

ADaM Reviewer's Guide - Interpretation and Implementation

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AGENDA

- Overview
- Section 1 - Introduction
- Section 2 - Protocol Description
- Section 3 - Analysis Considerations Related to Multiple Analysis Datasets
- Section 4 - Analysis Data Creation & Processing Issues
- Section 5 - Analysis Dataset Descriptions
- Section 6 - Data Conformance Summary
- Section 7 - Submission of Programs
- Conclusions

Overview

ADaM Reviewer's Guide (ADRG) optional submission component

Provides information pertaining to ADaM data and hopefully reduces number of question to sponsor.

7 Sections

Varying Number of Sub-Sections

Majority required, few optional

Keep all as FDA Reviewer may be used to particular numbering convention

Optional Appendices

Section 1 - Introduction

What is the purpose of the ADRG?

List non-industry standard / sponsor specific acronyms in tabular form

List ADaM, SDTM and Define versions used.

What is the source data for the analysis dataset creation?

Purely SDTM?

Possible data can come from alternative formats (ie, CSV files)

Section 2 - Protocol Description

Protocol and Protocol number self-explanatory

Include all versions (original and amendments)
and associated dates

Describe any effect any amendments may have
on the analysis

Section 2 - Protocol Description (Continued)

How do standard ADaM variables relate to the
protocol design?

Consider including a graphical protocol schema.

Included text to explain TRTxP / TRTxA (and
numeric versions), and definitions for APHASE(N).

Chose to add section describing the populations, and
associated flags.

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Section 3 - Analysis Considerations Related to Multiple Analysis Datasets

Has any data been removed (run-in / screening failures) and has a cut-off been applied?

Chose to list ADaM datasets containing run-in failures here, rather than discuss in Section 5.

Any further differences between ADaM & SDTM?

Original SDTM baseline derivation followed simple algorithm across all datasets and didn't match that needed for safety analysis.

Baseline for two domains based on triplicate values

Relative day values re-calculated

Table of core variables across all / most analysis datasets.

Minimum - STUDYID & USUBJID

Could list most of ADSL here

Section 3 - Analysis Considerations Related to Multiple Analysis Datasets (Continued)

Bullet questions to discuss:

ARM vs. Treatment
Planned vs. Actual treatment

Subject issues requiring specific rules

Comprehensive list of possible examples in PRUSE guidance

document

Important to describe in detail how to identify subjects / or how

any particular situation was dealt with.

Visit windowing / inclusion of unscheduled visits and record selection

should be explained

Study had complex visit windows differing between datasets.

Referenced RAP and copied visit slotting tables into appendices.

Multiple assessments assigned to same AVISIT(N).

Explained rules to distinguish assessments to be used (again

reference to RAP and section 5.2)

Date imputation used but not discussed until relevant section 5.2.x

BASETYPE not used in study. DTYPE explained at dataset level.

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Section 4 - Analysis Data Creation and Processing Issues

Split ADaM datasets

Optional, but worth including with 'N/A'
Could design ADaM to negate need to split

Data dependencies

All ADaM datasets have dependency on ADSL.
Others best displayed in table / flow chart

Intermediate datasets

Describe intermediate datasets and resultant analysis ADaM dataset(s)
'There were no intermediate datasets in this study'

Variable Conventions

Discuss important variable conventions introduced by sponsor not easily established in define.xml.
Could include how PARAMCD / PARAM are created within ADLB / ADVS to maintain uniqueness for differing units, positions etc.
Is there a naming convention used for analysis flagging (ANLzzFL)?

Section 5 - Analysis Dataset Descriptions

Do analysis datasets support protocol / SAP (RAP) objectives?

Study objectives copied from RAP, and ADaM datasets identified to assess objective

Objective	ADaM Dataset
Assess the effect of study drug on Health-related quality of life of ALS patients	ADALSFRS, ADALSAQ, ADCGI, ADCRSS, ADEQ5D
Assess the safety and tolerability of intravenous (IV) study drug	ADAE, ADEG, ADLB, ADVS, ADPSRAE, ADLIVER

Provide table inventory of all ADaM datasets starting with ADSL.

Class, functional category and structure

Start ADaM dataset details with ADSL.

Re-supplied population details

Supplied table matching variable to study covariate

Additional table identifying extra variables of interest

Section 5 - Analysis Dataset Descriptions

Separate sub-section for each analysis dataset

Non-BDS structure started with explanation on how dataset was constructed

ADaM was constructed according to draft 'ADaM Hierarchical Occurrence Data Standard v1.0'

Traceability (if not obvious)

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Rules for dealing with partial dates / times

Explain derivations (and DTYPE) - use of tables to summarize information (copied from RAP)

Derivations also included PARAMCD construction

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ADAE was constructed according to draft 'ADaM Hierarchical Occurrence Data Standard v1.0'

Traceability (if not obvious)

ADALS contains data from the MH and FAMH SDTM domains, sub-setting MH where MHTERM='AMYOTROPHIC LATERAL SCLEROSIS'.

or

ADEQ5D contains records from QS where QSCAT eq 'EQ-5D-5L'.

Rules for dealing with partial dates / times

Explain derivations (and DTYPE) - use of tables to summarize information (copied from RAP)

Derivations also included PARAMCD construction

Section 5 - Analysis Dataset Descriptions

Describe non population flags

Visit windowing applied?

Explanation of 'maximum at any time-point'
derived visits, and how they can be identified.

Rationale for certain dataset 'ballooning'
provided

Section 6 - Data Conformance Summary

Conformance Inputs

How was the ADaM data validated?
Define.xml validation

Issue Summary

Table with dataset name(s), diagnostic message, severity, count and explanation.
False positives for ODS domains, with lack of AVALC / AVAL variables
Company specific variables for treatment variables flagged.

Section 7 - Submission of Programs

Conclusion

Has potential to be a very long document
Especially when copying sections of the RAP

Areas open for interpretation

Some components in own ADRG could be
better suited in different section.

Recommend creation not left until end of reporting
process.

Creation is cyclic - future ADRGs could incorporate
answers from previous submission, thus
preempting question.

Thank you for listening



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