NDA Submissions with eCTD
eCDT标准的新药数据申报

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James Wu
吴坚

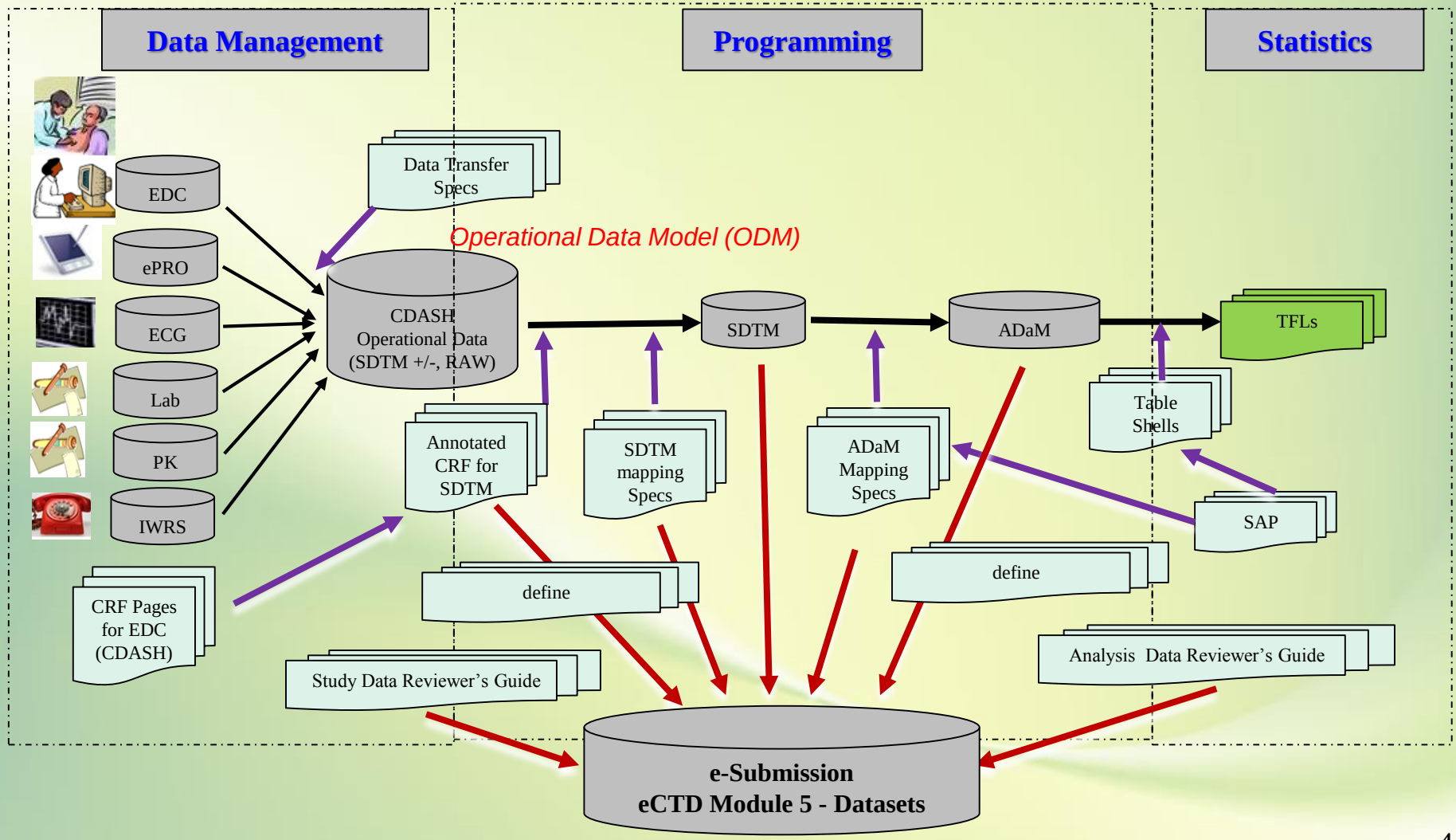
- 20年以上在默克和赛诺菲等公司制药行业的统计编程,FDA新药申报经验
- 6年以上 CRO 团队建设，资源管理，项目管理和业务发展方面的经验
- 10年以上教龄的讲师，美国费城大学SAS偏程培训班
- PharmaSUG 执行专业委员会成员，2010美国会议主席，2013中国会议主席
- 加拿大麦克马斯特大学工程博士，中国科学院理学硕士

- 20+ years of statistical programming experience in pharmaceutical industry at Merck, Sanofi, MTDA
- 6+ years of CRO experiences in team building, resources management, project management and business development
- 10+ years of instructor, Philadelphia University SAS Programming Certification Program
- PharmaSUG EC member, 2010 US Conference Chair, 2013 PharmaSUG China Conference Chair
- Ph.D., Engineering, McMaster University, Canada; M.S., Academy of Science of China

Agenda

- Clinical Data Analysis Flow and Submission
- e-Submission Guidance
- eCTD
- eCTD Module 5 Structure
- CDISC – SDTM and ADaM
- SDTM/ADaM Development
- OpenCDISC validation and reporting
- Data Reviewer's Guides
- Define.xml and define.pdf
- Submission Plan
- Questions and Discussions

Data Analysis Flow
CDASH – SDTM – ADaM – TFL- eSub



e-Submissions Guidance

ICH

ICH eCTD Specification V3.2.2, 2008

FDA

FDA e-submission Guidance
1999 Guidance, 2012 Draft

Study Data Specification

CDER Common Data Standard Issues Document

CDISC

CDASH

SDTM

ADaM

Controlled Terminology

中国国家药审中心

《eCTD技术规范（征求意见稿）》

《eCTD验证标准（征求意见稿）》

eCTD Submission Modules

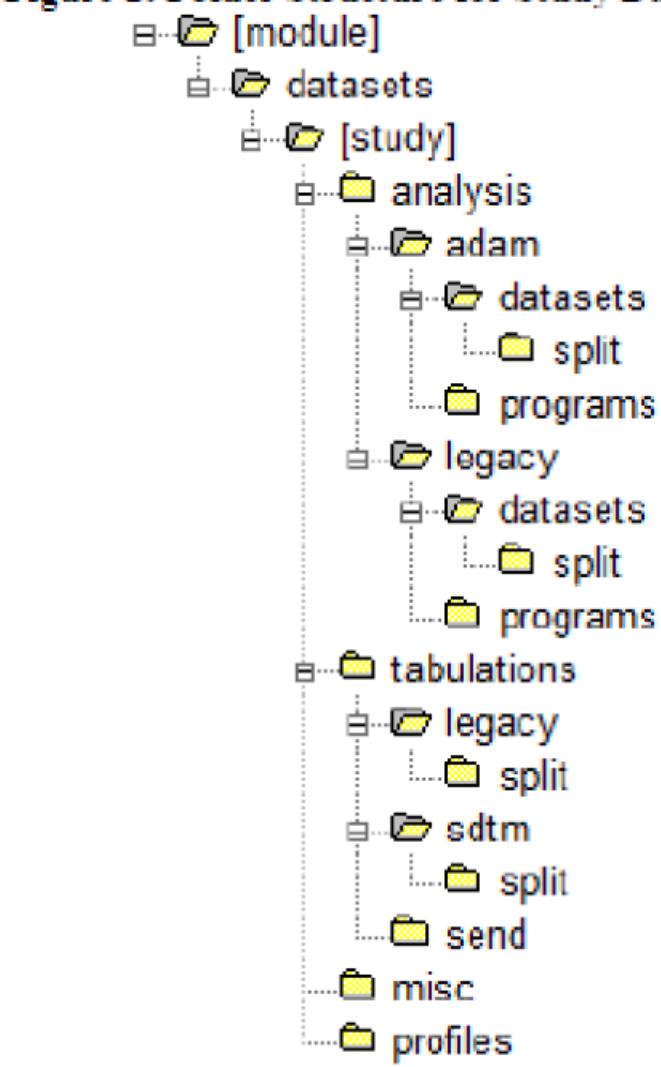
Electronic Common Technical Document (eCTD):

Five modules in the eCTD

- Module 1 - Administrative information and prescribing information
- Module 2 - CTD summary documents
- Module 3 - Information on quality
- Module 4 - Nonclinical study reports
- Module 5 – Clinical study reports
    - Tabular listing of all clinical studies
    - Study reports
    - Case report forms
    - Datasets (SDTM, ADS, SAS programs, Define, Stat review Aids)

eCTD Module 5 Structure

Figure 1: Folder Structure for Study Datasets



Submission File Structures

Folder Name	Folder Level	Description/Contents
[module]	1	Refers to the eCTD module in which study data is being submitted. Name this folder m4 for nonclinical data and m5 for clinical data. Do not place files at this level.
datasets	2	Resides within the module folder as the top-level folder for study data (nonclinical or clinical) being submitted for the specified module (m4 or m5). Do not place files at this level.
[study]	3	Name this folder with the study identifier or analysis type performed (e.g., study123, iss, ise). Do not place files at this level.
analysis	4	Contains folders for analysis datasets and software programs; arrange in designated level 6 subfolders. Do not place files at this level.
adam	5	Contains subfolders for ADaM datasets and corresponding software programs. Do not place files at this level.
datasets	6	Place ADaM datasets in this subfolder.
split	7	Place any split ADaM datasets in this subfolder.
programs	6	Place software programs for ADaM datasets, tables and figures in this subfolder.
legacy	5	Contains legacy formatted analysis datasets and corresponding software programs. Do not place files at this level.
datasets	6	Place legacy analysis datasets in this subfolder.
split	7	Place split legacy analysis datasets in this subfolder.
programs	6	Place software programs for legacy analysis datasets, tables and figures in this subfolder.
misc	4	Place miscellaneous datasets that don't qualify as analysis, profile, or tabulation datasets in this subfolder. This subfolder was formerly named "listings".
profiles	4	Place patient profiles in this subfolder.
tabulations	4	Contains subfolders for tabulation datasets. Do not place files at this level.
legacy	5	Place legacy (non-standardized) tabulation datasets in this folder.
split	6	Place any split legacy tabulations datasets in this subfolder.
sdtm	5	Place SDTM tabulation datasets in this subfolder. Should only be used in m5 for clinical data.
split	6	Place any split SDTM files in this subfolder.
send	5	Place SEND tabulation datasets in this subfolder. Should only be used in m4 for animal data.

eCTD Module 5
(General Rule for Folders)

- No empty folders
- CDISC compliant data to “sdtm” and “adam” sub-folder
- Non CDISC-compliant datasets to “legacy” sub-folder
- Possible to have both “legacy” and “sdtm”/“adam”
- External files, PK data, dictionary coding change summary to “legacy” sub-folder
- ISS/ISE can be treated as individual study

Files for eCTD Module 5 - Dataset

- .xpt for SAS datasets
- .xml and .pdf for define files
- .pdf for reviewer's guides, aCRF and other documents
- .txt for SAS programs
- .txt for EXCEL sheet files

eCTD File Naming Conventions

- No cap case (low case)
  t-aesumm.sas (not T-AESUMM.sas)
- No underscore (dash is OK)
  t-aesumm.sas (not t_aesumm.sas)
- Don’t use file name too long

国家药品监督管理局药品审评中心
CENTER FOR DRUG EVALUATION, NMPA

当前位置：新闻中心>>工作动态>>通知公告>>新闻正文

关于公开征求《eCTD技术规范》和《eCTD验证标准》意见的通知

发布日期：20190301

为贯彻实施中共中央办公厅、国务院办公厅《关于深化审评审批制度改革鼓励药品医疗器械创新的意见》（厅字〔2017〕42号）的有关要求，加快药品审评审批信息化建设，推进药品按照电子通用技术文档（electronic Common Technical Document）要求进行申报和受理，我中心组织起草了《eCTD技术规范（征求意见稿）》和《eCTD验证标准（征求意见稿）》，现向社会公开征求意见。

为了对《eCTD技术规范（征求意见稿）》和《eCTD验证标准（征求意见稿）》进行完整的评估和反馈，本次征求意见同时使用了我中心正在开展的一些过程性文件，具体文件列表详见附表。这些过程性文件仅作为本次征求意见的技术支撑文件，后续我中心将随着工作推进，根据CTD模块一的正式发布和研究讨论进一步修改完善，发布最终正式稿，敬请关注。

请将建议和修改意见按照《反馈意见模板》要求于2019年3月31日前通过电子邮件反馈至我中心。

联系人：李海玲、殷翠香

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国家药品监督管理局药品审评中心

2019年3月1日

介绍 表：文件列表

2019年3月1日国家药审中心发布《eCTD技术规范（征求意见稿）》和《eCTD验证标准（征求意见稿）》，这是我国eCTD申报管理体系建设的重要里程碑，标志着我国实施eCTD申报进入倒计时阶段；实施eCTD申报管理是国家药监局加入ICH后再次与国际技术和标准接轨，对我国进一步建立完善审评审批体系具有非常积极的意义。

CDISC

- Clinical Data Interchange Standard Consortium (CDISC) is a global, open, multidisciplinary, non-profit organization that has established standards to support the acquisition, exchange, submission and archive of clinical research data and metadata
- CDASH: Clinical Data Acquisition Standards Harmonization
- SDTM: Standard Data Tabulation Model
- ADaM: Analysis Data Model
- SDS: Submission Data Standards
- DDT: Data Definition Tables

Standard Data Tabulation Model (SDTM)

- The SDTM provides a general framework for describing the organization of information collected during human and animal studies.
- The model is built around the concept of observations, which consist of discrete pieces of information collected during a study. Observations normally correspond to rows in a dataset.
- Each observation can be described by a series of named variables. Each variable, which normally corresponds to a column in a dataset, can be classified according to its Role.
- Observations are reported in a series of domains, usually corresponding to data that were collected together. A domain is defined as a collection of observations with a topic-specific commonality about a subject.
- SDTM allows reviewers to develop a repository of all submitted studies and create stand alone tools to access, manipulate and view the study data.

SDTM Domains

Datasets containing observations are classified into three classes:

- Intervention: This class captures information regarding investigational treatment, therapeutic treatment and procedures. Ex: CM, EX, SU.
- Events: This class captures occurrences and incidents occurred during study trial. Ex: AE, MH, DS, DV.
- Findings: This class captures observation resulting from planned evaluation. Ex: IE, LB, QS, PE, PC, PP, SC, VS.

Special Purpose Domain:

- Include subject level data and do not conform to any of the three classes of observation datasets.
- Examples are:
  - Demographics (DM)
  - Comments (CO)
  - Subject Visits (SV)
  - Subject Elements (SE)

Controlled Terminology

- Controlled Terminology is defined as the terminology that controls the value of any variable.
- In almost all of SDTM domains, there are some variables which always have controlled terminology associated with them. If any variable is defined in the SDTMIG with the Controlled Terms or Formats as ACN, NY, STERF, NCOMPLT etc., then all the values of this variable must be populated using the Controlled terminology.

ADaM

- ADSL – Subject Level Analysis Datasets: treatments, population flags, demographic and disposition information, and other 1- record per subject variables to support stat analysis

- BDS – Basic Data Structure.
  - Used for tests, results, finding data such as Lab, vital, ECG, PK, TTE etc.
  - Vertical structure
  - One record per subject per analysis parameter per time point
  - Derived results are created as records similar to raw records
  - Easy for analysis table (select different parameters, and different time points or derived tests

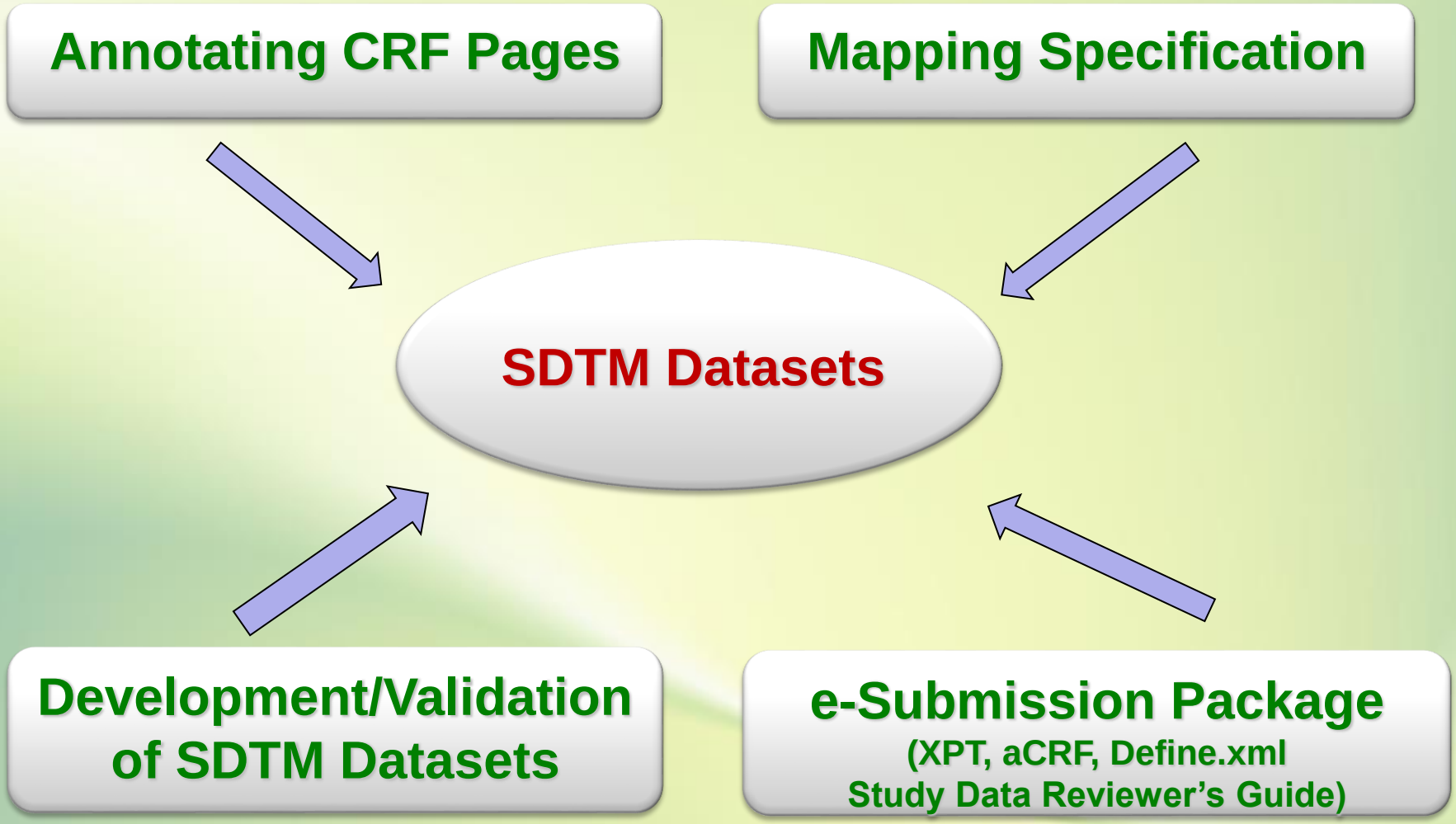
- OCCDS (Occurrence Data Structure) – ADAE, ADCM

- ADaM OTHERS - Other Datasets

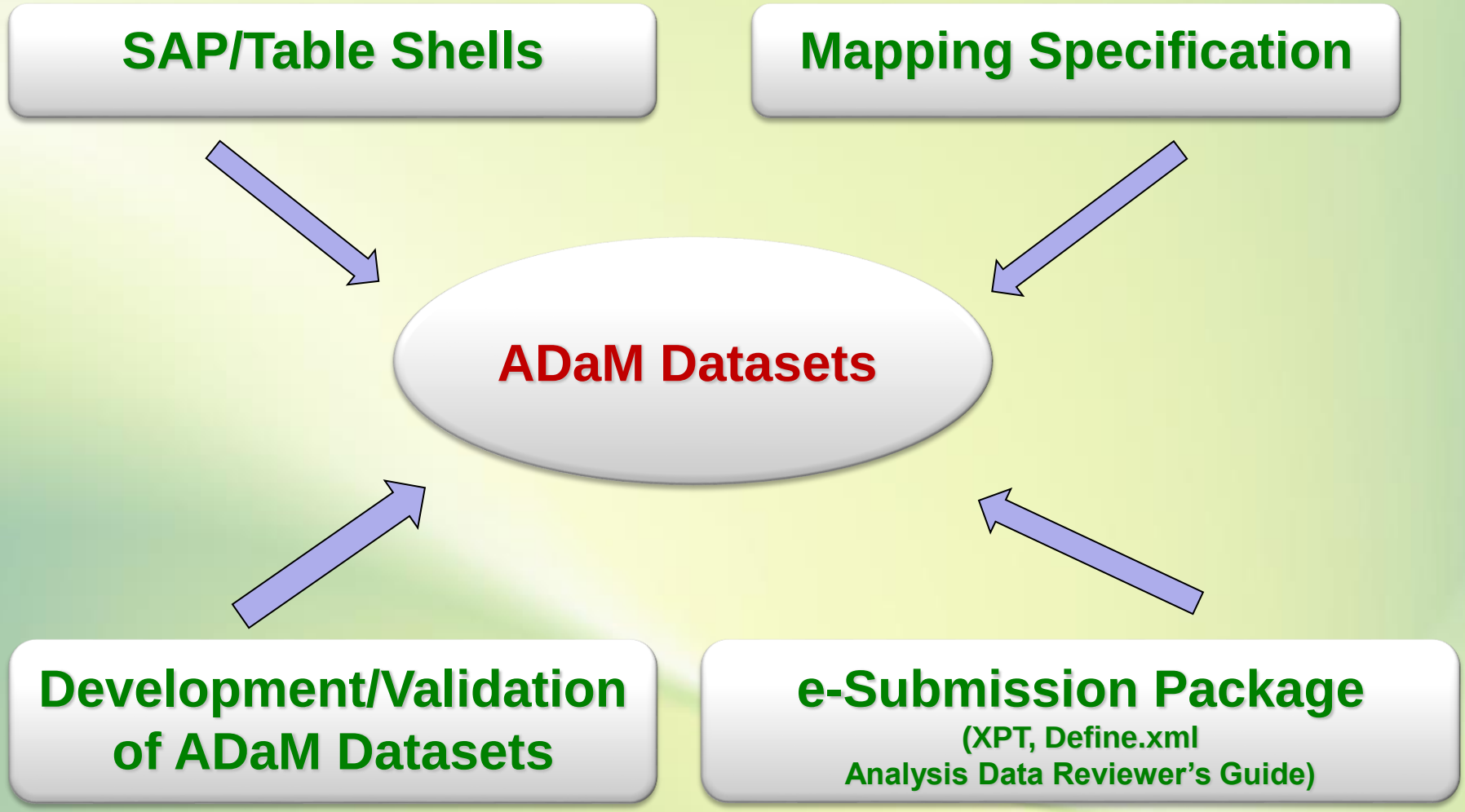
Analysis-Ready ADaM Datasets

- Datasets should be “analysis-ready,” meaning it should contain all of the variables needed for the specific analysis, so that the analysis can be replicated by performing the actual statistical test without first having to manipulate data.
  - baseline values
  - stratification or grouping variables,
  - selection flags (e.g., population flag),
  - predictor variables (also known as explanatory variables, independent variables, or covariates),
  - response variables (also known as dependent variables),
  - supportive variables for complex predictors and/or responses,
  - supportive variables to facilitate traceability.

SDTM Mapping Project Overview



ADaM Mapping Project Overview



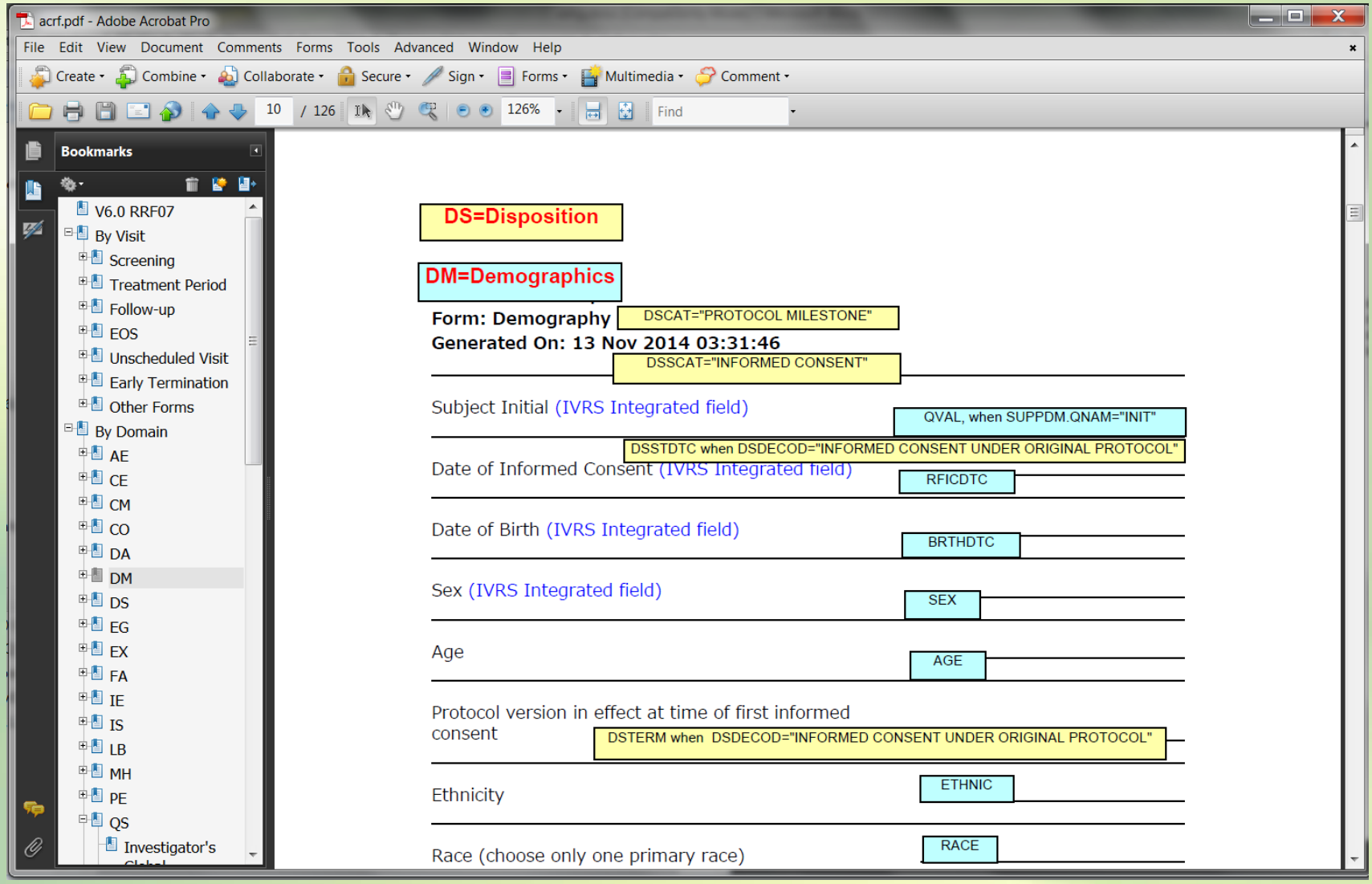
SDTM / ADaM
OpenCIDSC Validation Reports

- OpenCDISC Reports
- Common Errors
- Warning Messages
- Compliance Reports

Dataset Summary								
Dataset	Description	Class	Source	Records	Rejects	Errors	Warnings	Notices
DM	Demographics	PURPOSE		66	0	1	4	57
DS	Disposition	EVENTS		264	0	0	0	0
DV	Protocol Deviations	EVENTS		361	0	0	32	0
EG	ECG Test Results	FINDINGS		1813	0	0	2274	0
EX	Exposure	S		853	0	130	726	0
FA	Findings About Events or Interventions	FINDINGS		7036	0	0	13402	0
GLOBAL	Global Metadata			0	0	0	1	0
IE	Inclusion/ Exclusion Criteria Not Met	FINDINGS		10	0	0	1	0
IS	Immunogenicity Specimen Assessment	FINDINGS		432	0	0	78	0
LB	Laboratory Test Results	FINDINGS		68554	0	143	109591	0
MH	Medical History	EVENTS		1051	0	0	13	1
PC	Pharmacokinetic Concentrations	FINDINGS		900	0	0	370	0
PE	Physical Examination	FINDINGS		2635	0	0	1	0
QS	Questionaire	FINDINGS		105795	0	0	106276	0
SE	Subject Elements	PURPOSE		169	0	0	2	2
SUPPAE	Supplemental Qualifiers for AE	RELATIONSHIP		1311	0	0	0	0
SUPPCM	Supplemental Qualifiers for CM	RELATIONSHIP		7999	0	0	0	0
SUPPDA	Supplemental Qualifier for DA	RELATIONSHIP		324	0	0	0	0
SUPPDM	Supplemental Qualifiers for DM	RELATIONSHIP		781	0	0	0	0
SUPPDS	Supplemental Qualifier for DS	RELATIONSHIP		84	0	0	0	0
SUPPDV	Supplemental Qualifiers for DV	RELATIONSHIP		361	0	0	0	0
SUPPEG	Supplemental Qualifier for EG	RELATIONSHIP		484	0	0	73	0
SUPPEX	Supplemental Qualifiers for EX	RELATIONSHIP		4600	0	0	0	0
SUPPFA	Supplemental Qualifier for FA	RELATIONSHIP		8618	0	0	0	0
SUPPIS	Supplemental Qualifiers for IS	RELATIONSHIP		428	0	0	0	0
SUPPLB	Supplemental Qualifiers for LB	RELATIONSHIP		261776	0	0	0	0
SUPPMH	Supplemental Qualifiers for MH	RELATIONSHIP		1881	0	0	0	0
SUPPPE	Supplemental Qualifiers for PE	RELATIONSHIP		266	0	0	0	0
SUPPQS	Supplemental Qualifier for QS	RELATIONSHIP		27123	0	0	0	0
SUPPSV	Supplemental Qualifiers for SV	RELATIONSHIP		1444	0	0	27	0
SUPPXP	Supplemental Qualifiers for XP	RELATIONSHIP		96	0	0	96	0
SV	Subject Visit	PURPOSE		1244	0	0	1	0
TA	Trial Arms	TRIAL DESIGN		6	0	0	0	0
TE	Trial Elements	TRIAL DESIGN		4	0	0	0	0
TI	Trial Inclusion/ Exclusion Criteria	TRIAL DESIGN		42	0	0	0	0
TS	Trial Summary	TRIAL DESIGN		63	0	2	1	10
TV	Trial Visits	TRIAL DESIGN		27	0	0	0	0
VS	Vital Signs	FINDINGS		7418	0	0	2437	0
XE	Backgroud Treatment	S		8855	0	0	8855	0
XP	Clinical Procedure	EVENTS		16	0	0	16	0
Total				527687	0	276	244329	74

Dataset Summary								
Dataset	Description	Class	Source	Records	Rejects	Errors	Warning	Notices
ADAE	Events	ADAM OTHER		161	0	0	0	2
ADCM	Analysis Dataset for Conmeds	BASIC DATA STRUCTURE		953	0	3	0	1
ADDA	Analysis Dataset for Drug Accountability			591	0	0	1	0
ADDS	Analysis Dataset for Disposition			264	0	0	1	0
ADDV	Analysis Dataset for Protocol Deviations			361	0	0	1	0
ADEG	Analysis Dataset for ECG	BASIC DATA STRUCTURE		1926	0	0	106	1
ADEX	Analysis Dataset for Exposure	BASIC DATA STRUCTURE		1263	0	0	0	1
ADFA	About			21	0	0	1	0
ADISADA	Analysis Dataset for ADA	BASIC DATA STRUCTURE		448	0	0	1	1
ADLB	Analysis Dataset for Lab	BASIC DATA STRUCTURE		53787	0	0	782	1
ADLBBM	Analysis Dataset for Biomarker	BASIC DATA STRUCTURE		34842	0	1223	4894	1
ADMH	Analysis Dataset for Medical History			1051	0	0	1	0
ADPC	Analysis Dataset for Pk Concentrations	BASIC DATA STRUCTURE		900	0	0	1	1
ADPE	Analysis Dataset for Physical Exam	BASIC DATA STRUCTURE		2635	0	0	1	1
ADQSEASI	Analysis Dataset for QS-EASI	BASIC DATA STRUCTURE		51304	0	0	22309	1
ADQSIGA	Analysis Dataset for QS-IGA	BASIC DATA STRUCTURE		6690	0	0	3017	1
ADQSNRS	Analysis Dataset for QS - NRS	BASIC DATA STRUCTURE		40805	0	0	7074	1
ADQSPGA	Analysis Dataset for QS-PGA	BASIC DATA STRUCTURE		1112	0	0	441	1
ADQSQOL	Analysis Dataset for QS-QOL	BASIC DATA STRUCTURE		73762	0	0	28248	1
ADQSSCOR	Analysis Dataset for QS-SCOR	BASIC DATA STRUCTURE		34146	0	0	14889	1
ADSL	Subject Level Analysis Dataset	LEVEL ANALYSIS		66	0	0	3	8
ADTTE	Data for the Time to Event Analyses	BASIC DATA STRUCTURE		162	0	0	0	1
ADVS	Analysis Dataset for Vital Signs	BASIC DATA STRUCTURE		7797	0	0	380	1
ADXE	Analysis Dataset for Backgroud Treatment	BASIC DATA STRUCTURE		8929	0	0	0	1
ADXP	Analysis Dataset for Procedures	BASIC DATA STRUCTURE		16	0	3	0	1
Define.xml	Define.xml			0	0	28	0	0
GLOBAL	Global Metadata			0	0	0	0	0
Total				323992	0	1257	82151	28

Annotated CRF Pages



SDTM define - I

SDTM-IG 3.1.2

- Annotated Case Report Form
- Reviewers Guide
- Complex Algorithms
- ▶ Tabulation Datasets
- ▶ Value Level Metadata
- ▶ Controlled Terminology
- ▶ Computational Algorithms
- ▶ Comments

Tabulation Datasets for Study CDISC01 (SDTM-IG 3.1.2)

Dataset	Description	Class	Structure	Purpose	Keys	Location	Documentation
TA	Trial Arms	TRIAL DESIGN	One record per planned Element per Arm	Tabulation	STUDYID, ARMCD, TAETORD	ta.xpt	
TE	Trial Elements	TRIAL DESIGN	One record per planned Element	Tabulation	STUDYID, ETCD	te.xpt	
TI	Trial Inclusion/Exclusion Criteria	TRIAL DESIGN	One record per I/E criterion	Tabulation	STUDYID, IETESTCD	ti.xpt	
TS	Trial Summary	TRIAL DESIGN	One record per trial summary parameter value	Tabulation	STUDYID, TSPARMCD, TSSEQ	ts.xpt	
TV	Trial Visits	TRIAL DESIGN	One record per planned Visit per Arm	Tabulation	STUDYID, VISITNUM, ARMCD	tv.xpt	
DM	Demographics	SPECIAL PURPOSE	One record per subject	Tabulation	STUDYID, USUBJID	dm.xpt	See Reviewer's Guide, Section 2.1 Demographics Reviewers Guide
SE	Subject Elements	SPECIAL PURPOSE	One record per actual Element per subject	Tabulation	STUDYID, USUBJID, SESTDTC, SEENDTC, TAETORD, ETCD	se.xpt	

SDTM define - II

Value Level Metadata

Value Level Metadata - DA [DAORRES]

Variable	Where	Type	Length / Display Format	Controlled Terms or Format	Origin	Derivation/Comment
DAORRES	DATESTCD EQ DISPAMT (Dispensed Amount)	integer	2		CRF Page 19	
DAORRES	DATESTCD EQ RETAMT (Returned Amount)	integer	2		CRF Page 19	

Value Level Metadata - EG [EGORRES]

Variable	Where	Type	Length / Display Format	Controlled Terms or Format	Origin	Derivation/Comment
EGORRES	EGTESTCD EQ INTP (Interpretation)	text	8	["ABNORMAL", "NORMAL"] <Interpretation: Original Results>	CRF Page 12	

Controlled Terms

Action Taken with Study Treatment [CL.ACN, *C66767*]

Permitted Value (Code)
DOSE NOT CHANGED [*C49504*]
DOSE REDUCED [*C49505*]
DRUG INTERRUPTED [*C49501*]
DRUG WITHDRAWN [*C49502*]

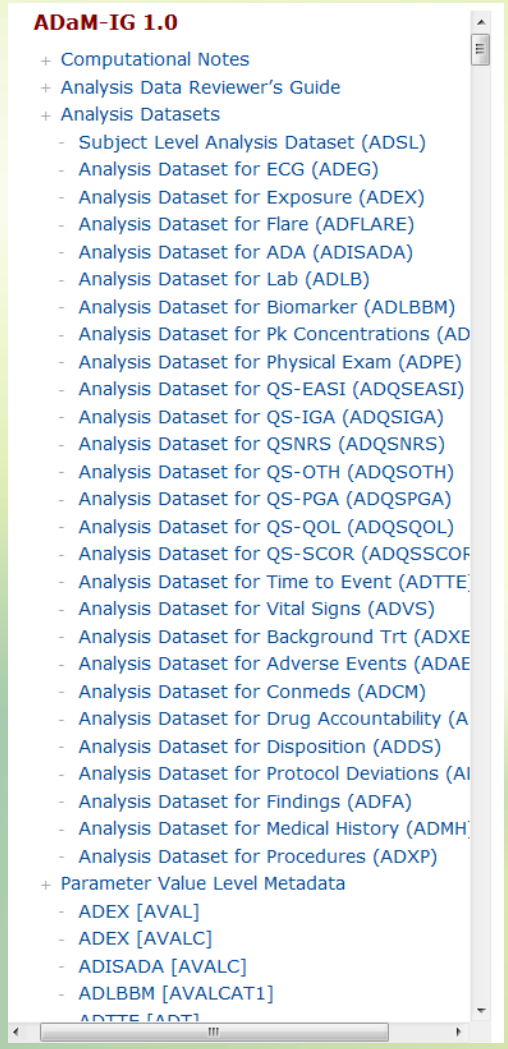
Domain Abbreviation (AE) [CL.AE.DOMAIN, *C66734*]

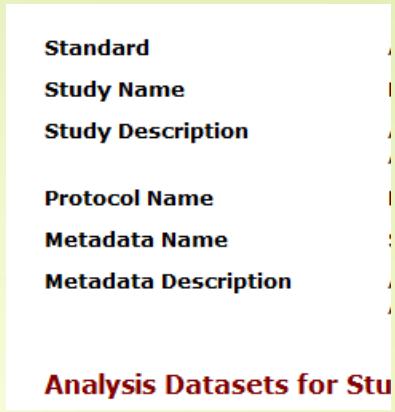
Permitted Value (Code)	Display Value (Decode)
AE [*C49562*]	Adverse Events

Computational Algorithms

Method	Type	Description
Algorithm to derive AEENDY	Computation	AEENDY = AEENDTC -RFSTDTC+1 if AEENDTC is on or afte
Algorithm to derive AESTDY	Computation	AESTDY = AESTDTC - RFSTDTC+1 if AESTDTC is on or afte
Algorithm to derive the AETRTEM flag	Computation	AETRTEM = "Y" if Adverse Event was not present prior to
Algorithm to derive AGE	Computation	Age at Screening Date (Screening Date - Birth date). For Complex Algorithms (complexalgorithms.pdf)
Algorithm to derive CLSIG	Computation	Only created if value qualifies as potentially clinically sign
Algorithm to derive CMENDY	Computation	CMENDY = CMENDTC - RFSTDTC +1 if CMENDTC is on or a

ADaM define - I





Dataset	Description	Class	Structure	Purpose	Keys	Location	Documentation
ADSL	Subject Level Analysis Dataset	SUBJECT LEVEL ANALYSIS DATASET	One record per subject	Analysis	STUDYID, USUBJID	adsl.xpt	
ADEG	Analysis Dataset for ECG	BASIC DATA STRUCTURE	One or more records per subject per analysis parameter per analysis timepoint	Analysis	STUDYID, USUBJID, PARAM, PARAMCD	adeg.xpt	
ADEX	Analysis Dataset for Exposure	BASIC DATA STRUCTURE	One or more records per subject per analysis parameter per analysis timepoint	Analysis	STUDYID, USUBJID, PARAM, PARAMCD	adex.xpt	
ADFLARE	Analysis Dataset for Flare	BASIC DATA STRUCTURE	One or more records per subject per analysis parameter per analysis timepoint	Analysis	STUDYID, USUBJID, PARAM, PARAMCD	adflare.xpt	
ADISADA	Analysis Dataset for ADA	BASIC DATA STRUCTURE	One or more records per subject per analysis parameter per analysis timepoint	Analysis	STUDYID, USUBJID, PARAM, PARAMCD	adisada.xpt	
ADLB	Analysis Dataset for Lab	BASIC DATA STRUCTURE	One or more records per subject per analysis parameter per analysis timepoint	Analysis	STUDYID, USUBJID, PARAM, PARAMCD	adlb.xpt	
ADLBBM	Analysis Dataset for Biomarker	BASIC DATA STRUCTURE	One or more records per subject per analysis parameter per analysis timepoint	Analysis	STUDYID, USUBJID, PARAM, PARAMCD	adlbbm.xpt	
ADPC	Analysis Dataset for Pk Concentrations	BASIC DATA STRUCTURE	One or more records per subject per analysis parameter per analysis timepoint	Analysis	STUDYID, USUBJID, PARAM, PARAMCD	adpc.xpt	
ADPE	Analysis Dataset for Physical Exam	BASIC DATA STRUCTURE	One or more records per subject per analysis parameter per analysis timepoint	Analysis	STUDYID, USUBJID, PARAM, PARAMCD	adpe.xpt	
ADQSEASI	Analysis Dataset for QS-EASI	BASIC DATA STRUCTURE	One or more records per subject per analysis parameter per analysis timepoint	Analysis	STUDYID, USUBJID, PARAM, PARAMCD	adqseasi.xpt	
ADQSIGA	Analysis Dataset for QS-IGA	BASIC DATA STRUCTURE	One or more records per subject per analysis parameter per analysis timepoint	Analysis	STUDYID, USUBJID, PARAM, PARAMCD	adqsiga.xpt	

ADaM Define - II

Individual Dataset Description

Subject Level Analysis Dataset (ADSL) [Location: adsl.xpt]

Variable	Label	Key	Type	Length / Display Format	Controlled Terms or Format	Source/Derivation/Comment
STUDYID	Study Identifier	1	text	12	["R668-AD-1415"] <Study Identifier>	Predecessor: DM.STUDYID
USUBJID	Unique Subject Identifier	2	text	22		Predecessor: DM.USUBJID
SUBJID	Subject Identifier for the Study		text	9		Predecessor: DM.SUBJID
SITEID	Study Site Identifier		text	6		Predecessor: DM.SITEID
COUNTRY	Country		text	3	Country	Predecessor: DM.COUNTRY
COUNTRYF	Country Full Name		text	14	Country Full Name	Assigned: Assign country full name according to ISO3166
AGE	Age		integer	8		Predecessor: DM.AGE
AGEU	Age Units		text	5	["YEARS"] <Age Units>	Predecessor: DM.AGEU
AGEGR	Age Group		text	8	[">=18-<40", ">=40-<65", ">=65"] <Age Group>	Derived: If 18<=AGE<40 then AGEGR=">=18-<40"; if 40<=AGE<65 then AGEGR=">=40 AGEGR=">=65"; if AGE is missing then AGEGR='Unsure'.
AGEGRN	Age Group (N)		integer	8		Assigned: Assigned based on AGE as follows: >=18-<40'=1; '>=40-<65'=2; '>=65'=3; 'U
SEX	Sex		text	1	["F", "M"] <Sex>	Predecessor: DM.SEX
SEXN	Sex (N)		integer	8		Assigned: if sex='M' then sexn=1; else if sex='F' then sexn=2;
RACE	Race		text	41	Race	Predecessor: DM.RACE
RACEN	Race (N)		integer	8		Assigned: Assigned based on RACE as follows: 'WHITE'=1; 'BLACK OR AFRICAN AMERICA 'AMERICAN INDIAN OR ALASKA NATIVE'=4; 'NATIVE HAWAIIAN OR OTHER PACI REPORTED', other=996
RACEOTH	Race, Other		text	27	Race, Other	Predecessor: DM.RACEOTH
RACEGR1	Pooled Race Group 1		text	20	Pooled Race Group 1	Derived: If RACE='WHITE' then RACEGR1='White', else if RACE='BLACK OR AFRI

Parameter Value Lists

Parameter Value Lists

Parameter Value List - ADEX [AVAL]

Variable	Where	Type	Length / Display Format	Controlled Terms or Format	Source/Derivation/Comment
AVAL	PARAMCD = "ESCOMCAT" (Compliance Category)	float	5		Derived: For "<80%" set to 1; For ">=80%" set to 2.
AVAL	PARAMCD = "ESCOMP" (Compliance (%))	float	5		Derived: Set to (ESTAKN/ESPLAN)*100 and keep 2 decimal points
AVAL	PARAMCD = "ESEXPOYR" (Patient Years of Exposure)	float	5		Derived: Set to ESDURN/365.25 and keep 2 decimal points
AVAL	PARAMCD = "ESOPCAT2" (Obs. Period Duration Category)	float	5		Derived: Assigned sequentially from 1 for each categories in AVALC
AVAL	PARAMCD = "ESOPDCAT" (Obs. Period Duration Cumulative Category)	float	5		Derived: Assigned sequentially from 1 for each categories in AVALC
AVAL	PARAMCD = "ESOPDUR" (Observation Period Duration (Days))	float	5		Derived: Set to ADSL.LASTVSDT-ADSL.RFSTDT+1
AVAL	PARAMCD = "ESPLAN" (Total Number Planned)	float	5		Derived: 1.Subset all records with EXKIT^=.; 2.Keep distinct EXTPT. If EXTPT has duplicates, keep the one with latest date. All unscheduled doses on different dates will be kept; 3.Sort all the records by EXSTDTC, find the latest one. If the latest one is scheduled with EXTPT=week x, calculate the plan dose number by x+1; if the latest one is uncheduled, calculate the plan dose number by the integer part of (unscheduled dose date-first dose date+1)/7 plus 1;

Controlled Terms

Controlled Terms

Baseline Record Flag [CL.ABLFL]

Permitted Value (Code)
Y

Description of Actual Arm [CL.ACTARM]

Permitted Value (Code)
300 mg dupilumab q2w
300 mg dupilumab q4w
300 mg dupilumab q8w
300 mg dupilumab qw
Not Treated
Placebo

Description of Actual Arm Code [CL.ACTARMCD]

Permitted Value (Code)	Display Value (Decode)
DUPILUMAB 300 MG Q2W	300 mg dupilumab q2w
DUPILUMAB 300 MG Q4W	300 mg dupilumab q4w
DUPILUMAB 300 MG Q8W	300 mg dupilumab q8w
DUPILUMAB 300 MG QW	300 mg dupilumab qw
NOTTRT	Not Treated
PLACEBO QW	Placebo

Analysis Derivation

Analysis Derivations

Method	Type	Description
Algorithm to derive ADAE.ADURN	Computation	= AENDT - ASTDT + 1 if both AENDT and ASTDT are not missing
Algorithm to derive ADAE.AEEOTPFL	Computation	If .<ASTDT<=ADSL.EOTPDT and TRTEMFL="Y" then AEEOTPFL='Y';
Algorithm to derive ADAE.AEFUFL	Computation	If ASTDT>ADSL.EOTPDT>. and TRTEMFL="Y" then AEFUFL='Y';
Algorithm to derive ADAE.AEHPSSFL	Computation	For AEDECOD in computational Note #8, set AEHPSSFL="Y"; see Computational Note #8. Computational Notes
Algorithm to derive ADAE.AENDT	Computation	Imputed Numeric Date derived from AEENDTC. See details in computational note #5 Computational Notes
Algorithm to derive ADAE.AENDY	Computation	Derived based on AENDT and first dose date: If .<AENDT<first dose date then AENDY=AENDT-first dose date; Else if .<first dose date<=AENDT then AENDY=AENDT-first dose date+1; Else AENDY=.;
Algorithm to derive ADAE.AENEW	Computation	If SUPPAE.AEPSP="New event" then set to 'Y'; otherwise set to 'N';
Algorithm to derive ADAE.AENTM	Computation	Numeric time derived from AEENDTC
Algorithm to derive ADAE.AEREL	Computation	if not missing(AE.AEREL) then =AE.AEREL; if missing then ="RELATED"
Algorithm to derive ADAE.AESI01	Computation	See Computational Note #6. Computational Notes
Algorithm to derive ADAE.AESI01FL	Computation	See Computational Note #6. Computational Notes

Data Reviewer's Guide

Study Data Reviewer's Guide

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Analysis Data Reviewer's Guide

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Reviewer's Guide - List of Datasets

3.3 SDTM Subject Domains

Dataset – Dataset Label	Efficacy	Safety	Other	SUPP-	Related Using RELREC	Observation Class
AE - Adverse Events		X		X		Events
CE - Clinical Events		X				Events
CM - Concomitant Medications		X		X		Interventions
CO - Comments			X			Special Purpose
DA - Drug Accountability		X				Findings
DM - Demographics			X	X		Special Purpose
DS - Disposition			X	X		Events
DV - Deviations			X	X		Events
EG - ECG Test Results		X		X		Findings

5.2 Analysis Datasets

The analysis datasets are listed in the following table:

Dataset – Dataset Label	Class	Efficacy	Safety	Baseline or other subject characteristics	PK/PD	Antibodies	Primary Endpoint	Structure
ADSL – Subject Level Analysis Dataset	SUBJECT LEVEL ANALYSIS DATASET			X				One record per subject
ADAE - Analysis Dataset for Adverse Events	OTHER		X					One record per subject per event
ADCM - Analysis Dataset for Conmeds	OTHER		X					One record per subject per medication
ADDA- Analysis Dataset for Drug Accountability	BDS		X					One record per subject per drug accountability record
ADDS – Analysis Dataset for Disposition	OTHER			X				One record per disposition status or protocol milestone per subject
ADDV – Analysis Dataset for Protocol Deviation	BDS			X				One or more records per subject per protocol deviation
ADEG - Analysis Dataset for ECG	BDS		X					One or more records per subject per analysis parameter per analysis timepoint
ADEX - Analysis Dataset for	OTHER		X					One or more records per

Reviewer's Guide – Individual Datasets

3.3.1. AE - Adverse Events

The AE domain includes events that were captured as free text. The reported terms for the adverse events (AETERM) were coded using MedDRA version 18.0. The following table presents the different levels of terms used in the coding.

Variable	Description
AESOC	Primary System Organ Class
AESOCCD	Primary System Organ Class Code
AELLT	MedDRA Lowest Level Term
AELLTCD	MedDRA Lowest Level Term Code
AEDECOD	Dictionary-Derived Term
AEPTCD	MedDRA Preferred Term Code
AEHLT	MedDRA High Level Term
AEHLTCD	MedDRA High Level Term Code
AEHLGT	MedDRA High Level Group Term
AEHGLTCD	MedDRA High Level Group Term Code
AEHGLTCD	MedDRA High Level Group Term Code

The external file "AE List.xlsx" is used to identify the skin infection adjudication.

Adjudication of Adverse Events (AE)

"Skin Infection" event includes data from CRF AE page and the adjudication is done by study medical monitor, in a blinded fashion before DBL. The process is specified as below:

a. The data are retrieved all AE terms with HLT and/or PT, etc. (see AE listing)
b. Study medical monitor will review all adverse events to identify terms (HLT and/or PT) consistent with skin infection event (Yes/No)
c. The results of adjudication are included in domains AE or SUPPAE

5.2.1 ADSL – Subject Level Analysis Dataset

Structure: One record per subject.

Source: DM, SUPPDM, VS, DS, SUPPDS, CM, SUPPCM, EX, SV, QS, MH, DV, IE,SUPPEX, SUPPMH, SUPPQS

The subject level dataset ADSL contains required ADaM variables for demographics, treatment groups, and population flags.

In addition, it contains the following baseline variables:

Variable	Description
WTGRFASN	Baseline Weight Group (N) - FAS
WTGRFAS	Baseline Weight Group - FAS
WGTBL	Baseline Weight (kg)
HGTBL	Baseline Height (cm)
BMIBL	Baseline BMI (kg/m2)
BSABL	Baseline Body Surface Area (%)
IGABL	Baseline IGA
EASITSBL	Baseline EASI Total Score
GISSTSBL	Baseline GISS Total Score

Reviewer's Guide - Conformance Summary

6. Data Conformance Summary

6.1 Conformance Inputs

- Were the analysis datasets evaluated for conformance with CDISC ADaM Validation Checks?

  Yes, using Pinnacle 21 Enterprise covered the CDICS ADaM Checks v 1.3

- Were the ADaM datasets evaluated in relation to define.xml?

  Yes.

- Was define.xml evaluated?

  Yes. Pinnacle 21 Enterprise covered the CDICS ADaM Checks v 1.3

6.2 Issues Summary

The analysis datasets have been checked using OpenCDISC. All violation or error messages have been reviewed and reported as follows:

Dataset(s)	Diagnostic Message and/or Check ID	Severity	Count and/or Issue Rate	Explanation
ADCM	Required variable is not present	Error	2	The dataset is a hierarchical occurrence structure, the message is not relevant to this structure.
ADCM	Neither AVAL nor AVALC are present in dataset	Error	1	The dataset is a hierarchical occurrence structure, the message is not relevant to this structure.
ADEG	APHASE is present but APERIOD is not present	Warning	1	This study only have one period, hence APERIOD was not derived.
ADEG	DTYPE value not found in 'Derivation Type'	Warning	105	Values are added into the extensible codelist. This is a precautious message

Reviewer's Guide - Submission of Programs

7. Submission of Programs

This section describes all SAS programs related to the integrated summary of efficacy (ISE) included in the submission. It also includes some results metadata in order to allow the reviewer to establish a link between an ISE output table and the data. Step-by-step instructions describe how a reviewer can run the submitted SAS programs.

7.1 Programs Description and Flowchart

The following SAS programs are included in the ISS-ISE submission package:

- The SAS macro and utility programs that are used in the dataset creation programs and result programs (see Appendix 2)
- The SAS programs that created the ISE analysis datasets (see Appendix 3)
- The SAS programs that produced ISE analysis results (tables, figures and listings, e.g. TFL) (see

Figure_1
Ctrl+Click to follow link

Figure 1 illustrates the process used in the analysis dataset creation programs:

- establishing the environment with LIBNAME references for source and output data and standard templates;
- using project-specific macros for standard formats, parameter naming conventions and visit windows;
- reading in source data;
- deriving analysis variables;
- producing the permanent SAS dataset.

Figure 2 illustrates the process used in the analysis TFL creation programs:

Sponsor Study Data Standardization Plan

- Study Data Technical Conformance Guide (Guide) provides specifications, recommendations, and general considerations on how to submit standardized study data

- For clinical and nonclinical studies, sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. The Study Data Standardization Plan (*SDSP*) assists FDA in identifying potential data standardization issues early in the development program.

- The *SDSP* should include, but is not limited to the following:
  1. List of the planned studies
  2. Type of studies (e.g., phase I, II or III)
  3. Study designs (e.g., parallel, cross-over, open-label extension)
  4. Planned data standards, formats, and terminologies and their versions or a justification of studies that may not conform to the currently supported standards

FDA Study Data Guide – Data and Traceability

❑ General Considerations: SDTM, SEND, and/or ADaM

- **Variables in SDTM and SEND: Required, Expected, and Permissible -** Baseline flags, EPOCH designators, Study Day variables (--DY)

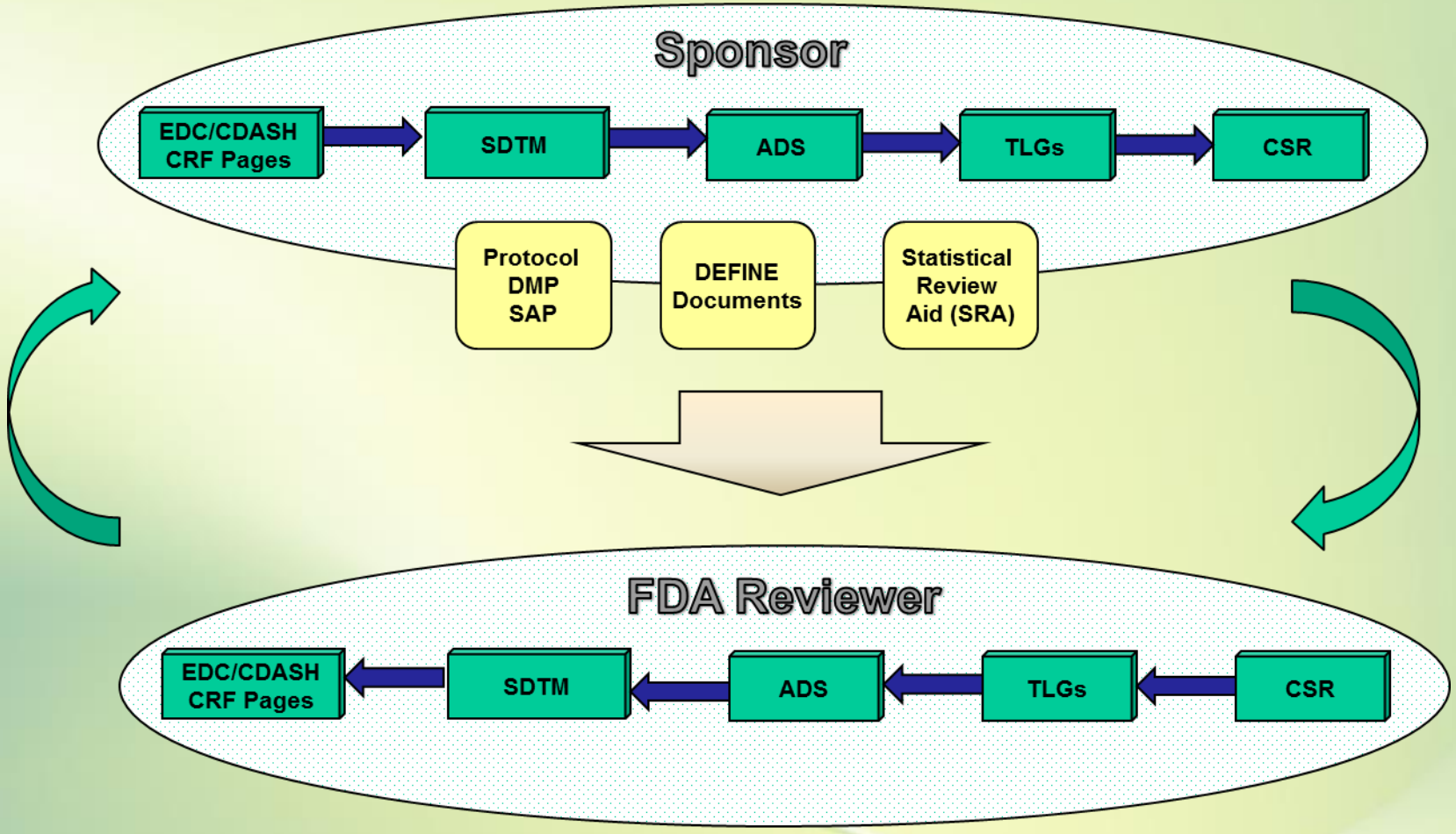
- Trial Summary (TS) dataset will be used to determine the time of study start.

❑ Study Data Traceability

An important component of a regulatory review is an understanding of the provenance of the data (i.e., traceability of the sponsor's results back to the CRF data). Traceability permits an understanding of the relationships between the analysis results (tables, listings and figures in the study report), analysis datasets, tabulation datasets, and source data. Traceability enables the reviewer to accomplish the following:

- Understand the construction of analysis datasets
- Determine the observations and algorithm(s) used to derive variables
- Understand how the confidence interval or the p-value was calculated in a particular analysis
- Relate counts from tables, listings, and figures in a study report to the underlying data

Traceability in e-Submission Package



Traceability – Transparent - Trust - Decision

THANK YOU!

Questions?

Discussion