-dose case report form page, which recorded the actual amount infused. The ADEX intermediate file was used to convert actual amounts infused to actual amounts in mg/kg using the last available body weight. This file was then used to create ADEXCYCL, which summarises the total amount received per treatment cycle, and to account for interruptions and changes in dosing regimens. ADEXCYCL was then used to derive summary variables in a one-record-per-subject structure, stored in ADEXTOT.

**Example 3:**

No intermediate analysis datasets were created.

**End of Examples**

## 5. Integrated Analysis Dataset Descriptions

### 5.1 Overview

This required section provides a summary orientation to the integrated analysis datasets.

Answers to the following questions must be provided <Yes/No/Not Applicable>:

Is an integrated statistical analysis plan included in the submission?

<Yes/No> <insert additional text here>

Do the integrated analysis datasets support all integrated statistical analysis plan-specified objectives?

<Yes/No/Not Applicable>

If an integrated statistical analysis plan is not submitted, provide details for where integrated analyses are specified, if any.

Include all objectives of the integrated analyses listed in the integrated statistical analysis plan which are not supported in the integrated analysis datasets and the reason for their absence.

**Additional Content of Interest** may include but is not limited to the following:

- ✓ Document details about any datasets or data which are included for supportive purposes but not utilised for submitted analyses.

## 5.2 Integrated Analysis Datasets

This section provides an inventory of the integrated analysis datasets. The content below is provided to describe standard practice for how to reference the analysis datasets.

List all integrated analysis datasets included in the submission and which are source to the integrated TFLs, starting with ADSL, followed by all others in alphabetical order by dataset name.

Include a separate row for each split integrated analysis dataset, if needed. For example, when an agency submission folder structure does not include a 'split' folder and sponsors decide to submit split datasets along with other datasets.

Provide a hyperlink for the dataset name to their corresponding dataset description in section 5.2.x. If there is no description in section 5.2.x, then no hyperlink is required.

Specify the ADaM class (ADSL, BDS, OCCDS, ADaM OTHER). If a SubClass exists, it can be documented in section 5.2.x. (See the latest Define-XML Specification for SubClass information.)

Specify the functional category or categories for each analysis dataset, using 'E' for Efficacy, 'S' for Safety, or 'I' for Immunogenicity.

Mark an 'X' in the fourth column if the dataset includes baseline or other subject characteristics.

Additional categories may be defined at the discretion of the sponsor.

In the 'All Studies Contribute' column, each dataset should be marked X if all studies are included in the dataset; otherwise, leave blank. When blank (not all studies contribute), provide rationale (if possible, a summary of studies not contributed) in the dataset-specific section of 5.2.x below.

Optionally, describe the structure of the integrated analysis dataset in the last column. If included in the table, the structure should align with the Define-XML.



*Example for ISE:*

<b>Dataset Name Dataset Label</b>	<b>Class</b>	<b>Efficacy (E)/ Safety (S)/ Immunogenicity (I)</b>	<b>Baseline or Other Subject Characteristics</b>	<b>All Studies Contribute</b>	<b>Structure</b>
<a href="#">ADSL</a> Subject-Level Analysis Dataset	ADSL		X	X	One record per subject
<a href="#">ADEFF</a> Primary Efficacy Analysis Dataset	BDS	E		X	One record per subject per parameter per visit
ADEX Exposure Analysis Dataset	ADaM OTHER	<E/S>		X	One record per subject per intervention
...					

*End of Example***5.2.1 ADSL – Subject-Level Integrated Analysis Dataset**

This section is required for the subject-level integrated analysis dataset. Provide explanation beyond which is documented in the Define-XML or the ADaM Implementation Guide and its supplements.

Content may include but is not limited to the following:

- ✓ Describe the breadth of coverage of ADSL.
- ✓ Does the number of subjects in the integrated ADSL differ from the sum of the subjects from the individual studies? If yes, then describe any difference.
- ✓ Describe the handling of subjects enrolled in multiple studies, if applicable.
- ✓ Document which analysis populations or pooled variables are defined in ADSL using their variable names.
- ✓ Describe notable sponsor extensions to CDISC controlled terminology.
- ✓ Are there other integrated analysis datasets that contain other subject-level information pertaining to baseline characteristics, disposition, etc.? If yes, then list the names of the other subject-level datasets.
- ✓ List the variable names for the covariates used for inferential statistical analysis relating to the analysis objectives.

- ✓ Are all covariates used for inferential statistical analysis relating to the analysis objectives included in ADSL? If no, then indicate where the other covariates can be found.
- ✓ Describe any other variables applied to this analysis dataset, those which are not used routinely or require additional information to aid interpretation.
- ✓ Are there screen failure and/or run-in failure data in this dataset? If yes, indicate as such.
- ✓ Are the same number of subjects included in this integrated analysis dataset (iAD) as there are in the combined source studies? If no, then describe the reason for the difference. If this difference is due to screen failure, then this should be described here.

### 5.2.x Dataset – Dataset Label

This section is recommended for each integrated analysis dataset (iAD) that would benefit from additional description. At a minimum, the dataset(s) containing the integrated analysis objectives would be described. Provide explanation beyond which is documented in the Define-XML or the ADaM Implementation Guide and its supplements. It is advisable to indicate the relevant parameter(s), variable(s) analysed, and flags or timing variables as appropriate.

Do not duplicate information that pertains to multiple integrated datasets that may be discussed in section 3 above. Provide a section number for each iAD requiring additional explanation (e.g. 5.2.2, 5.2.3, 5.2.4).

**Note that this section header is NOT a Word Heading Style. It must be manually edited. This avoids problems with automatic three-level section numbering that sometimes occurs with Word Heading Styles.**

Specify key parameters and/or variables of interest. At a minimum, those related to the integrated analysis objectives should be indicated. Note that it is not necessary to describe the derivation of the objectives as this would be in the integrated analysis plan (if applicable) and the Define-XML.

Content may include but is not limited to the following:

- ✓ Describe the purpose and breadth of coverage of the iAD.
- ✓ Describe the notable sponsor extensions to CDISC controlled terminology.
- ✓ Is there a substantial number of records in this iAD that is found in other iADs, for example a 'parent' and 'child' relationship with another iAD? If yes, then indicate the name of the other iADs.
- ✓ Document any separate integrated analysis datasets that contain similar content and the purpose for separating that data into multiple analysis datasets. Examples of this might be separation of different sensitivity analyses for time to event into multiple datasets, or the use of separate iADs for different baselines instead of employing Basetype.
- ✓ Are there derived variables in this iAD that are also in the source data, but the derivation differs from source data? If yes, then describe differences that are not easily understood from the derivation in the Define-XML.
- ✓ If there are multiple treatment variables in the iAD, then describe which treatment variables are used for the analyses generated from this iAD.

- ✓ Is BASETYPE used in this iAD? If yes, then briefly describe why BASETYPE is needed.
- ✓ Is DTYPE used in this iAD? If yes, then briefly describe why DTYPE is needed.
- ✓ Were any external reference data or look-up tables used for derivations in this iAD? If yes, then indicate whether they are included in the submission, and if so, note their location in section 1.4.
- ✓ Are there specific flag variables (excluding population flags) used in this iAD that are important for the analyses? If yes, then describe.
- ✓ Describe any derived variables which were created to mitigate issues relating to data that was demonstrably incorrect.
- ✓ If special windowing rules were used in this iAD, then describe.
- ✓ Describe any other variables applied to this analysis dataset, those which are not used routinely or require additional information to aid interpretation.
- ✓ Document rationale and explanation if WHO-DD unification was not possible at integrated level.

**Example:**

### **5.2.1 ADSL – Subject-Level Analysis Dataset**

In addition to supporting all analyses, ADSL contains variables to also support baseline characteristics and disposition analyses. All subjects from all source studies, except for screen failures, were included in the ADSL.

### **5.2.2 ADCM – Concomitant Medications Analysis Dataset**

This dataset contains data from three different source studies: ABC09, ABC07 and ABC06. Previous and concomitant medications are coded with WHO-DICT. For studies ABC07 and ABC06, the WHO-DD version is B2MAR2019, and for study ABC09, the WHO-DD version is MAR2014. No recoding was performed because only limited descriptive analyses of prior and concomitant medications were performed.

**End of Example**

## **6. Data Conformance Summary**

This section describes the validation checks and inputs used to evaluate conformance.

### **6.1 Conformance Inputs**

This section summarises how iADaM conformance was established. Answers to the following questions must be provided in the table:

Question	Description
Software name and version used for the integrated dataset validation	<In addition to software name and version used, if applicable include engine version>

Question	Description
Version of the validation rules (i.e. CDISC, FDA, PMDA) for the integrated datasets	
Software name and version for the Define-XML validation	<In addition to software name and version used, if applicable include engine version>
Version of the validation rules (i.e. CDISC, FDA, PMDA) for the Define-XML	

Provide any additional compliance evaluation information:

*(Text here)*

Because ADaM conformance is not solely established by computerised checks, sponsors may use other methods to assess conformance, such as manual review of the data or internal testing of the clarity of variable metadata. If such methods are used and are worthy of noting, then add additional text as desired.

## 6.2 Issues Summary

This required section summarises compliance findings.

- ✓ Summarise findings from an iADaM conformance report (e.g. the validation report's Issues Summary tab or similar) in table form.
- ✓ Include additional information regarding conformance to FDA or PMDA business rules and validator rules if not addressed in the iADaM conformance report.
- ✓ List only those findings that appear in the submission.
- ✓ Do not include skipped validation checks or validation checks for which datasets do not exist.
- ✓ If conformance diagnostics do include severity, populate the 'Severity' column. For example, current conformance rules for the PMDA expect to populate the 'Severity' column. If conformance diagnostics do not include severity, leave that column blank. For example, current conformance rules for the FDA don't expect to populate the severity column. In that case, leave the 'Severity' column blank (do not delete the column).
- ✓ If non-automated issues were detected, these should be explained as well.
- ✓ Explanations should be sufficiently detailed and data-specific (not generic or vague).
- ✓ Certain validation rules may not be applicable for integrated data, and those issues should still be included in this summary with explanation.
- ✓ Do not delete empty column(s). If any column(s) in the table is not applicable, then provide the reason.
- ✓ Define-XML related findings can be listed in the same table with the value in the 'Dataset' column as 'Define-XML'.

In addition, address any specific data quality issues that were not fixed. Note what the data should be, why it was not fixed, and any impact assessment that was done.

*Example:*

Dataset	Rule ID	Diagnostic Message	Severity	Count	Explanation
ADSL	XXX	Not one record per SUBJID	Error	X	SUBJID in the integrated dataset did not include the study number, therefore the site and subject number were repeated across multiple studies where the site participated in multiple studies
...					

*End of Example*

## 7. Submission of Programs

It is advisable for sponsors to discuss the submission of programs and/or analysis output specifications in ARM (analysis results metadata) with the specific regulatory authority division review team before preparing a submission. Sponsors should be prepared for regulatory reviewers to conduct independent quality validation to verify results in submitted clinical studies. The sponsor should try to understand as clearly as possible how their reviewer will use the submitted programs and what type of 'packaging' will best support the review.

For further clarification on what programs to submit, discuss with the appropriate review division.

Refer to the iADRG Template for sample text. Include the programming software (SAS, R, etc.) and the version. Also include the internal reference date used to create numeric representation of dates. Note: SAS software represents dates as the number of days since a reference date. The reference date, or date zero, used for SAS date values is 1 January 1960. Sponsors can indicate the operating platform (Linux, Windows, etc.) and version as per agency requirement.

Refer to the regulatory authority's Study Data Technical Conformance Guide for guidance regarding the format of submission programs.

### 7.1 Integrated ADaM Programs

Include one row for each analysis dataset program.

*Example:*

Program Name	Dataset	Macro Used
adsl.txt	adsl	attrib
...		

*End of Example***7.2 Integrated Analysis Output Programs**

Include one row for each analysis output program. If the list is large, then the sponsor may opt for adding it as an appendix in iADRG.

Document if the Analysis Results Metadata (ARM) is included in the submission as part of the Define-XML or pdf and provide rationale for the TFLs that are included in the ARM.

*Example:*

Program Name	Output Number	Title	Input
t_predopbo	7.1.1	Percent Reduction Over Placebo for – 28-Day Adjusted POS Frequency - ITT	ADSZP
...			

*End of Example***7.3 Macro Programs**

Include one row for each macro program. If no macros are submitted, the sponsor can specify here in this section as appropriate (NA, Not Submitted, etc.).

*Example:*

Program Name	Purpose
attrib.txt	Automatically set variable attributes based on specifications
...	

*End of Example*

Some points to consider might include:

- ✓ Which programs should be submitted?  
Sponsors should consult with their reviewing division to determine which programs to submit.
- ✓ Do the programs need to be executable?  
If there is a question about whether to do any extra work to make programs executable, it is best to discuss with the reviewer.
- ✓ How should programs that include macro code be handled?  
Reviewers consider macro code usable. Macro code may nevertheless be difficult for the sponsor to package. If submitting macro code is problematic, the sponsor may discuss with the reviewer whether an alternative approach is acceptable. Some possible alternative approaches might include:
  - 1) Submitting validation programs that do not contain macro code.

- 2) Submitting resolved macro code. If the results were programmed using SAS, the MFILE/MPRINT options can be used to write the resolved macro code to a separate file. The resolved macro code could be submitted in place of the original program.

Program files that are submitted should have documentation that identifies the inputs and outputs to the program and allows the reviewer to connect the program with the results that it supports. Industry best practice advises that the inputs/outputs be specified in the program header block. If this practice is adhered to, it might be worthwhile to note this. Internal comments to explain important sections of logic are highly recommended. It is worthwhile to accompany the programs with a statement about the reasoning for selecting the programs that were submitted. If there are any special methods for preparing the code (such as the alternatives described above), then the relationship between the submitted code and the outputs should be explained.

***Example 1 (ISE):***

All programs for integrated analysis datasets and key analysis results will be submitted. They were all created on a Linux <vXXX> platform using SAS v9.3. The internal reference date used to create dates in ADaM datasets is 1 January 1960.

The submitted programs include a macro that was used to standardise units of study drug dosing, which is referenced in several datasets.

### 7.1 Integrated ADaM Programs

Program Name	Output	Macro Used
adsl.sas	adsl	dsunit.sas
adtte.sas	adtte	dtdate.sas

### 7.2 Integrated Analysis Output Programs

Program Name	Output Number	Title	Input
teff.sas	Table 14.2.1.1	Time to Event Analysis	adtte
tsurv.sas	Table 14.2.2.1	Patient Demographics	adsl

### 7.3 Macro Programs

Program Name	Purpose
dsunit.sas	Standardised units of study drug dosing
dtdate.sas	Time to event calculations

***End of Example 1***

---

**Example 2 (ISS):**

All programs for integrated analysis datasets and key safety results will be submitted. They were all created on a Windows platform using SAS v9.3. The internal reference date used to create dates in ADaM datasets is 1 January 1960.

The name of the creation program is identical to the name of the analysis dataset. For example, ADSL.SAS produces the dataset ADSL. All inputs are specified in the program header. No macros were used in the production of analysis datasets.

The table below associates the table number with the program that produced it. The second table lists the macros that were used in table production. Note that one macro may be used to produce multiple tables. The header block in each table program clearly specifies this information as well.

**7.1 Integrated ADaM Programs**

Program Name	Output	Macro Used
adsl.sas	adsl	
adae.sas	adae	
adex.sas	adex	
adlb.sas	adlb	

**7.2 Integrated Analysis Output Programs**

Program Name	Output Number	Title	Input
subjdisp	14.1.1	Subject Disposition	adsl
demog	14.1.2	Demographics and Baseline Characteristics	adsl
teaesum	14.3.1.1	Overall Summary of Treatment Emergent Adverse Events	adae
teaesum	14.3.1.3	Treatment Emergent Adverse Events by Body System and Preferred Term	adae
labcfb	Table 14.3.4.1	Change from Baseline for Haematology Laboratory	adlb
labcfb	Table 14.3.4.2	Change from Baseline for Chemistry Laboratory	adlb

**7.3 Integrated Macro Programs**

Program Name	Purpose
statdesc.sas	Prepares descriptive statistics from the specified dataset and variable
statcnt.sas	Prepares count and percentage statistics from the specified dataset and variable



Program Name	Purpose
stacnp.sas	Prepares count/percentage and p-value from the specified dataset and variable
aeout.sas	Counts adverse events by body system and preferred term
auxlbout.sas	Summarises change from baseline values of lab and vital sign parameters

***End of Example 2***

---

## 8. Appendix

This is an optional section that can be used if needed. If it is not needed, then delete this section entirely. Be sure to update the table of contents.

### Legacy Data Conversion Plan and Report Appendix

This appendix provides information about legacy tabulation or analysis data that was converted to SDTM or ADaM during data integration. If there was no conversion, delete the appendix pages as they are not required and update the table of contents.

Include this appendix when any individual study datasets were converted from a legacy format to SDTM or ADaM in order to integrate with other studies. The conversion will be documented here when it is done during integration programming. Any legacy conversion done for a CSR or submission of individual study data should be documented in the cSDRG or ADRG for that study.

#### 1. Purpose

This section states the purpose of the Legacy Data Conversion Plan and Report Appendix. The iADRG Template includes standard text which should not be modified or removed.

#### 2. Conversion Data Flow

This section will contain a diagram showing the transformations performed (e.g. applying dictionary coding, updating lab conversions) to convert from legacy format to SDTM or ADaM. This is a forward view of the data flow. See the iADRG Example 2 document for an example. If multiple studies were converted, include a diagram for each conversion flow and note which studies apply for each diagram.

Also, when appropriate, explain the rationale for the data conversion.

#### 3. Converted Data Summary

This section provides a summary of the legacy data that was converted to SDTM or ADaM for integration. Content may include but is not limited to the following:

- ✓ Describe any changes in SDTM and/or ADaM controlled terminology.
- ✓ Describe any additional QC done on the data.

##### 3.1 Issues Encountered and Resolved

This section describes any issues encountered as a result of the conversion and the resolution of the issues. Generally, this section should list any differences between the original datasets and the converted datasets that would impact on results.

Content may include but is not limited to the following:

- ✓ MedDRA – describe any recoding that was performed and the result
- ✓ WHODrug – describe any recoding that was performed and the result
- ✓ How original CRF values were mapped through controlled terminology and the differences in counts (e.g. subject disposition, or race)

- ✓ If original analysis data used ADaM concepts incorrectly (e.g. the concept of periods did not always have a treatment component, so you used APHASE in the ADaMs)

#### **4. Outstanding Issues**

This section will describe any other issues not previously documented and which would be helpful to a reviewer. If there are no outstanding issues, do not delete the section. Add text such as 'There are no outstanding issues to be documented.'

Content may include issues related to the CSR or differences between the original datasets and the converted datasets that would impact on results but is not limited to the following:

- ✓ Changes in variable values in SAEs, deaths and disposition
- ✓ Changes in treatment-emergent adverse events
- ✓ Analysis issues found with the original analysis datasets and corrected in the converted datasets
- ✓ Any analysis dataset that could not be converted to use ADaM concepts

## Analysis Data Reviewer's Guide Finalisation Instructions

This section describes how to format the document for submission after completing the ADRG Template.

### 1. Create hyperlinks from dataset names in section 5.2 to descriptions in 5.2.x

Select the text in the first column in the table in section 5.2 that needs a hyperlink. **Right click the selected text** and choose **Hyperlink** from the menu. In the left panel of the Hyperlink window, make sure that **Place in this document** is selected. Then, in the list of document places, select the dataset name's header under ADaM Domains (e.g. ADAE – Adverse Events Analysis Dataset) and click **OK**. Ctrl+click the hyperlink to test it.

### 2. Do not remove unused sections from the document

For consistency, it is best to leave unused sections in the document and indicate 'NA' or 'This section does not apply'. It is acceptable to remove the optional Appendix 8 section.

### 3. Update the table of contents, document header and version date

After all edits have been completed, update the table of contents at the top of the document. **Right click on any line in the table** and select **Update Field**. In the dialog window, select **Update Entire Table**, then click **OK**.

**Do not edit the document header or footer.** The study number in the header references the study number on the title page. When you edit the study number on the title page, the study number in the header is updated automatically.

### 4. Convert the document to PDF format

These instructions are for Microsoft Word 2003 or newer, using either the Adobe Acrobat plug-in or the MS Office PDF creation feature.


#### 4.1 Using the Adobe Acrobat plug-in for Microsoft Office

Click the **Acrobat tab** in the Word menu at the top of the screen. Select **Create PDF**. If a dialog window pops up asking you to save and continue, click **Yes**. In the second dialog window, **navigate to the directory** in which you want to save the PDF, **name the file iadrg.pdf** and click **Save**.

#### 4.2 Conversion without the Adobe Acrobat plug-in

If not using Adobe Acrobat plug-in (e.g. proprietary tools within the organisation), sponsors should follow the internal process and save the **file as iadrg.pdf**.

#### 4.3 Formatting and verifying the PDF

Open the PDF. If bookmarks are not showing, go to the **View menu** and select **Navigation Panels**, then **Bookmarks**. If lower-level bookmarks are showing, click on the **Bookmarks Options** icon  and select **Collapse Top-Level Bookmarks**.

Go to the **File menu** and select **Properties**. Navigate to the **Initial View tab**. In the drop-down menu for the **Navigation tab**, select **Bookmarks Panel and Page**. In the drop-down menus for both **Page Layout** and **Magnification**, select **Default**.

Next navigate to the **Description tab** and delete the information in the **Title, Author, Subject** and **Keywords** boxes. Click **OK** and then **save the file**. While there, verify at the bottom of the dialog window that the **PDF version is 1.7** or lower.

If the version is too high, go to the **Document menu** and select **Reduce File Size**. In the drop-down list, select **Acrobat 8.0 and later**. Click **OK**, then **navigate to the directory** in which you want to save the PDF, **name the file iadrg.pdf** and click **Save**.

Go to **File** and select **Properties**. Verify at the bottom of the dialog window that the **PDF version is 1.7** or lower.

Refer to the agency data standard catalog for the supported PDF version and any PDF requirements.

## Project Team Acknowledgements

Core Team		
Name	Company/Organisation	Participation
Kiran Kumar Kundarapu	Loxo Oncology, Eli Lilly	Project Co-Lead
Satheesh Avvaru	Alexion AstraZeneca Rare Disease	Project Co-Lead
Srinivas G. Kovvuri	ADC Therapeutics USA	iADRG Example Sub-Team Co-Lead
Randi McFarland	Ephicity Consulting Services	iADRG Example Sub-Team Co-Lead
Sandy VanPelt Nguyen	Pfizer	iADRG Completion Guidelines Sub-Team Co-Lead
Christine Rossin	Pfizer	iADRG Completion Guidelines Sub-Team Co-Lead
Aurora Liao	Cytel	iADRG Completion Guidelines Sub-Team Co-Lead
Janet Low	Merck	PHUSE Optimizing the Use of Data Standards Working Group Co-Lead
Jane Lozano	Eli Lilly	PHUSE Optimizing the Use of Data Standards Working Group Co-Lead
Chris Price	PHUSE	PHUSE Working Groups Director
Wendy Dobson	PHUSE	PHUSE Working Groups Project Manager
Katie Warren	PHUSE	PHUSE Working Groups Project Assistant
Paula Rowley	PHUSE	PHUSE Working Groups Project Assistant

Project Members		
Abhilash Vasu Chimbirithy	Kala Chandra	Sameer Saxena
Acharya Mekhala	Kapil Anand	Sapan Patel
Adie Bonwick	Kapila Patel	Sarad Nepal
Adity Shelke	Krishna Varkur	Sharayu Nadkarni
Anand Jayaraman	Laura Schafer	Shitanshi Mehta
Anita Baniya	Lin Lisa	Shyamprasad Samiseti
Aron Anton	Lokesh Usher	Sunil Gupta
Athenkosi Nkonyeni	Mathura Ramanathan	Susheel Arkala
Beasley Bach Nhi	Michael Marroquin	Swathi Kotla
Bidhya Basnet	Michael Wise	Tanvi Gupta
Carey Smoak	Micky Salgao-Gomez	Vanitha Dareedy
Charanjit Kahlon	Mithun Ranga	Venkata Reddy
Ellen Asam	Mrudula Mogalla	Vishnu Kolliseti
Hanne Ellehoj	Pranab Mitra	Winkle Lu
Imran Syed	Priyanka Pollarine	Yaling Teng
James Gaiser	Raghava Regulla	Yoshiko Kitagawa
Jian Huang	Rajeswari Veeramallu	