

Template of Analysis Reviewer's Guide in Oncology

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Topics

- **Introduction**
 - ✓ ADRG
 - ✓ Challenges in completing ADRG
 - ✓ Needs for therapeutic area (TA) ADRG
- **Oncology: ADRG template**
 - ✓ Objectives
 - ✓ Scope
 - ✓ Details
 - ✓ Implementation
- **Conclusions**
- **Acknowledgment**
- **Q&A**

Introduction – ADRG

- The Analysis Data Reviewer's Guide (ADRG) provides context for ADaM datasets and terminology that benefit from additional explanation beyond the Data Definition document in a regulatory submission
- A high quality ADRG is essential to a smooth regulatory review process

Introduction - Challenges in Completing ADRG

Analysis Data Reviewer's Guide

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- General ADRG Template
- Due to the scope and details of the content, an intensive effort is expected to complete an ADRG
 - ✓ Add both study-specific and **non-study-specific** information to each section
 - ✓ ~1 week to complete
 - ✓ Prior to delivering to agency, there are multiple rounds of detailed review
- Significant resource is expected to be spent on non-study-specific information in ADRGs for all the filings within each TA

Introduction – Need for TA ADRG

- Many ADRG sections have similar components within a TA
 - ✓ Acronyms
 - ✓ Analysis datasets
 - ❖ Standards
 - ❖ Core variables
 - ❖ Variable derivations
 - ✓ Dataset programs
 - ❖ Source SDTM domains
 - ❖ Logic deriving the variables
- Prospect to standardize the common information within a TA
- TA ADRG template will ensure the efficiency and consistency across all fillings in the franchise.

Oncology: ADRG Template - Objectives



High-quality document with accurate description of the ADaM datasets and corresponding standards

Simplify

Ease of completion with pre-populated information



Significant time saving in writing and reviewing the document

Oncology: ADRG template - Scope

- **Incorporating PHUSE and company's ADRG Templates**
- **Adding notes for using the template**
- **Providing links/entries for the standards/tools**
 - ✓ [Study Data Standard Versions](#) (e.g. SDTM, ADaM, Medication Dictionary, etc.)
 - ✓ [Tool to generate the figure of Data Dependencies](#)
 - ✓ [Rational for ADaM data conformance/define.xml validation issues](#)
- **Including sample text for common sections across ADRG**
 - ✓ Acronyms
 - ✓ Analysis consideration related to multiple analysis datasets
 - ✓ Analysis dataset/core variables' description
 - ✓ Dataset programs and source datasets

Oncology: ADRG Template – Details

- ***Notes for using the template***

<Sample text for Oncology>

1.2 Acronyms

<Note to author: Update table with terms as appropriate>

2.2 Protocol Design in Relation to ADaM Concepts

<May include the information from the 1st paragraph of Section 2.1 Protocol Design in the protocol>

3.1 Core Variables

<Note for Oncology: These are the variables listed in the column “Core Variable” in the ADSL tab of the ADaM dataset spec for the study.>

Acronym	Translation
ADaM	Analysis Data Model
AE	adverse event(s)
AEOSI	adverse event(s) of special interest
ASaT	All Subjects as Treated
BICR	blinded independent central review
BOR	best overall response
CM	concomitant medication
CR	complete response
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
ECI	events of clinical interest
ECOG	Eastern Cooperative Oncology Group
EX	exposure
FAS	full analysis set
GHS	global health score
IA	interim analysis
ICH	International Conference on Harmonization
INV	investigator
IRC	independent review committee
ITT	intent-to-treat
IVRS	interactive voice response system
LS	least square
OS	overall survival
MH	medical history
PD	progressive disease
PD-L1	Programmed death-ligand 1
PFS	progression-free survival
PK/PD	pharmacokinetics/pharmacodynamics
PR	partial response
ePRO	electronic patient reported outcomes
Q3W	every 3 weeks
RECIST 1.1	response evaluation criteria in solid tumors, version 1.1

Oncology: ADRG Template - Details

1.2 Acronyms

- Consideration
 - ✓ Template includes all commonly used TA acronyms in the template
 - ✓ Study team adds/removes the terms as appropriate

Oncology: ADRG Template - Details

2.2 Protocol Design in Relation to ADaM Concepts

2.2 Protocol Design in Relation to ADaM Concepts

<Complete by Statistician>

<Sample text for Oncology> This is a <randomized/non-randomized, multi-site, double-blinded/open-label> trial of generic name of the medicine (dose regimen: MK-0000 200mg Q3W) in subjects with <xxx> cancer(s).

Pre-populated terms to choose from

Text to be updated or removed

- Consideration
 - ✓ Template pre-populates the trial design terms
 - ✓ Study team selects a term as appropriate

Variable Name	Variable Description
USUBJID	Unique Subject Identifier
STUDYID	Study Identifier
SUBJID	Subject Identifier for the Study
AGE	Age
AGEU	Age Units
SEX	Sex
SEXN	Sex (N)
RACE	Race
RACEN	Race (N)
RANDFL	Randomized Population Flag
ITTFL	Intent-To-Treat Population Flag
TRTFL	Treated Population Flag
SAFFL	Safety Population Flag
ASATEFL	Efficacy Analysis Flag
FASFL	Full Analysis Set Population Flag
PPROTFL	Per-Protocol Population Flag
COMPLFL	Completers Population Flag
FUFL	Subject Follow-up Flag
TRT01P	Planned Treatment for Period 01
TRT01PN	Planned Treatment for Period 01 (N)
TRT01A	Actual Treatment for Period 01
TRT01AN	Actual Treatment for Period 01 (N)
TR01PG1	Planned Pooled Treatment 1 for Period 01
TR01PG1N	Planned Pooled Treatment 1 for Period 01 (N)
TR01AG1	Actual Pooled Treatment 1 for Period 01
TR01AG1N	Actual Pooled Treatment 1 for Period 01 (N)
TRTSDT	Date of First Exposure to Treatment
TRTSDTM	Datetime of First Exposure to Treatment
TRTEDT	Date of Last Exposure to Treatment
TRTEDTM	Datetime of Last Exposure to Treatment
TR01SDT	Date of First Exposure in Period 01
TR01SDTM	Datetime of First Exposure in Period 01
TR01EDT	Date of Last Exposure in Period 01
TR01EDTM	Datetime of Last Exposure in Period 01

Oncology: ADRG Template - Details

3.1 Core Variables

- Consideration
 - ✓ Template includes all core variables commonly listed in the data specification for ADSL
 - ✓ Study team adds/removes the variable(s) as appropriate

Oncology: ADRG Template - Details

3.2 Treatment Variables

3.2 Treatment Variables

<Complete by Statistician>

ARM versus TRTxxP

Are the values of ARM equivalent in meaning to values of TRTxxP?

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

<Sample text for Oncology> Yes, the values of ARM are equivalent in meaning to the values of TRT01P.

- Consideration
 - ✓ Template includes sample answer to questions
 - ✓ Study team revises as needed

Dataset Dataset Label	Class	Regimen or other Safety subject characteris tics	PK/PD Primary Objective	Structure <Be consistent with Define>
ADSL Subject-Level Analysis Dataset	ADSL		X	One record per subject
ADAE Adverse Event Analysis Dataset	OCCDS	X		One record per subject, per each AE recorded in SDTM AE
ADBASE Subject-Level Baseline Characteristics Dataset	OTHER		X	One record per subject
ADCM Concomitant Medications Analysis Dataset	OCCDS	X		One record per subject, per each CM recorded in SDTM CM, per APERIOD
ADDILI DILI Reporting Analysis Dataset	BDS	X		One record per subject, parameter, and analysis time point.
ADEX Exposure Analysis Dataset	OTHER	X		One record per subject, per each EX recorded in SDTM EX
ADEXSUM Exposure Summary Analysis Dataset	BDS	X		One record per subject, analysis parameter and/or analysis time point
ADINTDT Interim Dataset of Dates Used for ADTTE	BDS	X		One record per subject, per parameter
Dataset Dataset Label	XXX	X		One record per subject

Oncology: ADRG Template - Details

5.2 Analysis Datasets

- Consideration
 - ✓ Template includes all common analysis datasets in Oncology TA
 - ✓ Study team adds/removes the datasets as appropriate

Oncology: ADRG Template - Details

5.2.2 ADAE – Adverse Event Analysis Dataset

ADAE contains adverse events from SDTM AE and SUPPAE for <insert your text here, e.g. ASaT> subjects. Adverse Events are graded based on NCI CTCAE version X.XX.

TRTEMFL is a flag used to include AE on and after the treatment start date and before the treatment end date + 30 days for a non-serious AE, or + 90 days for a serious AE. PDEXCFL allows exclusion of MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" when these AEs were not related to the drug.

5.2.2 ADAE – Adverse Event Analysis Dataset

- Consideration
 - ✓ Template includes the common descriptions to the analysis datasets in Oncology TA
 - ✓ Study team revises the description as appropriate

Oncology: ADRG Template - Details

7.1 ADaM Programs

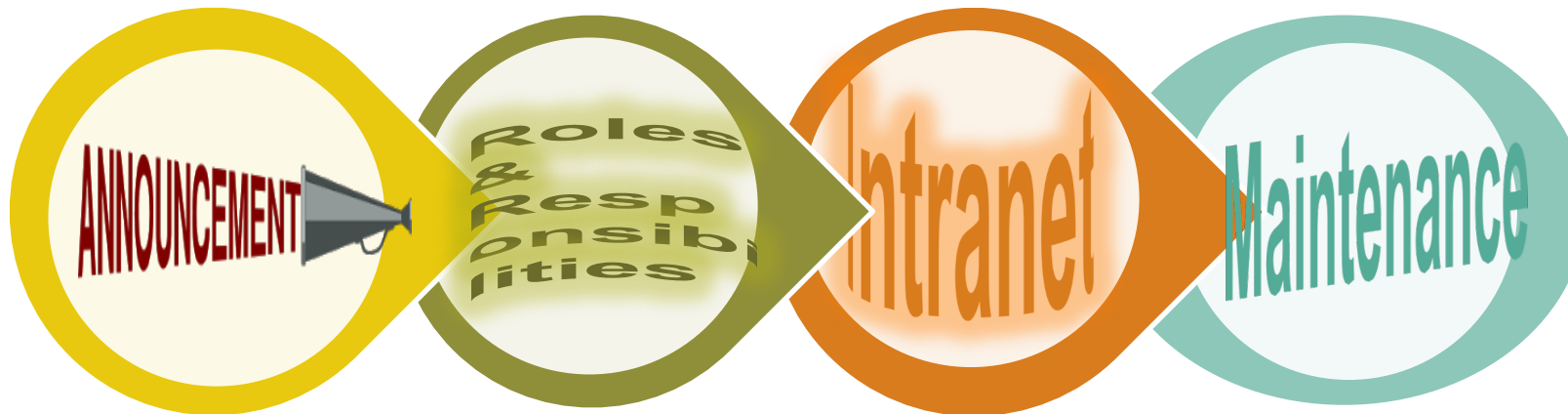
Analysis Dataset	Description	SAS Program Name	Input Dataset	
			Tabulation	Analysis
adtl.xpt	Analysis Target Lesions Measurement	adtl.txt	rs.xpt, supprs.xpt, tr.xpt, supptr.xpt	adsl.xpt

7.1 ADaM Programs

- Consideration
 - ✓ Template includes all common ADaM programs and input datasets in Oncology TA
 - ✓ Study team revises the information as appropriate

Oncology: ADRG Template - Implementation

The template has been adopted by multiple Oncology filings since its release in 2020



- Announce in the team meeting
- Release the location
- Set expectations

- Clarify roles & responsibilities

- Publish the link on the department website

- Update based on:
 - ✓ Industrial and company's template release
 - ✓ ADaM IG
 - ✓ Users' feedback

Conclusions

- **The ADRG template of Oncology TA has been implemented by all the oncology submissions and received positive feedback from the users and management reviewers since its release in 2020**
- **Its standardized feature has advantages including**
 - (1) high-quality document with accurate description of the ADaM datasets and corresponding standards
 - (2) ease of completion with pre-populated information
 - (3) significant time saving in writing and reviewing the document
 - (4) potential to leverage to other TAs
 - (5) possibility for automation

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- **Merck Statistical Programming Leadership Team**

Q & A

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