

Single Day Events

How to create analysis result metadata file in
an efficient way

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Disclaimer



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Overview

- History and Background
- Metadata Perspective
- How to implement ARM
- Challenge and Future

History and Background

What is ARM?

- Analysis Result Metadata
 - Was released on 2014 and as part of Define-XML 2.0
 - Provide traceability for a given analysis result to the specific ADaM data that were used as input to generating the analysis result.
 - Provide information about the analysis method used and the reason the analysis was performed.
 - An optional ADaM metadata component according to the ADaM version 2.1 document.
 - Assist the reviewer by identifying the critical analyses, providing links between results, documentation, and datasets, and documenting the analyses performed.
 - FDA doesn't specifically mention the necessity of ARM as one of the requirements.

PMDA Requirements

- PMDA Technical Conformance Guide
 - <http://www.pmda.go.jp/files/000215100.pdf>
- If the definitions are provided in the analysis result report, it would be sufficient to mention this fact and clearly state the relevant page number in the analysis result report.
- Corresponding analyses covered by ARM will be
 - Primary and secondary efficacy analysis
 - Primary safety analyses and basic analysis for adverse events
 - Analyses to investigate the effect of major factors on efficacy and safety
- Allows sponsors to submit ARM in PDF format because PMDA considers content is more important than a format of ARM

ARM in PDF

Table 14-1-1	Statistical Analysis of Incidence of PHN (MITT Population) (Solid Tumor Malignancy Population)
Analysis Result	Statistical Analysis of Incidence of PHN
Analysis Parameter (s)	NA
Analysis Variable (s)	EFFICACY.PHN90 , EFFICACY.THZMT
Analysis Reason	Efficacy analysis
Analysis Purpose	Secondary Efficacy Endpoints
Data References (incl. Selection Criteria)	ADSL.MITTFN=1 and and ADSL.STRATA1N='Y' MITT(Modified Intent-To-Treat) population is the primary analysis population for analysis, this population included all randomized patients who received at least one dose of the vaccination.(mittfn=1) Subjects with Solid Tumor Malignancy were included in the stratum group " strata1n eq 1". PHN90 is a variable with 1 or 0, if have Postherpetic Neuralgia when greater or equal than 90 days, then PHN90=1, else PHN90=0 Variable THZMT is HZ follow-up time for MITT population.
Documentation	Refer to XXX, Protocol 011-04, section 3.5 STATISTICAL ANALYSIS PLAN
Programming Statements	<pre> ***analysis population; data efficacy; set xx.efficacy; where mittfn=1 and strata1n eq 1; if trt01pn=1 then trt_cd='01'; else if trt01pn=2 then trt_cd='02'; run; ***summary; data _templ; set efficacy; thzmt_y=thzmt/365.25; if trt01pn=1 then _trt=1; if trt01pn=2 then _trt=0; run; proc sort data=_templ; by _trt; run; </pre>

ARM in XML

ADaM-IG 1.0

- Analysis Data Reviewer's Guide
- Analysis Results Metadata
- Analysis Datasets
- Parameter Value Level Metadata
- Controlled Terminology
- Analysis Derivations
- Comments

Analysis Results Metadata (Summary) for Study CDISC-Sample

Table 14-3.01 Primary Endpoint Analysis: ADAS-Cog - Summary at Week 24 - LOCF (Efficacy Population)
Dose response analysis for ADAS-Cog changes from baseline
Pairwise comparisons to placebo for ADAS-Cog changes from baseline
Table 14-5.02 Incidence of Treatment Emergent Serious Adverse Events by Treatment Group
Incidence of Treatment Emergent Serious Adverse Events by Treatment Group

Analysis Results Metadata (Detail) for Study CDISC-Sample

Table 14-3.01

Display	Table 14-3.01 Primary Endpoint Analysis: ADAS-Cog - Summary at Week 24 - LOCF (Efficacy Population)
Analysis Result	Dose response analysis for ADAS-Cog changes from baseline
Analysis Parameter(s)	PARAMCD = "ACTOT" (Adas-Cog(11) Subscore)
Analysis Variable(s)	CHG (Change from Baseline)
Analysis Reason	SPECIFIED IN SAP
Analysis Purpose	PRIMARY OUTCOME MEASURE
Data References (incl. Selection Criteria)	ADQSADAS [PARAMCD = "ACTOT" and AVISIT = "Week 24" and EFFFL = "Y" and ANL01FL = "Y"]
Documentation	Linear model analysis of CHG for dose response; using randomized dose (0 for placebo; 54 for low dose; 81 for high dose) and site group in model. Used PROC GLM in SAS to produce p-value (from Type III SS for treatment dose). SAP Section 10.1.1
Programming Statements	[SAS version 9.2] <pre>proc glm data = ADQSADAS; where EFFFL='Y' and ANL01FL='Y' and AVISIT='Week 24' and PARAMCD="ACTOT"; class SITEGR1; model CHG = TRTPN SITEGR1; run;</pre>

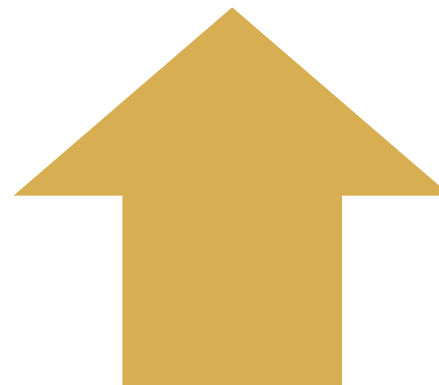
XML vs. PDF



Traceability – Link all related materials
Less Format Work – Display by stylesheet
Quality Control – Validated by open rules



Printable
Easy to create



Metadata Perspective

XML Structure

```
<?xml version="1.0" encoding="UTF-8"?>
<ODM xmlns="http://www.cdisc.org/ns/odm/v1.3"
  xmlns:def="http://www.cdisc.org/ns/def/v2.0"
  xmlns:xlink="http://www.w3.org/1999/xlink"
  xmlns:arm="http://www.cdisc.org/ns/arm/v1.0"
  ODMVersion="1.3.2" FileType="Snapshot" FileOID="CDISC-Sample"
  CreationDateTime="2014-03-28T11:07:23:00"
  Originator="CDISC ADaM Metadata Team">
  <Study OID="cdisc01">
    <GlobalVariables>
      <StudyName>CDISC Sample</StudyName>
      <StudyDescription>CDISC-Sample Data Definitions</StudyDescription>
      <ProtocolName>CDISC-Sample</ProtocolName>
    </GlobalVariables>
    <MetaDataVersion OID="MDV.CDISC01.ADaMIG.1.0.ADaM.2.1"
      Name="Study CDISC-Sample, Data Definitions"
      Description="Study CDISC01, Data Definitions"
      def:DefineVersion="2.0.0"
      def:StandardName="ADaM-IG"
      def:StandardVersion="1.0">
```

```

    < Supplemental Data Definitions (def:SupplementalDoc) >
    < Value Level Metadata (def:ValueListDef) >
    < Where Clause Definitions (def:WhereClauseDef) >
    < Domain Level Metadata (ItemGroupDef) >
    < Variable Level Metadata (ItemDef) >
    < Controlled Terminology Metadata (CodeList) >
    < Computational Algorithms (MethodDef) >
    < Comments (def:CommentDef) >
    < Referenced Documents (def:leaf) >
    < Analysis Results Metadata (arm:AnalysisResultDisplays) >
  </MetaDataVersion>
</Study>
</ODM>
```

Reference: Analysis Results
Metadata Specification
(Version 1.0) for
Define-XML (Version 2)

Key Elements and Attributes of ARM

- Analysis Display Metadata
- Analysis Result Metadata
- Analysis Parameters
- Analysis Datasets
- Documentation
- Programming Statements

Sample from CDISC

Table 14-3.01

Display	Table 14-3.01 Primary Endpoint Analysis: ADAS-Cog - Summary at Week 24 - LOCF (Efficacy Population)
Analysis Result	Dose response analysis for ADAS-Cog changes from baseline
Analysis Parameter(s)	PARAMCD = "ACTOT" (Adas-Cog(11) Subscore)
Analysis Variable(s)	CHG (Change from Baseline)
Analysis Reason	SPECIFIED IN SAP
Analysis Purpose	PRIMARY OUTCOME MEASURE
Data References (incl. Selection Criteria)	ADQSADAS [PARAMCD = "ACTOT" and AVISIT = "Week 24" and EFFFL = "Y" and ANL01FL = "Y"]
Documentation	Linear model analysis of CHG for dose response; using randomized dose (0 for placebo; 54 for low dose; 81 for high dose) and site group in model. Used PROC GLM in SAS to produce p-value (from Type III SS for treatment dose). SAP Section 10.1.1
Programming Statements	[SAS version 9.2] <pre>proc glm data = ADQSADAS; where EFFFL='Y' and ANL01FL='Y' and AVISIT='Week 24' and PARAMCD="ACTOT"; class SITEGR1; model CHG = TRTPN SITEGR1; run;</pre>

Key Elements and Attributes – View

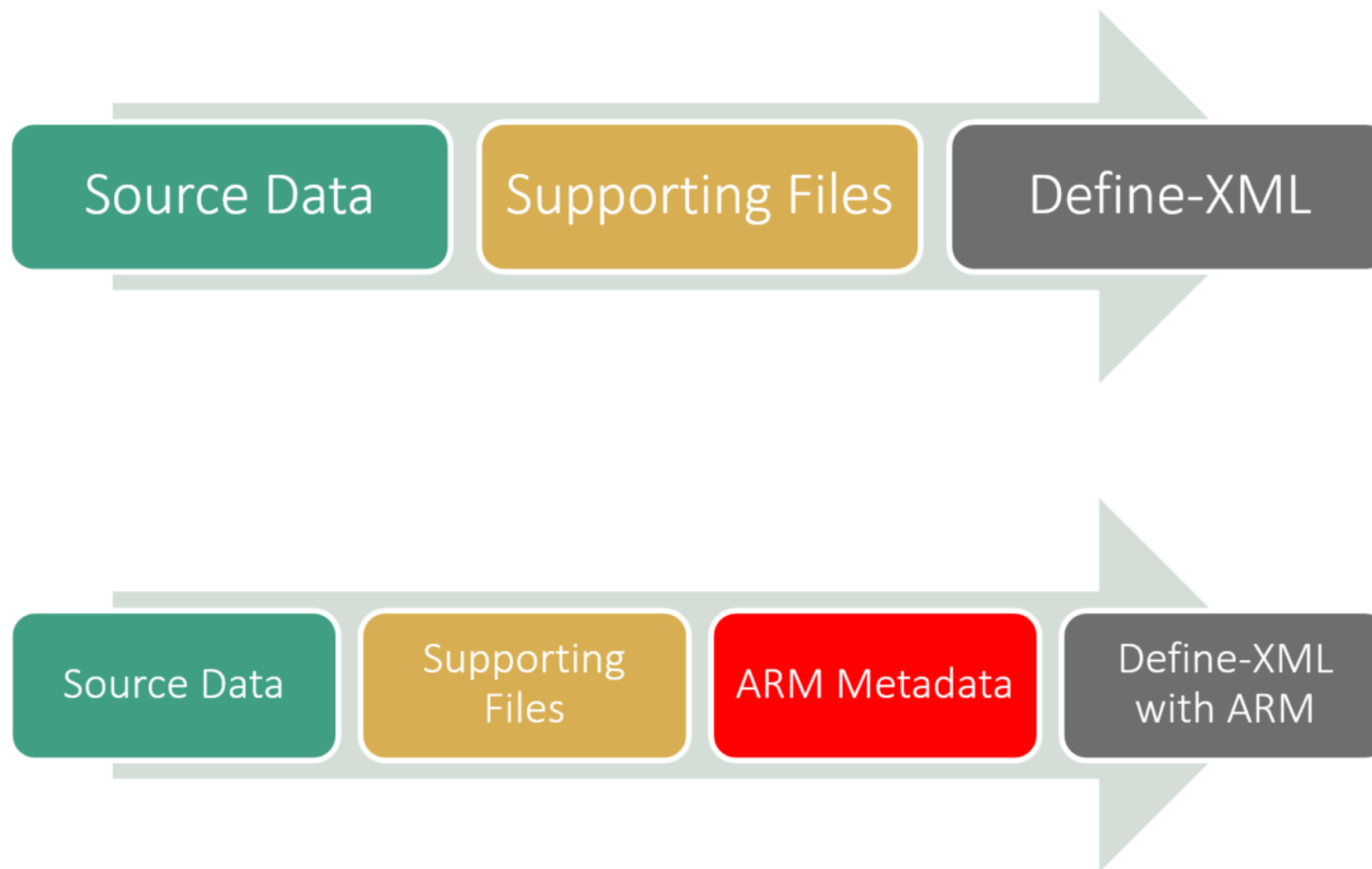
- Analysis Display Metadata: 1, 2
- Analysis Result Metadata: 3, 5, 6, 7
- Analysis Parameters: 4
- Analysis Datasets: 8, 9
- Documentation: 10, 11
- Programming Statements: 12

Key Elements and Attributes – Data

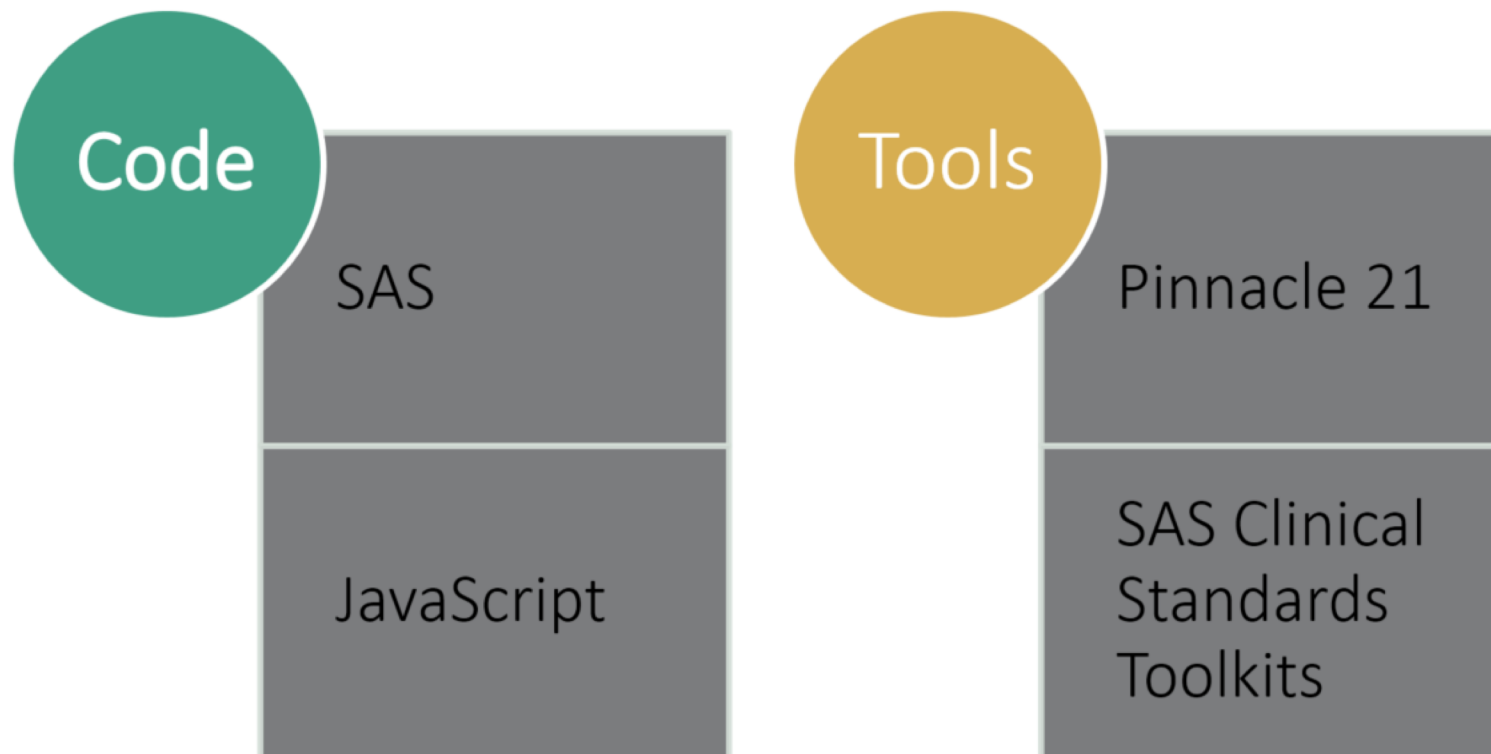
- Analysis Display Metadata: `arm:ResultDisplay`
- Analysis Result Metadata: `arm:AnalysisResult`
- Analysis Parameters: `ParameterOID`
- Analysis Datasets: `arm:AnalysisDatasets`
- Documentation: `arm:Documentation`
- Programming Statements: `arm:ProgrammingCode`

How to Implement

Generation Process



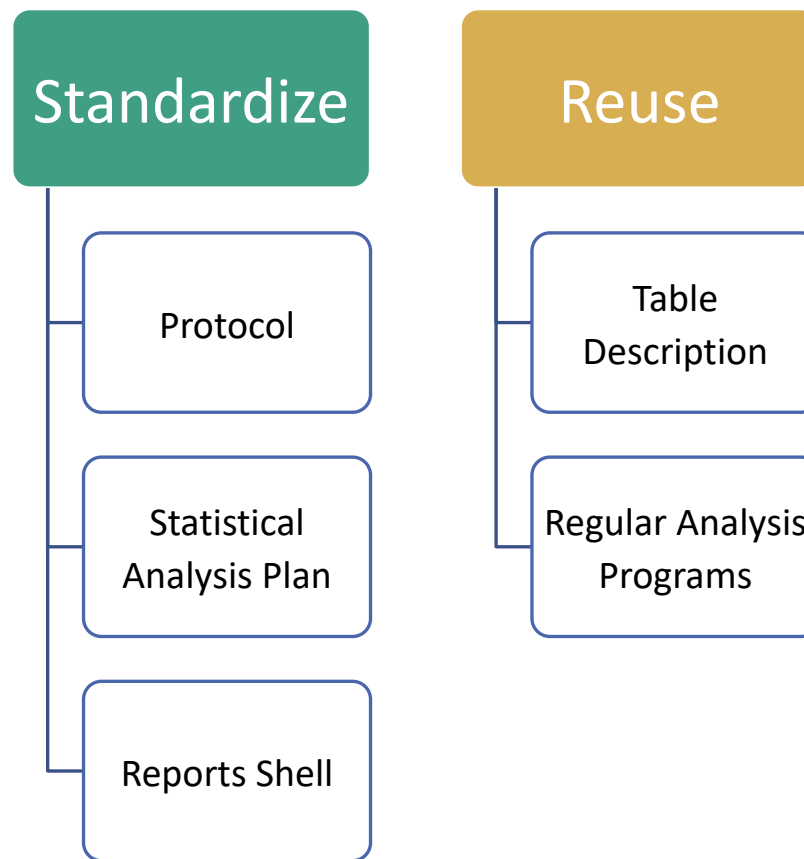
How to Create



ARM Metadata

DisplayNo	ResultID	Attributes	Value
Table 14-3.01	1	DisplayName	Primary Endpoint Analysis: ADAS-Cog - Summary at Week 24 - LOCF (Efficacy Population)
Table 14-3.01	1	ResultName	Dose response analysis for ADAS-Cog changes from baseline
Table 14-3.01	1	ParameterCode	ACTOT
Table 14-3.01	1	Parameter	Adas-Cog(11) Subscore
Table 14-3.01	1	Variable	CHG
Table 14-3.01	1	VariableLabel	Change from Baseline
Table 14-3.01	1	Reason	SPECIFIED IN SAP
Table 14-3.01	1	Purpose	PRIMARY OUTCOME MEASURE
Table 14-3.01	1	Data	ADQSADAS
Table 14-3.01	1	DataCriteria	PARAMCD^"ACTOT" AVISIT^"Week 24" EFFFLL^"Y" ANL01FL^"Y"
Table 14-3.01	1	Documentation	Linear model analysis of CHG for dose response; using randomized dose (0 for placebo; 54 for low dose; 81 for high dose) and site group in model. Used PROC GLM in SAS to produce p-value (from Type III SS for treatment dose).
Table 14-3.01	1	ExternalReference	dummy-csr.pdf(section 10.1.1)
Table 14-3.01	1	ExternalReferenceName	SAP Section 10.1.1
Table 14-3.01	1	ReferenceLocation	Page 2
Table 14-3.01	1	FileLocation	../dummy-csr/dummy-csr.pdf
Table 14-3.01	1	SASVersion	SAS version 9.2
Table 14-3.01	1	Code	proc glm data = ADQSADAS; where EFFFLL='Y' and ANL01FL='Y' and AVISIT='Week 24' and PARAMCD="ACTOT"; class SITEGR1; model CHG = TRTPN SITEGR1; run;

Minimize Extra Work



Challenge and Future

Common Issues

- Both XML and PDF are required?
- Encoding Issues: UTF-8
- Legacy vs. CDISC
- Folder Structure: eCTD M4/M5
- Balance Multi-lingual Characters

Japanese Version – Partial

表14.3.1.1-1

Display	表14.3.1.1-1 有害事象及び副作用の発現頻度及び死亡状況
Analysis Result	有害事象発現者数
Analysis Parameter (s)	
Analysis Variable(s)	TRTEMFL (Treatment Emergent Analysis Flag)
Analysis Reason	SPECIFIED IN SAP
Analysis Purpose	EXPLORATORY OUTCOME MEASURE
Data References (incl. Selection Criteria)	ADAE [SAFFL = "Y" and TRTEMFL = "Y"] ADSL [SAFFL = "Y"] For analysis outputs in Japanese, a Japanese mirror dataset to ADAE is used. Get denominators for percentages from ADSL and counts and numerators from ADAE(Japanese).
Documentation	Statistical Analysis Plan
Programming Statements	[SAS version 9.3 or later] <pre>proc sort data=ADAE nodupkey; by USUBJID; run; proc freq data=ADAE; tables <Variables>; run;</pre>

Japanese Version – Full

表示	Table 14-3.01 主要エンドポイント分析：ADAS-Cog - 24週目の要約 - LOCF (有効性集団)
分析結果	ADASのための用量反応分析 - 基準値からのCogの変動
分析パラメーター	PARAMCD = "ACTOT" (Adas-Cog(11)サブスコア)
分析変数	CHG (基準値からの変動)
分析理由	SAPに明示
分析目的	主要評価項目測定
データ参照 (選択基準を含む)	ADQSADAS [PARAMCD = "ACTOT" and AVISIT = "Week 24" and EFFFL = "Y" and ANL01FL = "Y"]
ドキュメンテーション	用量反応のためのCHGの線形モデル分析；二つ共変量ランダム化された用量グループ (0 プラセボ； 54 低用量；81 高用量) 及び施設グループをモデルに取り込む。P 値得るためSASのproc GLMを使用 (投与量に対して、ここではType IIIの平方和を用いる) SAP Section 10.1.1
プログラミング ステートメント	[SAS version 9.2] <pre>proc glm data = ADQSADAS; where EFFFL='Y' and ANL01FL='Y' and AVISIT='Week 24' and PARAMCD="ACTOT"; class SITEGR1; model CHG = TRTPN SITEGR1; run;</pre>

Thanks for your attention!

Further Information



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 PhUSE China
 phuse.eu
 [@PhUSETwitta](https://twitter.com/PhUSETwitta)
 [/PhUSE](https://www.facebook.com/PhUSE)
 phusewiki.org

