Analysis Data Model Metadata Submission Guidelines (ADaM MSG): Human Clinical Trials

Version 1.0 (Final)

Developed by the CDISC ADaM MSG Team

Notes to Readers

- This is Version 1.0 of the Analysis Data Model Metadata Submission Guidelines (ADaM MSG): Human Clinical Trials.
- This document is based on the principles, structures, and standards described in the CDISC Define-XML v2.1 and the Analysis Data Model Version 2.1 and Implementation Guide v1.2.

Revision History

Date	Version
2023-04-18	1.0 Final

See Appendix C for Representations and Warranties, Limitations of Liability, and Disclaimers.

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1 Introduction

1.1 Purpose

The purpose of the Analysis Data Model Metadata Submission Guidelines: Human Clinical Trials (ADaM-MSG) is to provide guidance for preparing the components of the International Conference on Harmonisation (ICH) electronic Common Technical Document (eCTD) Module 5 (M5): Clinical Study Reports "adam" folder. This document and the associated example submission package illustrate the components recommended for electronic submission of ADaM data for an individual study, but can be used as a template for integrated studies as well. These guidelines are based on Define-XML v2.1, ADaM v2.1, and the ADaM Implementation Guide (ADaMIG) v1.1.

Example Submission Package

The example files included with the ADaM-MSG package are intended to illustrate regulatory submission best practices from a CDISC standpoint. The example package is therefore considered fictitious and not indicative of an actual regulatory submission. The supporting example submission package includes the following:

- Define-XML document describing the metadata of the submitted ADaM datasets (define.xml)
    - **Note**: The Define-XML document was evaluated manually and programmatically by the CDISC ADaM MSG Team. At the time ADaM-MSG v1.0 was prepared for internal review, the CDISC Define-XML v2.1 conformance rules were not published, nor available by any publicly available validation tools to validate. Please ensure that any official regulatory submission of an Define-XML v2.1 document is done in accordance with the respective regulatory health authority's requirements/guidance.
- Analysis Data Reviewer's Guide (adrg.pdf)
- ADaM datasets in SAS Version 5 transport file format (*.xpt, where the asterisk (*) represents the ADaM dataset name expressed in lower case, e.g., adsl)
    - Note: The ADaM v2.1/ADaMIG v1.1 datasets were evaluated manually and programmatically by the CDISC ADaM MSG Team. At the time ADaM-MSG v1.0 was prepared for internal review, the CDISC ADaM v2.1/ADaMIG v1.1 conformance rules were recently published and not yet incorporated into any publicly available validation tools to validate.
- Supplemental documents
- Programs

Best Practice

Developing the Define-XML and the analysis data reviewer's guide (ADRG) early in the study development life cycle aids in overall efficiency, allowing study teams to manage potential incremental changes during the course of a study's development, and ensuring alignment between the various components. This is especially important when those components are intended for regulatory submission, thereby helping propagate a more expedited submission package compilation process.

General Note

Regulatory health authority requirements may evolve after publication of this version of the ADaM-MSG. Therefore, when compiling a regulatory submission package, it is always advisable to reference each respective regulatory health authority's most up-to-date requirement(s) and/or guidance (e.g., US FDA via Study Data Standards Resources, https://www.fda.gov/industry/; Japan Pharmaceuticals and Medical Devices Agency (PMDA) via New Drug Review with Electronic Data, https://www.pmda.go.jp/english/review-services/).

It should be noted that the MSG package is based on ADaMIG v1.1 and Define-XML 2.1. The principles provided within can be applied to other versions of these standards until future versions of the ADaM-MSG are developed.

1.2 Organization of this Document

This document is organized into the following sections:

- Section 1, Introduction, describes the purpose and organization of this document.
- Section 2, Define-XML Document, explains the metadata definition portion of the submission datasets.
- Section 3, Analysis Data Reviewer's Guide, explains the ADRG preparation in support of the sample submission.
- Section 4, Submission Datasets, outlines the ADaM datasets contained in the sample submission.
- Section 5, Supplemental Documents, describes documents that can be included as separate hyperlinked PDF files at a sponsor's discretion.
- Section 6, Programs, describes how to reference the specific software and software versions utilized in the analysis.
- Appendices

2 Define-XML Document

The Define-XML document (actual filename used in the Define-XML package: "define.xml") is the metadata intended to describe the format and content of the data for a study, including datasets, variables, value-level metadata, and codelists. In addition, the Define-XML document contains metadata describing the analysis results. Please see the Define-XML specification (available at https://www.cdisc.org/standards/data-exchange/define-xml/) for all necessary details. This document will contain only a small subset of the necessary information to implement define.xml.

General Note

A Define-XML document is a machine-readable document containing only plain text. It contains no formatting for viewing or printing. Instead, formatting is handled by a stylesheet which controls how the Define-XML document is displayed and what values are displayed.

Define-XML Display

The stylesheet in the sample submission (define2-1.xsl) is the stylesheet included with the Define-XML v2.1 package. There are no specific requirements regarding which stylesheet should be included in a submission, but sponsors should ensure the file renders properly, including any hyperlinks. Depending on the PDF viewer and the browser and its settings, users may encounter differences in display and functionality in the rendered XML. Adjusting browser settings can rectify this, but due to so many combinations it is not possible for this document to describe them all.

Codelists

No definitive guidance exists as to whether codelists in Define-XML should contain all of the possible values for a given study. The ADaM MSG Team recommends that, for all Study Data Tabulation Model (SDTM) predecessor variables which are incorporated into analysis datasets, the entire range of possible values in from the corresponding SDTM codelist used in the study be included. For all other variables, the sponsor should decide whether to include all possible values or only those present in the data. For example, suppose only mild adverse events have been reported for a study where the data collection instrument collected AE severity as Mild, Moderate, or Severe. In this case, the recommendation is to include all 3 possible terms in the codelist, as shown in the example submission in this guide. However, in the case of AVISIT where the total range of possible values is not necessarily known ahead of time, the sponsor could choose whether or not it is reasonable to include all values in the codelist.

Also included in the sample submission:

- If there is a codelist for the variable coming from the SDTM dataset, then applicable values from the same codelist must be carried forward into ADaM.

  Example:

Variable	Label/Description	Type	Controlled Terms	Origin / Source / Method / Comment
AESEV	Severity/Intensity	text	AESEV	Predecessor: AE.AESEV

- If the same variable exists in multiple ADaM datasets and has an associated codelist, then the associated codelist name should be differentiated if the list of allowed values is different from one dataset to another.

  Example:

  The codelist name for PARAMCD in ADLB could be PARAMCD_ADLB. The codelist name for PARAMCD in ADVS could be PARAMCD_ADVS.

Dataset Order

All analysis datasets must be included in the dataset-level metadata. A standard order of display has not been established for regulatory submissions of ADaM datasets.

Derivations

Derivations should be represented as human-readable descriptions or pseudocode as opposed to executable programming statements. Long, complex algorithms can be described in a supplemental complex algorithms document hyperlinked from the Define-XML document.

2.1 Analysis Results Metadata (ARM)

Analysis results metadata (ARM) provide traceability for a given analysis result to the specific ADaM data that were used as input to generating the analysis result. They also provide information about the analysis method used and the reason the analysis was performed. Although ARM are an optional ADaM metadata component according to ADaM v2.1, they can be provided to assist the reviewer by identifying the critical analyses; providing links between results, documentation, and datasets; and documenting the analyses performed. The PMDA is the first agency to request ARM on primary endpoints and key safety tables for submissions starting from October 2016 onward. Therefore, ARM should be included as requested by the appropriate regulatory agencies.

When submitting ARM, it is preferred to include ARM in the Define-XML document. When ARM cannot be included directly into the Define-XML document, these should be made part of the ADRG and included in an appendix subsection (e.g., 8.1 Analysis Results Metadata).

For descriptive statistics and frequency analyses (e.g., safety tables), the focus should be on variables used for data selection. For example: standardized MedDRA query (SMQ) details (SMQzzNAM/CD/SC), complex query (CQzzNAM) specifications, or multi-response criteria (MCRITy/ML) for treatment-emergent adverse events (TEAEs) of particular interest (as per PMDA requirement).

For incidence and event rates, more details should be added regarding the time-at-risk determination. For example, it should be clarified where the day of event onset is considered (time at risk/non-risk) as well as details on risk censoring at the end of analysis period, especially where this is not explicitly and comprehensively specified in the statistical analysis plan (SAP).

For more information and examples on submission of ARM, see Analysis Results Metadata (ARM) v1.0 for Define-XML v2.0 (available at https://www.cdisc.org/standards/foundational/define-xml/).

3 Analysis Data Reviewer's Guide

The ADRG provides additional information and clarification for reviewers about the submitted data that is not present in the Define-XML document and/or the SAP. The US FDA *Study Data Technical Conformance Guide*[1] recommends the inclusion of the ADRG, whereas the PMDA *Technical Conformance Guide on Electronic Study Data Submissions*[2] requires it. The ADRG should help to facilitate the review process by describing any special considerations, such as derivations that are used across several datasets (e.g., visit windowing, date imputation), dataset dependencies, and complex algorithms that are incompatible with the Define-XML from a presentation point of view. Although the specific format of the reviewer's guide is not explicitly addressed by regulatory health authorities (e.g., the FDA or the PMDA), there may be references to the PHUSE template. See the PHUSE website for the latest ADRG version (https://phuse.global/Deliverables/1).

General Note
At the time of publication of ADaM-MSG v1.0, the US FDA specifies that the ADRG should be named "adrg.pdf." The PMDA prefers it be named "analysis-data-reviewers-guide.pdf", "adrg.pdf", or something similar, so that the contents are identifiable. The ADaM MSG Team named the reviewer's guide in the sample submission "adrg.pdf", but sponsors should check for the latest recommendation from their regulatory health authority.

3.1 Conformance, Validation, and Tools

It is expected that sponsors will perform conformance checks on the study data package throughout the submission development life cycle in order to identify issues related to data and programming as early as possible. Conformance checks are discussed here in the context of the reviewer's guide, as that is where conformance issues should be explained in the submission study data package.

- The ADaM data should be checked for conformance to ADaM and the ADaMIG (available at https://www.cdisc.org/standards/foundational/adam/).
- The ADaM data should be checked for consistency with SDTM datasets.
- The Define-XML document should be checked against the Define-XML conformance rules (available at https://www.cdisc.org/standards/foundational/define-xml/).
- The ADaM data should be checked for consistency with Define-XML.
- When the ADaM data and the Define-XML document are reviewed for conformance to standards, any findings must be evaluated.
    - All conformance findings that are generally within the sponsor's control should be corrected. However, the goal is not to get a "clean" report. Tools sometimes flag content that is allowable (e.g., controlled terminology that is extensible can be extended). There are also often data issues resulting in conformance findings that should not be corrected just to avoid the findings.
    - Any conformance findings that cannot be resolved should be explained in the ADRG.
    - Regulatory health authorities may have their own sets of business requirements for evaluating conformance and validation, as well as the scope of findings to be documented in the ADRG.
        - Third-party tools may be used to evaluate ADaM data for conformance. These tools may have their own interpretation of the requirements for properly formed ADaM datasets. Sponsors should understand and evaluate these interpretations.
        - Validation issues related to an interpretation of a requirement should be noted in the ADRG.
- Sponsors should explain their conformance-check findings.
    - Sponsors should be careful to avoid generic explanations, or explanations which simply repeat the wording of the conformance check, when providing explanations for the conformance check finding. For example, in response to a conformance check finding indicating "BASE or BASEC is populated for a unique USUBJID, PARAMCD but no baseline record exists," simply explaining that baseline values were not collected with the data is not sufficient. Instead, a response such as "Baseline values

were obtained from historical information collected on the CRF and stored in Findings About" should be provided.

- Providing greater detail can help the regulatory health authority and the corresponding review division understand the reasons for the identified conformance-check findings.

4 Submission Datasets

The ADaM Subject-Level Analysis Dataset (ADSL) is required for all CDISC submissions. Additionally, all datasets used for analysis purposes or referenced in the metadata should be included in the submission, in the appropriate eCTD folder. This section describes the datasets in the sample ADaM-MSG package, which are limited to a few examples for illustration purposes only. Because these are examples, the subsections that follow describe implementation choices made by the ADaM MSG Team. This information would typically be included in the ADRG.

4.1 ADSL - Subject-Level Analysis Dataset

The ADSL contains all subject-level variables for demographics, subject characteristics, treatment assignments, and population flags. The population indicator variables, treatment variables, and variables used for subgroups analyses are copied into other datasets for statistical analysis. The population indicator variables include: Safety Population Flag (SAFFL), Intent-To-Treat Population Flag (ITTFL), Efficacy Population Flag (EFFFL), Completers of Week 8 Population Flag (COMP8FL), Completers of Week 16 Population Flag (COMP16FL), and Completers of Week 24 Population Flag (COMP24FL). All subjects in SDTM.DM were included in ADSL.

In the sample submission, the subjects were assigned USUBJID values of "01-701-XXXX" to "01-718-XXXX" and STUDYID values as "CDISCPILOT01" in SDTM. This should not be perceived as a recommended format, but rather illustrates that sponsors are free to assign USUBJID and STUDYID values in whatever format they wish.

4.2 All Other Analysis Datasets

This subsection describes the datasets with ADaM Basic Data Structure (BDS), Structure for Occurrence Data (OCCDS), and ADAM OTHER structures provided in the sample ADaM-MSG package.

4.2.1 ADAE – Adverse Events Analysis Data

The Adverse Events Analysis Dataset (ADAE) contains 1 record per subject per adverse event. Subjects who did not report any adverse events are not represented in this dataset. The data reference for ADAE is the SDTM Adverse Events (AE) domain and there is a 1:1 correspondence between records in the source and this analysis dataset. These records can be linked uniquely by STUDYID, USUBJID, and AESEQ. As with the SDTM AE dataset, all MedDRA code variables (i.e., those variables that end in CD) have missing values and dummy terms have been applied to the MedDRA High-Level Term (HLT) and High-Level Group Term (HLGT). This is due to the proprietary nature of the MedDRA and the fact that the data with this project will be made available to the public. In a standard submission, these codes and terms should be non-missing and properly populated.

Events of particular interest (dermatologic) are captured in the customized query variable (CQ01NAM) in this dataset. Because the ADAE is a source for the Time to Event Analysis Dataset (ADTTE), the first chronological occurrence based on the start dates (and sequence numbers) of the treatment emergent dermatological events are flagged (AOCC01FL) to facilitate traceability between these 2 analysis datasets. The ADAE also contains additional occurrence flags to facilitate traceability, reviewability, and ease of reporting between the analysis dataset and the unique counts in the summary tables. For treatment-emergent adverse events, refer to the Define-XML documentation (https://www.cdisc.org/standards/data-exchange/define-xml) for the following variables: AOCCFL, AOCCSFL, and AOCCPFL (for summarization at the subject, system organ class (SOC), and preferred term levels, respectively). Similarly, refer to the Define-XML documentation for AOCC02FL, AOCC03FL, and AOCC04FL for summarization of serious adverse events at the subject, SOC, and preferred term levels.

The 3 deaths reported during the conduct of this study are captured in the Results in Death Flag (AESDTH = "Y") and Outcome of Adverse Event (AEOUT = "FATAL"). The start date of the adverse event in ADAE is imputed to the first of the month if the day is missing. The Study Day of Event Start (ASTDY) and the Treatment Emergent Analysis Flag (TRTEMFL) are derived based on this imputation and may differ from their corresponding SDTM AE/SUPPAE variables Study Day of Start of Adverse Event (AESTDY) and Treatment Emergent Flag (AETRTEM).

4.2.2 ADLBC – Analysis Dataset Lab Blood Chemistry

The ADLBC contains 1 record per subject per parameter per analysis visit. The ADLBC consists of lab chemistry parameters, with standardized lab values derived from the SDTM LB (Laboratory Tests) domain. In some of the summaries, the derived end-of-treatment visit (AVISITN = 99) is also presented.

4.2.3 ADLBH – Analysis Dataset Lab Hematology

The ADLBH contains 1 record per subject per parameter per analysis visit. The ADLBH consists of lab hematology parameters, with standardized lab values derived from the SDTM LB domain. In some of the summaries, the derived end-of-treatment visit (AVISITN = 99) is also presented.

4.2.4 ADLBHY – Analysis Dataset Lab Hy's Law

The ADLBHY contains 1 record per subject per parameter per analysis visit. The ADLBHY is derived from the ADLBC analysis dataset. It contains derived parameters based on Hy’s law.

4.2.5 ADADAS – ADAS-Cog Analysis

The ADADAS contains analysis data from the ADAS-Cog scale, one of the primary efficacy endpoints. It contains 1 record per subject per parameter (ADAS-Cog questionnaire item) per analysis visit per analysis date. Visits are placed into analysis visits (represented by AVISIT and AVISITN) based on the date of the visit and the visit windows. If multiple visits fall into the same visit window, then the one closest to the target date is chosen for analysis. Records where ANL01FL = "Y" are those that were used for analysis. The last observation carried forward (LOCF) algorithm only considered records used for analysis as candidates to carry forward. Records where DTYPE = "LOCF" signify those where AVAL was imputed using the LOCF algorithm. Source data can be traced back to the SDTM Questionnaires (QS) domain using USUBJID and QSSEQ. Details on how to derive the primary efficacy result based on ADAS-Cog data can be found in the ARM in the define.xml.

4.2.6 ADCIBC – CIBIC+ Analysis

The ADCIBC contains analysis data from the from CIBIC+ questionnaire, one of the primary efficacy endpoints. It contains 1 record per subject per parameter per analysis visit per analysis date. Note that for all records, PARAM = "CIBIC Score". Visits are placed into analysis visits (represented by AVISIT and AVISITN) based on the date of the visit and the visit windows. If multiple visits fall into the same visit window, then the one closest to the target date is chosen for analysis. Records where ANL01FL = "Y" are those that were used for analysis. The LOCF algorithm only considered records used for analysis as candidates to carry forward. Records where DTYPE = "LOCF" signify those where AVAL was imputed using the LOCF algorithm. Source data can be traced back to the SDTM QS domain using USUBJID and QSSEQ. Details on how to derive the primary efficacy result based on CIBIC+ data can be found in the analysis results metadata in the define.xml.

4.2.7 ADNPIX – NPI-X Item Analysis Data

The ADNPIX contains 1 record per subject per parameter (NPI-X questionnaire item, total score, and mean total score from week 4 through week 24) per analysis visit (AVISIT) per analysis date. The analysis visits (represented by AVISIT and AVISITN) are derived from days between assessment date and randomization date and based on the visit windows specified in the SAP. If multiple assessments fall into the same visit window, then the one closest to the target day is chosen for analysis. Records where ANL01FL = "Y" are those that were used for analysis. The LOCF algorithm was not used for these data. Source data can be traced back to the SDTM QS domain using USUBJID and QSSEQ. All the NPI-X parameters, except for the mean total score from week 4 through week 24 (NPTOTMN), are from the SDTM QS domain. The value of parameter (NPTOTMN) contains the mean total score for each patient who had any assessments from week 4 through week 24. The baseline value of the parameter (NPTOTMN) is the same as the baseline value of total score. The baseline value is a covariate in the analysis of covariance (ANCOVA) model.

4.2.8 ADVS - Vital Signs Analysis Dataset

The Vital Signs Analysis Dataset (ADVS) contains 1 record per subject per parameter. It contains the vital sign results from the SDTM VS domain. The baseline results (BASE) and change from baseline (CHG) are provided. Different baselines are identified using the BASETYPE variable. Records used for analysis are identified using the analysis record flag (ANL01FL).

4.2.9 ADTTE - AE Time To 1st Derm. Event Analysis

The ADTTE dataset contains 1 record per subject per parameter (the Time to First Dermatologic Event analysis parameter). It contains the necessary variables (ADT, CNSR, EVNTDESC) to identify the occurrence of the event. The records in ADTTE are derived from the ADSL and the ADAE.

4.2.10 ADLBCPV - Analysis Dataset Lab Blood Chemistry (Previous Visit)

The ADLBCPV contains 1 record per subject per parameter per analysis visit. The ADLBCPV is derived from the ADLBC. These laboratory parameters hold "change from the previous visit, relative to normal range".

4.2.11 ADLBHPV - Analysis Dataset Lab Hematology (Previous Visit)

The ADLBHPV contains 1 record per subject per parameter per analysis visit. The ADLBHPV is derived from the ADLBH. These laboratory parameters hold "change from the previous visit, relative to normal range".

5 Supplemental Documents

Additional documents can be included as separate hyperlinked PDF files at a sponsor's discretion. Examples of appropriate materials to represent in a separate PDF file include complex algorithms or derivation methods such as scoring material provided in support of a questionnaire or oncology-related derivations that are too extensive to be displayed in a readable manner in the Define-XML. Please note that some regulatory agencies have specific requirements regarding PDF files (e.g., version, file size) and file-naming conventions. As an alternative to a separate complex algorithms document, such information could instead be included as an appendix to the ADRG. Sponsors that choose to submit a separate complex algorithms document should consider including language in the ADRG describing why this information was included in a separate document instead of the ADRG.

The ADaM-MSG v1.0 sample submission package includes an example of these supplemental documents. The Define-XML document should contain explicit references to these documents; sponsors may refer to the Define-XML documentation (https://www.cdisc.org/standards/data-exchange/define-xml) for further details.

6 Programs

Discussion should take place with the relevant agency as to what programs are expected to be included in the submission. In addition, sponsors should consult the relevant technical conformance guide (e.g., FDA,[1] PMDA[2]) for current guidance. The specific software and software versions utilized should be noted in the ADRG. In general, the main purpose of requesting the submission of these programs is to understand the process by which the variables for the respective analyses were created and to confirm the analysis algorithms and results. Macros important to this understanding should also be included in the submission.

6.1 ADaM Dataset Creation Programs

This is a list of all the programs used to create the ADaM datasets in the submission. File types would be dependent on the agency to which sponsors are submitting (e.g., text, SAS). Relevant technical conformance guides should be reviewed to understand program submission expectations.

6.2 TFL Creation Programs

This is a list of the TFL creation programs included in the submission. File types would be dependent on the agency to which sponsors are submitting (e.g., text, SAS). Relevant technical conformance guides should be reviewed to understand program submission expectations.

7 Appendices

Appendix A: Glossary

The following table lists some of the abbreviations and terms are used in this document. Additional definitions can be found in the text, and in the CDISC Glossary (available at https://www.cdisc.org/standards/glossary).

ADAE	Adverse Events Analysis Dataset
ADaM	CDISC Analysis Dataset Model
ADaMIG	ADaM Implementation Guide
ADaM-MSG	Analysis Data Model Metadata Submission Guidelines (Human Clinical Trials)
ADAS-Cog	Alzheimer's Disease Assessment Scale–Cognitive Subscale
ADLB	Laboratory Analysis Dataset
ADRG	Analysis data reviewer's guide
ADSL	(ADaM) Subject-Level Analysis Dataset
ADTTE	Time to Event Analysis Dataset
ADVS	Vital Signs Analysis Dataset
ANCOVA	Analysis of covariance (model)
ARM	Analysis results metadata
BDS	(ADaM) Basic Data Structure
CDISC	Clinical Data Interchange Standards Consortium
CIBIC+	Clinician's Interview-Based Impression of Change with Caregiver Input
eCTD	(ICH) electronic Common Technical Document
Define-XML	CDISC metadata standard that describes any tabular dataset structure
FDA	(US) Food & Drug Administration
HLGT	High-Level Group Term (MedDRA)
HLT	High-Level Term (MedDRA)
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
LOCF	Last observation carried forward (algorithm)
MedDRA	Medical Dictionary for Regulatory Activities
MSG	Metadata Submission Guidelines
NPI-X	Neuropsychiatric Inventory
OCCDS	(ADaM) Structure for Occurrence Data
PDF	Portable document format
PMDA	(Japan) Pharmaceuticals and Medical Devices Agency
SAP	Statistical analysis plan
SDTM	Study Data Tabulation Model
SDTMIG	Study Data Tabulation Model Implementation Guide: Human Clinical Trials
SMQ	Standardized MedDRA Query
SOC	System organ class
TEAE	Treatment-emergent adverse event
XML	Extensible Markup Language

Appendix B: References

1. US Food & Drug Administration. *Study Data Technical Conformance Guide - Technical Specifications Document*. US Department of Health and Human Services; 2022. Accessed November 4, 2022. https://www.fda.gov/media/153632/download

2. Pharmaceuticals and Medical Devices Agency. *Technical Conformance Guide on Electronic Study Data Submissions*. PMDA; 2022. Accessed November 4, 2022. https://www.pmda.go.jp/files/000247157.pdf

Appendix C: Representations and Warranties, Limitations of Liability, and Disclaimers

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