PhUSE SDE

Reflecting on CDISC/ADaM and Metadata from a CDER Statistical Reviewer's Perspective

Behrang Vali, M.S.
Mathematical Statistician
Division of Biometrics III, CDER
U.S. Food and Drug Administration

Disclaimer

The views expressed in this presentation do not necessarily represent those of the U.S. Food and Drug Administration.

Outline

- Background on what an OB Statistician does at FDA/CDER/OB
  - Our Role at FDA/CDER/OB
- Analysis Data within the Clinical Data Lifecycle
- Metadata for ADaM Datasets
  - The Road Map for a Regulatory Reviewer

Outline

- ADaM Datasets
  - The “Delicate Balance”
- 2 Case Examples using Actual Submissions
- Quick Word on Comment/Derivation Fields
- Boilerplate Language

Statisticians at FDA/CDER/OB

IND Reviews – What We Review

- Pre-IND meeting packages with mapped out clinical development programs
- INDs with clinical trial protocols and Statistical Analysis Plans (SAPs) - Generally Phase 2 and 3 (rarely Phase 1)
- Special Protocol Assessments (SPAs) – these have highest priority
  - OB reviewer is very active in Protocol, SAP, and, potentially, Case Report Form (CRF) development
- Commercial INDs (i.e. from Pharma/Biotech companies) – these have high priority
- Investigator INDs (i.e. from independent clinical researchers) – these have less priority (reviews conducted only if there is time)

Statisticians at FDA/CDER/OB

Statistical Review of Efficacy

- Key Questions to ask during Review:
  - Are there any concerns about the design and conduct of the key trials?
  - Are the statistical analyses appropriate?
    - Conduct further analyses with support and insight from Medical Officer
  - Are the key results correct?
    - Quality Review i.e. programmatically validate all major results **IMPORTANT! NEED TABULATION AND ANALYSIS DATA (AND METADATA) FOR THIS!**

Statisticians at FDA/CDER/OB

Further Roles of the Statistical Reviewer

- Creates an open and clear review process
  - reviewer active in IND protocol development
  - clear NDA submission requirements
- Works with sponsors to File an understandable submission
  - verifies sponsor's analysis before filing
  - communicates the need for CDISC (SDTM/ADaM) data standards
- Identifies all key issues by mid-cycle
  - provide solutions and analyses
- Takes active role in medical division post-review actions
  - approvable and complete response actions
  - labeling

Analysis Data within the Clinical Data Lifecycle

Source Documents → Case Report Forms (CRFs) → Clinical Database → **Analysis Database** → Tables, Listings, and Figures (TLFs) → Clinical Study Report (CSR) → Product Label → Promotional Materials

- Let's try and standardize the process (a win-win-win proposition)

Analysis Data within the Clinical Data Lifecycle

- Content Standard: CDISC Analysis Data Model (ADaM) v2.1 and corresponding Implementation Guide (ADaMIG) v1.0

- Metadata Standard: CDISC Define.XML v1.0

A WORK IN PROGRESS

Metadata for ADaM Datasets

- Typical Industry Process
  - Produce ADaM Datasets and then produce corresponding Metadata File
    - Same process applies for Production of SDTM Datasets
- Regulatory Review Process
  - Comprehensively Review Metadata File prior to engaging ADaM Datasets
    - Again, same process applies for utilizing SDTM Datasets during a review

Metadata for ADaM Datasets

- For a Regulatory Reviewer, Metadata is as important as the content, i.e. datasets, of the submission
- Metadata serves as the guide/road map for the Regulatory Reviewer
- Consequently a sponsor should focus adequate time and energy into producing satisfactory Metadata files

Metadata for ADaM Datasets Levels of Metadata

- Dataset
  - Dataset Name, Description, Location (Hyperlinked), Structure (e.g. 1 Record per Patient), Key Variables that Index the Records, Class, Documentation
- Variable
  - Dataset Name, Variable Name, Variable Label, Variable Type (e.g. Character, Numeric), display format, code list/controlled terms, source/derivation

Metadata for ADaM Datasets Levels of Metadata

- Parameter Value (Nice to have for ADaM BDS Datasets)
  - Dataset name, Variable name (PARAM, AVAL, etc.), Parameter Identifier, code list/controlled terms (corresponding to Parameter Identifier), source/derivation
- Results Level Metadata (Unique to ADaM)
  - Display Identifier, Display Name, Result Identifier, PARAM, PARAMCD, Analysis Variable, Reason, Dataset, Selection Criteria, Documentation, Programming Statements

Metadata for ADaM Datasets

- So what format do Regulatory Reviewers really want for their metadata files?
  - Define.XML?
  - Define.PDF?
  - Both?

ADaM Datasets

- ADSL, Any ADaM BDS dataset, etc.

- Modeling analysis data in general is more 'gray' than 'black and white'
  - Multi-purpose (a dataset may support many different analyses) hence less modeling rules

ADaM Datasets

- ADaM delicately tries to balance 'Traceability' and 'Analysis-Ready' with a predictable structure
  - Contains derived data along with data directly imported from SDTM datasets
  - In lieu of dropping records/observations not used for analyses (e.g. data from unscheduled visits), it implements various analysis flags
- 'Traceability' is the key for reviewers
  - Less is NOT more
  - ADaM appropriately emphasizes this

Case Example 1 using an Actual Submission Dataset Level Metadata in DEFINE.XML

Datasets for Study -ADaM

Dataset	Description	Class	Structure	Purpose	Keys	Location
ADSL	Subject-Level	SPECIAL PURPOSE	One record per subject	Analysis	USUBJID	adsl.xpt
ADSLSF	Subject-Level Analysis Data - Scr. Fail.	SPECIAL PURPOSE	One record per subject	Analysis	USUBJID	adslsf.xpt
ADCM	Concomitant Medications, Therapies and Procedures	INTERVENTIONS	One record per conmed per subject	Analysis	USUBJID, CMCAT, CMSTDTC, CMDECOD, CMTRT	adcm.xpt
ADAE	Adverse Event	EVENTS	One record per AE term per subject	Analysis	USUBJID, AESTDTC, AETERM	adae.xpt
ADDV	Protocol Deviations	EVENTS	One record per reported term per visit per subject	Analysis	USUBJID, VISITNUM, DVSTDT, DVTERM	addv.xpt
ADAB	Antibody	FINDINGS	One record per antibody parameter per time point per subject	Analysis	USUBJID, PARAMN, VISITNUM, ADT	adab.xpt
ADEFF	Efficacy	FINDINGS	One record per efficacy parameter per time point per subject	Analysis	USUBJID, PARAMN, AVISITN, ADT	adeff.xpt
ADEFFQS	Efficacy - QS	FINDINGS	One record per parameter per time point per subject	Analysis	USUBJID, PARAMCAT, VISITNUM, PARAMN	adeffqs.xpt
ADEG	ECG	FINDINGS	One record per ECG observation per visit per subject	Analysis	USUBJID, PARAMN, VISITNUM, ADT	adeg.xpt
ADIVS	Infusion Vital Signs	FINDINGS	One record per vital sign measurement per visit per time point per subject	Analysis	USUBJID, PARAMN, VISITNUM, ADTM, SRCSEQ	adivs.xpt
ADLB	Laboratory	FINDINGS	One record per lab test per visit per time point per subject	Analysis	USUBJID, PARAMN, VISITNUM, ADTM	adlb.xpt
ADMH	Medical History	FINDINGS	One record per medical history event per subject	Analysis	USUBJID, MHGRPID, MHTERM	admh.xpt
ADPE	Physical Exam	FINDINGS	One record per body system per visit per subject	Analysis	USUBJID, PARAMN, VISITNUM, ADT	adpe.xpt
ADTIME	Time to Event	FINDINGS	One record per parameter per time point per subject	Analysis	USUBJID, PARAMN, AVAL	adtime.xpt

Case Example 1 using an Actual Submission Variable Level Metadata in DEFINE.XML

Efficacy Dataset (ADEFF) — adeff.xpt

Variable	Label	Type	Controlled Terminology	Origin	Role	Comment
STUDYID	Study Identifier	text	STUDYID	Derived	Subject Identifier	SDTM involved domain STUDYID.
USUBJID	Unique Subject Identifier	text		Derived	Subject Identifier	SDTM involved domain USUBJID.
TRT1P	Planned Treatment	text	TRT	ADSL.TRT1P	Treatment	
TRT1PN	Planned Treatment Number	integer	TRTN	ADSL.TRT1PN	Treatment	
TRT1A	Actual Treatment	text	TRT	ADSL.TRT1A	Treatment	
TRT1AN	Actual Treatment Number	integer	TRTN	ADSL.TRT1AN	Treatment	
ITTFL	Intent-To-Treat Population Flag	text	ALLYN	ADSL.ITTFL	Indicator	
SAFFL	Safety Population Population Flag	text	ALLYN	ADSL.SAFFL	Indicator	
MITTFL	Modified Intent-To-Treat Population Flag	text	ALLYN	ADSL.MITTFL	Indicator	
PPROTFL	Per Protocol Population Flag	text	ALLYN	ADSL.PPROTFL	Indicator	
DSREAS	Completion Status/Why Terminated (CRF)	text	DSREAS	ADSL.DSREAS	Analysis-Enabling	
SEX	Sex	text	SEX	ADSL.SEX	Analysis-Enabling	
SEXN	Sex, Numeric	integer	SEXN	ADSL.SEXN	Analysis-Enabling	
BRTHDT	Date/Time of Birth	integer		ADSL.BRTHDT	Timing	
AGEGRP	Age Group	text	AGEGRP	ADSL.AGEGRP	Analysis-Enabling	
AGEGRPN	Age Group, Numeric	integer	AGEGRPN	ADSL.AGEGRPN	Analysis-Enabling	

Case Example 1 using an Actual Submission Variable Level Metadata continued

AVAL	Analysis Value	float		Derived	Analysis Parameter	=--STRESN. For HGB, PLAT, LIVER SPLEEN, CHI Missing baseline is imputed by median baseline in the co and missing post-baseline result is imputed by either LO corresponding age group at the visit. Baseline can't be ca for weight). LOCF is applied first. When calcualte the gr only include the records that are considered baseline. W median for spleen, the patients had splenectomy at basel should be excluded. When calculate then group median f with ADSL.CHITOGT='DETECTED' or CHITOGT='I with baseline CHITO<5700 should be excluded. For CI there are more more than 1 record on the same visit and result will be used for that visit. No imputation for Growt and PFT. (Annualized growth velocity)=round(365.25*(date1),.1). (Normalized Organ Volume)=round(Organ V *100,.1). For normalized spleen and liver volume, LOC volume and weight before calculating the normalized org VS data on all visits are considered for LOCF.
AVALC	Character Analysis Value	text		Derived	Analysis Parameter	For tanner stage AVALC=XT.XTSTRESC if XTSTRES XTSTRESC=' ' and the analysis visit week number is aft AVALC='NA', otherwise AVALC='ND'.
BASE	Baseline Value	float		Derived	Analysis Parameter	=--STRESN where ABLFL='Y'.
BASEC	Character Baseline Value	text		Derived	Analysis Parameter	=--STRESC where ABLFL='Y' (for tanner stage only).
CHG	Change from Baseline	float		Derived	Analysis Parameter	=AVAL-BASE
PCHG	Percent Change from Baseline	float		Derived	Analysis Parameter	=((AVAL-BASE)/BASE)*100
DTYPE	Derivation Type	text	EFFDTYPE	Derived	Analysis Descriptor	='LOCF' if the observed result is missing and AVAL is f missing AVAL. EOS/UNSCH results fall out of analysis windowing won't be used for LOCF. ='MEDIAN' for th post-baseline visit result or missing baseline visit result. = derived modified baseline record. ='DERIVED' for the A and normalized organ volume. DTYPE='MISSING' if a imputed by LOCF and MEDIAN.
CRIT	Analysis Criterion	text	EFFCRIT	Derived	Categorical	Depending on PARAMCD. Response analysis is for HG Liver and Spleen volume. Please refer to SAP for definiti

Case Example 1 using an Actual Submission Controlled Terminology in DEFINE.XML

- Laboratory (ADLB)
- Medical History (ADMH)
- Physical Exam (ADPE)
- Time to Event (ADTIME)
- Value Level Metadata
- Controlled Terminology
- Code Lists
  - STUDYID
  - TRT
  - TRTN
  - ALLYN
  - DSREAS
  - ABSRCDOM
  - ABSRCVAR
  - ABPARAMCAT
  - ABPARAMCD
  - ABPARAM
  - ABPARAMN
  - ABVISITNUM
  - ABVISIT
  - ALLY
  - ABAVALC
  - ABDTYPE
  - AGEGRP
  - AGEGRPN
  - SEX
  - SEXN
  - AESEV
  - AEACN
  - AEREL
  - AEOUT
  - AECMTRT
  - AEAVISIT
  - CMCMCAT
  - DVVISNM
  - DVVISTX
  - DVDECOD
  - DVACAT
  - DVCAT

ABVISITNUM, Reference Name (ABVISITNUM)

Code Value	Code Text
0.9	Baseline Visit
3.01	Unscheduled Labs
7	Week 7
9.01	Unscheduled Labs
13	Week 13
19	Week 19
23.01	Unscheduled Labs
25	Week 25
31	Week 31
33.01	Unscheduled Labs
35.01	Unscheduled Labs
37	Week 37
41.01	Unscheduled Labs
43	Week 43
49	Week 49
53	Week 53/EOS
99999	Overall

ABVISIT, Reference Name (ABVISIT)

Code Value	Code Text
Baseline Visit	Baseline Visit
Overall	Overall
Unscheduled Labs	Unscheduled Labs
Week 13	Week 13
Week 19	Week 19

Case Example 1 using an Actual Submission ADSL

	USUBJID	AGEGRP	AGEGRPN	SEX	SEXN	TRT1PN	TRT1AN	ITTFL	SAFFL	MITTFL	PPROTFL	ICFDT	RANDDT	TRTSTDT	TRTENDT	DS
1		>= 18 years	2	F	2	2	2	Y	Y	Y	Y	04APR2007	20APR2007	22APR2007	08APR2008	Completed
2		>= 18 years	2	M	1	1	1	Y	Y	Y	N	04APR2007	20APR2007	22APR2007	06APR2008	Completed
3		>= 18 years	2	M	1	2	2	Y	Y	Y	Y	11APR2007	01MAY2007	02MAY2007	16APR2008	Completed
4		>= 18 years	2	F	2	2	2	Y	Y	Y	Y	03FEB2008	21FEB2008	24FEB2008	13FEB2009	Completed
5		>= 18 years	2	F	2	2	2	Y	Y	Y	Y	25FEB2008	17MAR2008	17MAR2008	05MAR2009	Completed
6		2 - 17 years	1	F	2	2	2	Y	Y	Y	Y	26FEB2008	20MAR2008	20MAR2008	05MAR2009	Completed
7		2 - 17 years	1	M	1	2	2	Y	Y	Y	Y	26FEB2008	20MAR2008	20MAR2008	05MAR2009	Completed
8		>= 18 years	2	M	1	1	1	Y	Y	Y	N	10MAR2008	26MAR2008	02APR2008	16MAR2009	Completed
9		>= 18 years	2	M	1	2	2	Y	Y	Y	Y	11MAR2008	28MAR2008	03APR2008	17MAR2009	Completed
10		>= 18 years	2	M	1	1	1	Y	Y	Y	N	12MAR2008	28MAR2008	04APR2008	18MAR2009	Completed
11		>= 18 years	2	M	1	1	1	Y	Y	Y	N	11JAN2007	14FEB2007	15FEB2007	14FEB2008	Completed
12		>= 18 years	2	M	1	2	2	Y	Y	Y	Y	24FEB2007	14MAR2007	15MAR2007	28FEB2008	Completed
13		2 - 17 years	1	M	1	2	2	Y	Y	Y	Y	24FEB2007	14MAR2007	15MAR2007	28FEB2008	Completed
14		>= 18 years	2	F	2	1	1	Y	Y	Y	N	13MAR2007	27MAR2007	29MAR2007	13MAR2008	Completed
15		2 - 17 years	1	M	1	1	1	Y	Y	Y	N	09APR2007	25APR2007	25APR2007	08APR2008	Completed
16		>= 18 years	2	F	2	2	2	Y	Y	Y	Y	09APR2007	07MAY2007	08MAY2007	22APR2008	Completed
17		>= 18 years	2	F	2	1	1	Y	Y	Y	N	09MAY2007	15JUN2007	18JUN2007	03JUN2008	Completed
18		2 - 17 years	1	F	2	1	1	Y	Y	N	N	09MAY2007	28JUN2007	29JUN2007	10JUN2008	Completed
19		>= 18 years	2	M	1	2	2	Y	Y	Y	Y	03JUL2007	25JUL2007	26JUL2007	10JUL2008	Completed
20		2 - 17 years	1	M	1	2	2	Y	Y	N	N	10SEP2007	04OCT2007	05OCT2007	18SEP2008	Completed
21		2 - 17 years	1	M	1	1	1	Y	Y	Y	N	23JAN2008	05FEB2008	08FEB2008	20JAN2009	Completed
22		>= 18 years	2	M	1	1	1	Y	Y	Y	N	22OCT2007	26NOV2007	27NOV2007	17NOV2008	Completed
23		>= 18 years	2	F	2	1	1	Y	Y	Y	N	07FEB2008	13MAR2008	14MAR2008	02MAR2009	Completed
24		>= 18 years	2	M	1	1	1	Y	Y	Y	N	28FEB2008	20MAR2008	21MAR2008	06MAR2009	Completed
25		>= 18 years	2	F	2	1	1	Y	Y	Y	N	11MAR2008	26MAR2008	28MAR2008	13MAR2009	Completed

Case Example 1 using an Actual Submission ADEFF

	USUBJID	SRCDOM	SRCVAR	SRCSEQ	PARAMCD	PARAM	PARAMN	VISITNUM	AVISITN	AVISIT	ADT
1		LB	LBSTRESN	65	HGB	Hemoglobin (g/dL)	1	0.5	-2	Screening	04APR2007
2		LB	LBSTRESN	146	HGB	Hemoglobin (g/dL)	1	0.9	-1	Baseline Visit	17APR2007
3		LB	LBSTRESN	.	HGB	Hemoglobin (g/dL)	1	.	0	Modified Baseline	.
4		LB	LBSTRESN	172	HGB	Hemoglobin (g/dL)	1	3	3	Week 3	07MAY2007
5		LB	LBSTRESN	203	HGB	Hemoglobin (g/dL)	1	5	5	Week 5	21MAY2007
6		LB	LBSTRESN	232	HGB	Hemoglobin (g/dL)	1	7	7	Week 7	05JUN2007
7		LB	LBSTRESN	260	HGB	Hemoglobin (g/dL)	1	9	9	Week 9	18JUN2007
8		LB	LBSTRESN	290	HGB	Hemoglobin (g/dL)	1	11	11	Week 11	02JUL2007
9		LB	LBSTRESN	371	HGB	Hemoglobin (g/dL)	1	13	13	Week 13	16JUL2007
10		LB	LBSTRESN	394	HGB	Hemoglobin (g/dL)	1	15	15	Week 15	30JUL2007
11		LB	LBSTRESN	423	HGB	Hemoglobin (g/dL)	1	17	17	Week 17	13AUG2007
12		LB	LBSTRESN	452	HGB	Hemoglobin (g/dL)	1	19	19	Week 19	27AUG2007
13		LB	LBSTRESN	481	HGB	Hemoglobin (g/dL)	1	21	21	Week 21	10SEP2007
14		LB	LBSTRESN	510	HGB	Hemoglobin (g/dL)	1	23	23	Week 23	24SEP2007
15		LB	LBSTRESN	591	HGB	Hemoglobin (g/dL)	1	25	25	Week 25	08OCT2007
16		LB	LBSTRESN	615	HGB	Hemoglobin (g/dL)	1	27	27	Week 27	22OCT2007
17		LB	LBSTRESN	645	HGB	Hemoglobin (g/dL)	1	29	29	Week 29	06NOV2007
18		LB	LBSTRESN	676	HGB	Hemoglobin (g/dL)	1	31	31	Week 31	20NOV2007
19		LB	LBSTRESN	705	HGB	Hemoglobin (g/dL)	1	33	33	Week 33	04DEC2007
20		LB	LBSTRESN	734	HGB	Hemoglobin (g/dL)	1	35	35	Week 35	18DEC2007
21		LB	LBSTRESN	812	HGB	Hemoglobin (g/dL)	1	37	37	Week 37	02JAN2008
22		LB	LBSTRESN	840	HGB	Hemoglobin (g/dL)	1	39	39	Week 39	15JAN2008
23		LB	LBSTRESN	869	HGB	Hemoglobin (g/dL)	1	41	41	Week 41	29JAN2008
24		LB	LBSTRESN	898	HGB	Hemoglobin (g/dL)	1	43	43	Week 43	12FEB2008
25		LB	LBSTRESN	927	HGB	Hemoglobin (g/dL)	1	45	45	Week 45	26FEB2008
26		LB	LBSTRESN	956	HGB	Hemoglobin (g/dL)	1	47	47	Week 47	11MAR2008
27		LB	LBSTRESN	985	HGB	Hemoglobin (g/dL)	1	49	49	Week 49	25MAR2008
28		LB	LBSTRESN	1014	HGB	Hemoglobin (g/dL)	1	51	51	Week 51	08APR2008
29		LB	LBSTRESN	1095	HGB	Hemoglobin (g/dL)	1	53	53	Week 53	29APR2008
30		LB	LBSTRESN	56	PLAT	Platelets (10^9/L)	2	0.5	-2	Screening	04APR2007
31		LB	LBSTRESN	137	PLAT	Platelets (10^9/L)	2	0.9	-1	Baseline Visit	17APR2007
32		LB	LBSTRESN	.	PLAT	Platelets (10^9/L)	2	.	0	Modified Baseline	.
33		LB	LBSTRESN	163	PLAT	Platelets (10^9/L)	2	3	3	Week 3	07MAY2007
34		LB	LBSTRESN	194	PLAT	Platelets (10^9/L)	2	5	5	Week 5	21MAY2007
35		LB	LBSTRESN	223	PLAT	Platelets (10^9/L)	2	7	7	Week 7	05JUN2007
36		LB	LBSTRESN	251	PLAT	Platelets (10^9/L)	2	9	9	Week 9	18JUN2007
37		LB	LBSTRESN	281	PLAT	Platelets (10^9/L)	2	11	11	Week 11	02JUL2007
38		LB	LBSTRESN	362	PLAT	Platelets (10^9/L)	2	13	13	Week 13	16JUL2007
39		LB	LBSTRESN	385	PLAT	Platelets (10^9/L)	2	15	15	Week 15	30JUL2007
40		LB	LBSTRESN	414	PLAT	Platelets (10^9/L)	2	17	17	Week 17	13AUG2007
41		LB	LBSTRESN	443	PLAT	Platelets (10^9/L)	2	19	19	Week 19	27AUG2007
42		LB	LBSTRESN	472	PLAT	Platelets (10^9/L)	2	21	21	Week 21	10SEP2007
43		LB	LBSTRESN	501	PLAT	Platelets (10^9/L)	2	23	23	Week 23	24SEP2007
44		LB	LBSTRESN	582	PLAT	Platelets (10^9/L)	2	25	25	Week 25	08OCT2007
45		LB	LBSTRESN	606	PLAT	Platelets (10^9/L)	2	27	27	Week 27	22OCT2007

Case Example 1 using an Actual Submission ADEFF continued

ADY	ABLFL	AVAL	AVALC	BASE	BASEC	CHG	PCHG	DTYPE	CRIT	ANLFL	ANL1F
-18		10.6		.		.	.				
-5		10.4		.		.	.				
.	Y	10.5		10.5		0	0	AVERAGE		Y	Y
16		11.2		10.5		0.7	6.7				Y
30		11.2		10.5		0.7	6.7				Y
45		11.4		10.5		0.9	8.6				Y
58		11		10.5		0.5	4.8				Y
72		10.6		10.5		0.1	1				Y
86		11.3		10.5		0.8	7.6		Moderate	Y	Y
100		11.7		10.5		1.2	11.4				Y
114		11.8		10.5		1.3	12.4				Y
128		12.1		10.5		1.6	15.2				Y
142		11.7		10.5		1.2	11.4				Y
156		11.7		10.5		1.2	11.4				Y
170		12.1		10.5		1.6	15.2		Good	Y	Y
184		11.6		10.5		1.1	10.5				Y
199		11.9		10.5		1.4	13.3				Y
213		11.6		10.5		1.1	10.5				Y
227		11.6		10.5		1.1	10.5				Y
241		13.8		10.5		3.3	31.4				Y
256		11.8		10.5		1.3	12.4		Moderate	Y	Y
269		11.7		10.5		1.2	11.4				Y
283		13.3		10.5		2.8	26.7				Y
297		12		10.5		1.5	14.3				Y
311		11.3		10.5		0.8	7.6				Y
325		11.3		10.5		0.8	7.6				Y
339		11.2		10.5		0.7	6.7				Y
353		12		10.5		1.5	14.3				Y
374		12.1		10.5		1.6	15.2		Good	Y	Y
-18		54		.		.	.				
-5		40		.		.	.				
.	Y	47		47		0	0	AVERAGE		Y	Y
16		38		47		-9	-19.1				Y
30		50		47		3	6.4				Y
45		48		47		1	2.1				Y
58		55		47		8	17				Y
72		63		47		16	34				Y
86		59		47		12	25.5		No Response	Y	Y
100		86		47		39	83				Y
114		82		47		35	74.5				Y
128		65		47		18	38.3				Y
142		71		47		24	51.1				Y
156		88		47		41	87.2				Y
170		96		47		49	104.3		Good	Y	Y
184		105		47		58	123.4				Y

Case Example 1 using an Actual Submission ADTIME (ADTTE)

USUBJID	TRT1PN	TRT1AN	PARAMCD	PARAM	AVAL	CENSORFL
	2	2	DY2HGBRP	Days to HGB Response	100	0
	2	2	DY2GCBAB	Days to Anti-GCB Antibody Positive	374	1
	1	1	DY2HGBRP	Days to HGB Response	183	0
	1	1	DY2GCBAB	Days to Anti-GCB Antibody Positive	374	1
	2	2	DY2HGBRP	Days to HGB Response	83	0
	2	2	DY2GCBAB	Days to Anti-GCB Antibody Positive	370	1
	2	2	DY2HGBRP	Days to HGB Response	113	0
	2	2	DY2GCBAB	Days to Anti-GCB Antibody Positive	367	1
	2	2	DY2HGBRP	Days to HGB Response	56	0
	2	2	DY2GCBAB	Days to Anti-GCB Antibody Positive	368	1
	2	2	DY2HGBRP	Days to HGB Response	141	0
	2	2	DY2GCBAB	Days to Anti-GCB Antibody Positive	362	1
	2	2	DY2HGBRP	Days to HGB Response	71	0
	2	2	DY2GCBAB	Days to Anti-GCB Antibody Positive	362	1
	1	1	DY2HGBRP	Days to HGB Response	84	0
	1	1	DY2GCBAB	Days to Anti-GCB Antibody Positive	366	1
	2	2	DY2HGBRP	Days to HGB Response	82	0
	2	2	DY2GCBAB	Days to Anti-GCB Antibody Positive	363	1
	1	1	DY2HGBRP	Days to HGB Response	14	0
	1	1	DY2GCBAB	Days to Anti-GCB Antibody Positive	363	1
	1	1	DY2HGBRP	Days to HGB Response	253	0
	1	1	DY2GCBAB	Days to Anti-GCB Antibody Positive	365	1
	2	2	DY2HGBRP	Days to HGB Response	99	0
	2	2	DY2GCBAB	Days to Anti-GCB Antibody Positive	365	1
	2	2	DY2HGBRP	Days to HGB Response	99	0
	2	2	DY2GCBAB	Days to Anti-GCB Antibody Positive	365	1
	1	1	DY2HGBRP	Days to HGB Response	85	0
	1	1	DY2GCBAB	Days to Anti-GCB Antibody Positive	365	1
	1	1	DY2HGBRP	Days to HGB Response	42	0
	1	1	DY2GCBAB	Days to Anti-GCB Antibody Positive	364	1
	2	2	DY2HGBRP	Days to HGB Response	183	0
	2	2	DY2GCBAB	Days to Anti-GCB Antibody Positive	365	1
	1	1	DY2HGBRP	Days to HGB Response	44	0
	1	1	DY2GCBAB	Days to Anti-GCB Antibody Positive	366	1
	1	1	DY2HGBRP	Days to HGB Response	56	0
	1	1	DY2GCBAB	Days to Anti-GCB Antibody Positive	364	1
	2	2	DY2HGBRP	Days to HGB Response	57	0
	2	2	DY2GCBAB	Days to Anti-GCB Antibody Positive	365	1
	2	2	DY2HGBRP	Days to HGB Response	42	0
	2	2	DY2GCBAB	Days to Anti-GCB Antibody Positive	364	1
	1	1	DY2HGBRP	Days to HGB Response	40	0
	1	1	DY2GCBAB	Days to Anti-GCB Antibody Positive	362	1
	1	1	DY2HGBRP	Days to HGB Response	46	0
	1	1	DY2GCBAB	Days to Anti-GCB Antibody Positive	371	1

Case Example 1 using an Actual Submission ADAE

USUBJID	AESEQ	AETERM	AEBODSYS	AEDECOD	AESEV	AESER	AEACN	AEREL	AEOUT
			disorders						
	3	FEELING COLD AFTER INFUSION	General disorders and administration site conditions	Feeling cold	MILD	N	DOSE UNCHANGED	POSSIBLY RELATED	RESOLVED WITHOUT SEQUELAE
	2	SHIVERING AFTER INFUSION	General disorders and administration site conditions	Chills	MILD	N	DOSE UNCHANGED	POSSIBLY RELATED	RESOLVED WITHOUT SEQUELAE
	4	OTITIS MEDIA	Infections and infestations	Otitis media	MILD	N	DOSE UNCHANGED	NOT RELATED	RESOLVED WITHOUT SEQUELAE
	5	SMALL, CRUSTY LESIONS ON FACE AND FOREARM AND A FEW ELSEWHERE	Skin and subcutaneous tissue disorders	Skin lesion	MILD	N	DOSE UNCHANGED	NOT RELATED	RESOLVED WITHOUT SEQUELAE
	6	TENDERNESS AROUND KIDNEY AREA - BILATERAL	Musculoskeletal and connective tissue disorders	Flank pain	MILD	N	DOSE UNCHANGED	NOT RELATED	RESOLVED WITHOUT SEQUELAE
	7	COLD/FLU	Infections and infestations	Influenza	MILD	N	DOSE UNCHANGED	NOT RELATED	RESOLVED WITHOUT SEQUELAE
	1	FELT COLD	General disorders and administration site conditions	Feeling cold	MILD	N	DOSE UNCHANGED	POSSIBLY RELATED	RESOLVED WITHOUT SEQUELAE
	2	WORSENING OF PAIN IN RIGHT LEG	Musculoskeletal and connective tissue disorders	Pain in extremity	MILD	N	DOSE UNCHANGED	NOT RELATED	RESOLVED WITH SEQUELAE
	3	FLU (CHILLS, FEVER, LASSITUDE)	Infections and infestations	Influenza	MILD	N	DOSE UNCHANGED	NOT RELATED	RESOLVED WITHOUT SEQUELAE
	4	SLIGHT WORSENING OF BONE (HIP) PAIN	Musculoskeletal and connective tissue disorders	Bone pain	MILD	N	DOSE UNCHANGED	NOT RELATED	RESOLVED WITH SEQUELAE
	5	PINK SPOT ON BACK	Skin and subcutaneous tissue disorders	Rash	MILD	N	DOSE UNCHANGED	NOT RELATED	RESOLVED WITHOUT SEQUELAE
	6	MUSCLE SPASMS IN ENTIRE BODY	Musculoskeletal and connective tissue disorders	Muscle spasms	MILD	N	DOSE UNCHANGED	NOT RELATED	RESOLVED WITHOUT SEQUELAE
	7	FAINTING	Nervous system disorders	Syncope	SEVERE	N	DOSE UNCHANGED	NOT RELATED	RESOLVED WITHOUT SEQUELAE
	8	FEVER	General disorders and administration site conditions	Pyrexia	MILD	N	DOSE UNCHANGED	NOT RELATED	RESOLVED WITHOUT SEQUELAE
	9	NO APPETITE	Metabolism and nutrition disorders	Anorexia	MILD	N	DOSE UNCHANGED	NOT RELATED	RESOLVED WITHOUT SEQUELAE
	10	WEAKNESS	General disorders and administration site conditions	Asthenia	MODERATE	N	DOSE UNCHANGED	NOT RELATED	RESOLVED WITHOUT SEQUELAE
	11	VOMITING (ONE TIME)	Gastrointestinal disorders	Vomiting	MILD	N	DOSE UNCHANGED	NOT RELATED	RESOLVED WITHOUT SEQUELAE
	12	WORSENING OF PAIN IN RIGHT HIP	Musculoskeletal and connective tissue disorders	Arthralgia	MODERATE	N	DOSE UNCHANGED	NOT RELATED	NOT YET RESOLVED
	1	(BONE) PAIN IN LEGS AND FEET	Musculoskeletal and connective tissue disorders	Bone pain	MILD	N	DOSE UNCHANGED	NOT RELATED	NOT YET RESOLVED
	3	ITCH OF RIGHT ARM	Skin and subcutaneous tissue disorders	Pruritus	MILD	N	DOSE UNCHANGED	NOT RELATED	RESOLVED WITHOUT SEQUELAE
	2	REDNESS OF RIGHT ARM	Skin and subcutaneous tissue disorders	Erythema	MILD	N	DOSE UNCHANGED	NOT RELATED	RESOLVED WITHOUT SEQUELAE
	4	(MUSCULOSKELETAL) PAIN IN LEFT ARM FROM ELBOW TO SHOULDER	Musculoskeletal and connective tissue disorders	Musculoskeletal pain	MILD	N	DOSE UNCHANGED	NOT RELATED	NOT YET RESOLVED
	5	CLINICALLY SIGNIFICANT LOW IRON LEVELS (TOTAL IRON = 7.3 FROM 8.8 AT BASELINE)	Investigations	Blood iron decreased	MILD	N	DOSE UNCHANGED	NOT RELATED	RESOLVED WITHOUT SEQUELAE
	6	PAIN IN HIP JOINTS WHEN BENDING	Musculoskeletal and connective tissue disorders	Arthralgia	MILD	N	DOSE UNCHANGED	NOT RELATED	NOT YET RESOLVED
	7	ABNORMALLY ELEVATED CRP (7.47MG/L)	Investigations	C-reactive protein increased	MILD	N	DOSE UNCHANGED	NOT RELATED	RESOLVED WITHOUT SEQUELAE
	1	COMMON COLD	Infections and infestations	Nasopharyngitis	MILD	N	DOSE UNCHANGED	NOT RELATED	RESOLVED WITHOUT SEQUELAE
	2	PAIN IN RIGHT GROIN AREA	Musculoskeletal and connective tissue disorders	Groin pain	MILD	N	DOSE UNCHANGED	NOT RELATED	RESOLVED WITHOUT SEQUELAE
	3	PELVIC PAIN	Reproductive system and breast disorders	Pelvic pain	MILD	N	DOSE UNCHANGED	NOT RELATED	RESOLVED WITHOUT SEQUELAE
	4	FATIGUE	General disorders and administration site conditions	Fatigue	MILD	N	DOSE UNCHANGED	NOT RELATED	RESOLVED WITHOUT SEQUELAE
	5	PAIN IN RIGHT TOE	Musculoskeletal and connective tissue disorders	Pain in extremity	MILD	N	DOSE UNCHANGED	NOT RELATED	NOT YET RESOLVED

Case Example 2 using an Actual Submission Dataset Level Metadata in DEFINE.PDF

Dataset Name	Dataset Description
ADae	Adverse Events
ADspleen	Spleen Volume (mL)
ADsplen2	Spleen Volume (mL)
ADhemog	Hemoglobin (g/dL)
ADliver	Liver Volume (mL)
ADliver2	Liver Volume (mL)
ADplate	Platelet Counts
ADbiomk	Biomarker - Chitotriosidase
ADbiomk2	Biomarker – CCL18

Case Example 2 using an Actual Submission Variable Level Metadata in DEFINE.PDF

DATASET=ADPLATE

Variable Name	Variable Label	Variable Type	Source / Computational Method
PCHGCAT1	Clinically Relevant Deterioration or Not?	Char	CLINICALLY RELEVANT DETERIORATION: if PCHG < -20 when base platelet counts <= 120,000; or PCHG < -40 when base platelet counts > 120,000. NOT CLINICALLY RELEVANT DETERIORATION otherwise.

What Should be in the Comment/Derivation Field?

ADXE

Varnum	Name	Label	Type	Length	Decodes	Origin	Comments
1	STUDYID	Study Identifier	char	11		ADSL.STUDYID	
2	USUBJID	Unique Subject Identifier	char	25		ADSL.USUBJID	
3	SAFETY	Safety Population Flag	char	1	Y = 'Yes' and N = 'No'.	ADSL.SAFETY	
4	MITT	Modified Intent to Treat Populaion Flag	char	1	Y = 'Yes' and N = 'No'.	ADSL.MITT	
5	MITTREC	Modified Intent to Treat Recurrence	char	1	Y = 'Yes' and N = 'No'.	ADSL.MITTREC	
6	PP	Per Protocol Population Flag	char	1	Y = 'Yes' and N = 'No'.	ADSL.PP	
7	PPREC	Per Protocol Recurrence	char	1	Y = 'Yes' and N = 'No'.	ADSL.PPREC	
8	CLINCURE	Clinical Cure	char	1	Y = 'Yes' and N = 'No'.	Derived	If XCORRES = 'YES' and XRORRES ^= 'YES' then 'Y'; else 'N'
9	RECURR	Recurrence of CDI	char	1		Derived	If cured and recurred then 1; if cured and not recurred then 0
10	GLOBCURE	Global Cure	char	1		DM.RFENDTC and ADXE.RECURR	
11	RESDIA	Resolution of Diarrhea	char	1	1 = Event, 0 = Censor	Derived	1) Patients who never used rectal collection device: If <= 3 unformed bowel movements are observed for 2 consecutive days and it is sustained through the end of therapy/day 10 (XUDY). 2) Patients who only used rectal collection device: If the volume (over a 24-hour period) is decreased by 75% compared to admission and the 75% decrease is sustained until Day 10. 3) Patients who periodically used rectal collection device: Convert volume of stool to number of unformed bowel movements using formula - 60 cc (or ml) = 1 unformed bowel movement. Then use criteria specified in (1).
12	RDANAL	Included for Resolution of Diarrhea	char	1		Derived	
13	RESDIDTC	Date of Resolution of Diarrhea	char	19	1 = Event, 0 = Censor	Derived	1) Patients who never used rectal collection device: Date/time of last unformed bowel movement (XUDTC) the day prior to the first of 2 consecutive days of <= 3 unformed bowel movements (XUORRES) that are sustained through the end of therapy/day 10 (XUDY). 2) Patients who only used rectal collection device: Date when the volume (over a 24-hour period) is decreased by 75% compared to admission and the 75% decrease is sustained until Day 10. 3) Patients who periodically used rectal collection device: Convert volume of stool to number of unformed bowel movements using formula - 60 cc (or ml) = 1 unformed bowel movement. Then use criteria specified in (1).

What Should be in the Comment/Derivation Field?

POP (SAS dataset Name: POP)				
VARIABLE	**LABEL**	**TYPE**	**CODES**	**COMMENTS**

ENCOHORT	encohort	Num		Derived
				=1
				`if s4_01 =1`
				`  and 11 <= agec <= 17`
				`  and confirm_2 =1`
				`  and confirm_3 =1`
				`  and confirm_4 =1`
				`  and confirm_5 =1`
				`  and confirm_6 =1`
				`then encohort=1;`
				`else encohort=.;`
				
				`Per Clinical:`
				`Subject  was eligible.`
				`Subject  was not eligible.`

CON7_0M	con7_0m	Num		Subject Informed Consent Date - Month
CON7_0D	con7_0d	Num		Subject Informed Consent Date - Day
CON7_0Y	con7_0y	Num		Subject Informed Consent Date - Year
CONSDT	consdt	Date		Subject Informed Consent Date Derived from CON7_0M, CON7_0D, CON7_0Y
REFUSE01	refuse01	Num	1=Yes 2=No time 3=Opposes study procedure(s) 4=Concerned about confidentiality 5=Not interested 99=Other (SPECIFY)	Screening Questionnaire: Did the subject agree to participate?
CONSENT	consent	Num		Subject Informed Consent flag Derived =1 if refuse01=1 and consdt is not missing

Boilerplate Language

DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for product registration. Such Implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at the following link:

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

Thank You for your Attention

Comments are appreciated

Please send to Behrang.Vali@fda.hhs.gov