This single PDF file contains the slides for all three presentations in the webinar:

Optimizing Your Study Data Submissions to FDA – Updates from CDER and CBER

Please page down to find the slides for all the presentations

CDER SBIA Webinar Series

U.S. FOOD & DRUG ADMINISTRATION

Update on the Study Data Technical Conformance Guide

Ron Fitzmartin, PhD, MBA
Senior Advisor
Office of Strategic Programs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

July 13, 2017

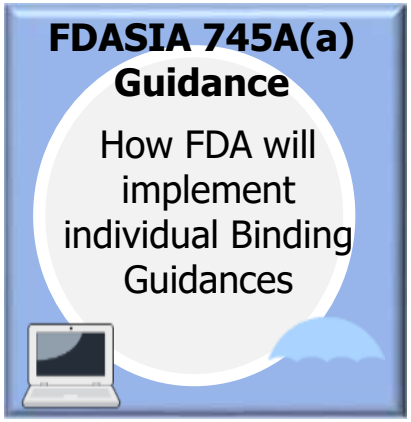
FDA DISCLAIMER

The views and opinions presented here represent those of the speaker and should not be considered to represent advice or guidance on behalf of the U.S. Food and Drug Administration.

Study Data Standards:
Road Ahead and the Road Left Behind

FDA Statute to Require Data Standards

2012 FDASIA amended FD&C Act added Sec 745A (21 USC 379 k-1(a))



Study Data Technical Conformance Guide (TCG)

- Focus is on helping sponsors & applicants to submit better standardized data.
- Most up-to-date guide on standardized study data submissions to CBER / CDER.
- Posted at least twice per year: March / October.

Study Data Technical Conformance Guide (TCG)

- **2.3** An ADRG for clinical data should be called an ADRG and the document should be a PDF file 'adrg.pdf' upon submission.

- **4.1.1.3** When there is more than one disposition event, the EPOCH or DSCAT variable should be used. This will allow identification of the EPOCH in which each event occurred or DSCAT to differentiate if the disposition is for treatment or study.

- **4.1.2, 4.1.3.3, 4.1.4.1** Clarifications for SEND

- **5.1** Updated & clarified that TAs are not data standards but rather extensions of the CDISC foundational standards.

Study Data Technical Conformance Guide (TCG)

- **5.2** FDA now supports *Diabetic Kidney Disease*, *Ebola*, *Kidney Transplant*, and *Malaria*, and *Rheumatoid Arthritis*

- **8.0 Types of Study Data Validation Rules**

  1. Standards Development Organizations (e.g., CDISC) provide rules that assess conformance to its published standards (See www.CDISC.org).

  2. FDA eCTD Technical Rejection Criteria for Study Data that assess conformance to the standards listed in the FDA Data Standards Catalog (See above).

  3. FDA Business and Validator rules to assess that the data support regulatory review and analysis.

- **8.3.1 & 8.3.2** Added paragraphs on SEND

Study Data Technical Conformance Guide (TCG)

Selected KEY Points

- **2.1:** SDSP should be located in the eCTD M1,Section 1.13.9 (General Investigational Plan)

- **4.1.1.2:** Each submitted SDTM dataset should have its contents described with complete metadata in the **define.xml**. Not PDF!

- **4.1.1.3:** ts.xpt must be in *legacy studies* that started prior to 12/17/2016.

- FDA has not yet published the 30 day notice date for technical rejection due to non-standardized study data.

For questions please contact the CDER eData Team at: eDATA@fda.hhs.gov

U.S. FOOD & DRUG ADMINISTRATION

Providing Clinical Study Data to the Office of Vaccines

SBIA: Study Data Technical Conformance Webinar

July 13, 2017

Brenda Baldwin, Ph.D.

and

Kirk Prutzman, Ph.D.

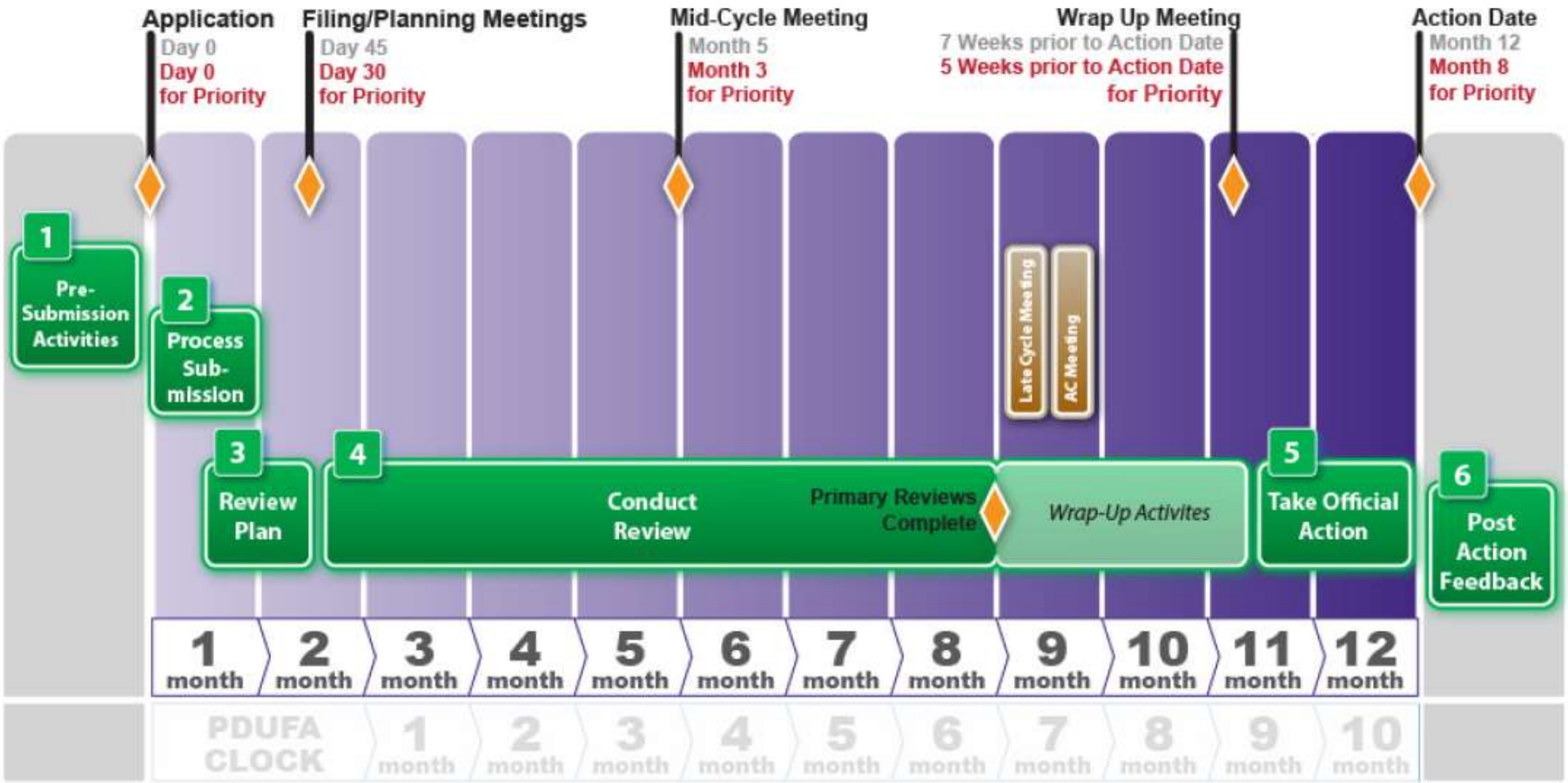
FDA DISCLAIMER

The views and opinions presented here represent those of the speakers and should not be considered to represent advice or guidance on behalf of the Food and Drug Administration.

Goals of Presentation

- Timing of submission of CBER Study Data Standardization Plan (SDSP) checklist and annotated Case Report Form (aCRF) for Study Data Tabulation Model (SDTM)
- Use of SDTM DOMAINS for vaccine clinical study data
- Understanding where errors have occurred in SDTM datasets and how to avoid them
- Traceability of data

BLA Timelines



From CDER's *21st Century Review Process Desk Reference Guide*

How does Standardized Clinical Data help us in our review

- Locating specific data is easier
- Integrating is easier
- Analyzing is easier

Timing of submission (CBER SDSP and aCRF)

- Annotated CRF (aCRF) for proposed SDTM datasets should be submitted prior to the start of a vaccine clinical study that will have data submitted to OVRR
  - important to begin using proposed data standards so that study data traceability is not an issue
- CBER Study Data Standardization Plan (SDSP) should be submitted at the end-of-phase 2 meeting
  - Plan should be agreed upon with OVRR prior to the beginning of your phase 3 clinical trial
- Follow most recent version of the Technical Conformance Guide (TCG) for guidance on data submission

Annotated Case Report Forms (aCRF)

According to the Technical Conformance Guide (March 2017) –page 19

- When data are recorded on the CRF but are not submitted, the CRF should be annotated with the text "NOT SUBMITTED.” There should be an explanation in the Study Data Reviewers Guide (SDRG) stating why data have not been submitted.

aCRF example

Measured Assessments		
Measurements are to be reported in Mm. If the reaction is ongoing, report the Maximum Measurement available at the time of reporting. When the stop date is obtained, please ensure that the Maximum Measurement is still correct while considering the entire duration.		
1.	Action Taken	◯ 0 = None ◯ 1 = Medication (self-medication with an existing prescription or over-the-counter medication) ◯ 2 = Health care provider contact (no new medication prescribed) ◯ 3 = Health care provider contact and prescription of a new medication (health care provider instructed subject to take a new medication either an over-the-counter medication or one requiring a written prescription) ◯ 4 = Hospitalization (inpatient) (Complete the SAE Form)
2.	Measurement at Day 00	◯ ____ Mm ◯ Non Measurable (too large to measure) ◯ Missing Data
3.	Measurement at Day 01	◯ ____ Mm ◯ Non Measurable (too large to measure) ◯ Missing Data

Bad example -not annotated

aCRF – where “not submitted” is utilized

Demographics [frmDemographics_4]		
1.* ✔	Assigned Subject Number	[itmSubjectNumber] A7 DM.SUBJID
2.* ✔	Subject Code	[itmSubjectCode_Demog] A3 [NOT SUBMITTED]
3.* ✔	Date of Birth	[itmDateOfBirth] Req/Unk / Req/Unk / Req/Unk (1900-1945) DM.BRTHDTC
4.*	Age *[read-only]* DM.AGEU = "YEARS"	[itmAge] N3 DM.AGE
5.* ✔	Gender	[itmGender] *[A:1]* ◯ Male *[A:2]* ◯ Female DM.SEX

Another aCRF example

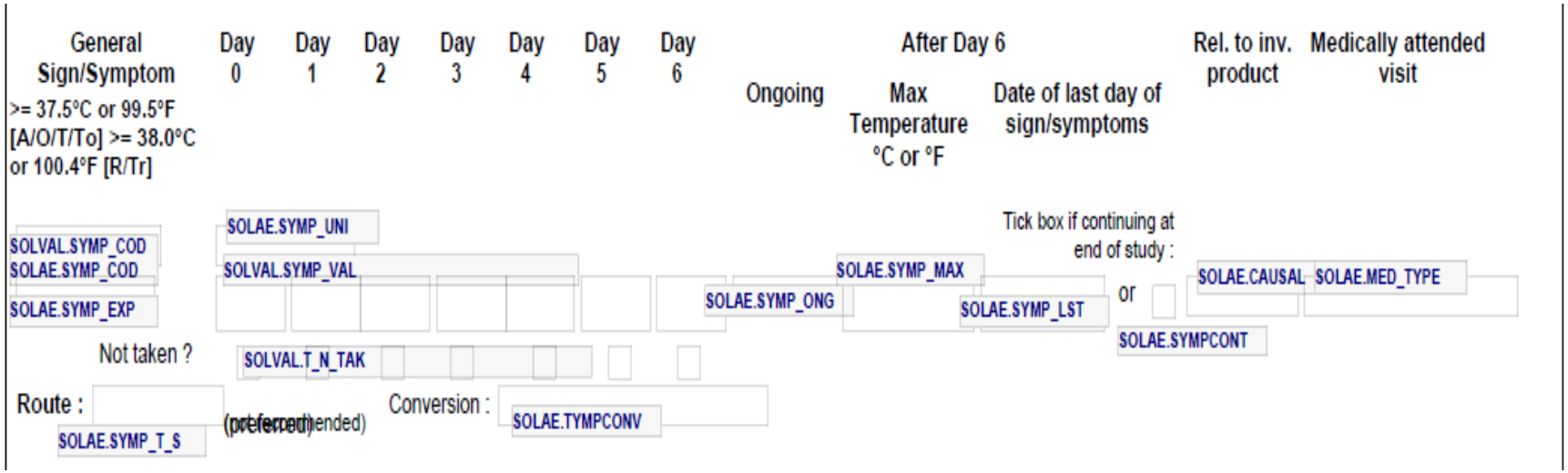
Complete this form and then enter details in the following forms.		
Solicited Systemic Reactions - Presence		
Did the subject experience any of the following reactions between Day 00 and Day 14 after the vaccination:		
1.	Headache?	◯ Yes ◯ No
2.	Malaise?	◯ Yes ◯ No
3.	Myalgia?	◯ Yes ◯ No
4.	Asthenia?	◯ Yes ◯ No
Unsolicited Systemic Events - Presence		
If the Unsolicited Systemic Event is a Serious Adverse Event (SAE), please do not record the event on this form but complete the SAE form.		
5.	Did the subject have any Unsolicited Systemic Events?	◯ Yes ◯ No

CECAT - Reactogenicity

CEOCCUR – Y/N

– annotation is better, but…

aCRF must be correctly annotated for the data being submitted



This applicant submitted their data in SDTM format, but provided their aCRF with annotation for “legacy” data

CBER
Study Data Standardization Plan (SDSP)

CBER SDSP checklist

SDTM Version				
STUDY ID:		**TITLE:**		
DOMAIN		**Select Domains to be Submitted (X)**	**VARIABLES to be UTILIZED (besides required)**	**ADDITIONAL COMMENTS**
Trial Design				
	TA (Trial Arms)	<X>		
	TE (Trial Elements)	<X>		
	TI (Trial Inclusion/ Exclusion Criteria)	<X>		
	TS (Trial Summary)	<X>		
	TV (Trial Visits)	<X>		
	TD (Trial Disease Assessments)	<X>		
Special Purpose				
	CO (Comments)	<X>		
	DM (Demographics)	<X>		
	SE (Subject Elements)	<X>		
	SV (Subject Visits)	<X>		

Not showing – Interventions, Events, Findings, Findings About, Relationships and Custom Domains for SDTM; as well as tables where proposed analysis will be provided

SDSP Standard Version Number

SDTM	1.1	1.2	1.3
SDTMIG	3.1.1	3.1.2	3.1.3
ADaM	N/A	2.1	2.1
ADaM IG	N/A	1.0	1.0
Define.xml	2.0	2.0	
MedDRA Version	Study 1 MedDRA 12.0 Study 2 MedDRA 10.1 Study 3 MedDRA 11.0 Study 4 MedDRA 11.0 Study 5 MedDRA 11.0 Study 6 MedDRA 11.0 Study 7 MedDRA 11.0 Study 8 MedDRA 12.0 Study 9 MedDRA 13.0 Study 10 MedDRA 13.0 Study 11 MedDRA 14.0 Study 12 MedDRA 14.0 Study 13 MedDRA 14.0 Study 14 MedDRA 14.0 Study 15 MedDRA 14.0 Study 16 MedDRA 14.0 Study 17 MedDRA 14.0		
CDASH	N/A		

1 table/study

NOT multiple as this example is showing

Usage of SUPPQUAL (special SDTM dataset that contains non-standard variables which cannot be represented in the existing SDTM domains)

Relationships			
	RELREC (Related Records)	☒	
	SUPPQUAL (Supplemental Qualifiers)	☒	SUPPAE, SUPPCE, SUPPCM, SUPPDM, SUPPDS, SUPPHO, SUPPLB, SUPPMH

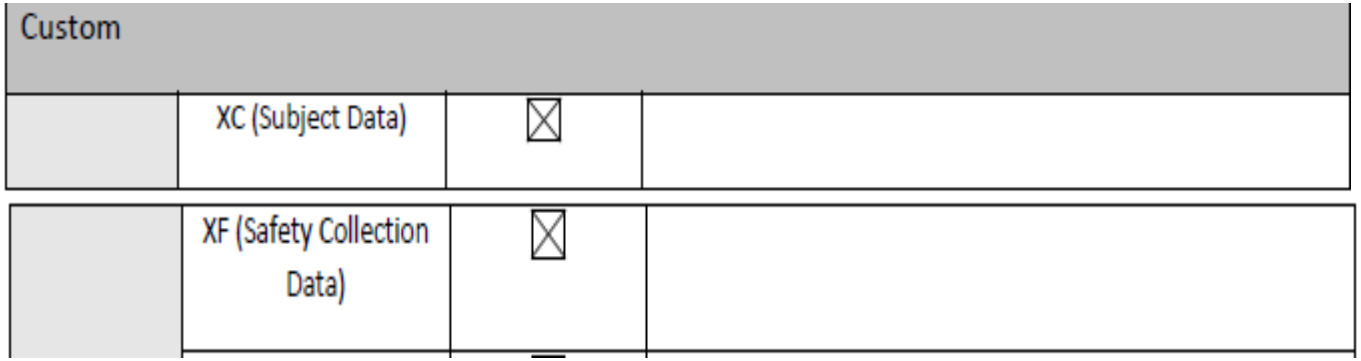
9. SUPPLEMENTAL QUALIFIERS

NOTE: Add rows as necessary for all SUPPQUAL variables

Supplemental Qualifier Domain	Qualifier Variable Name	Qualifier Variable Label (QLABEL)	Corresponding CRF Question or Derivation
NA	NA	NA	NA

If SUPPQUAL proposed – need to provide details in the SUPPLEMENTAL QUALIFIERS table

Custom domain usage



Custom			
	XC (Subject Data)	☒	
	XF (Safety Collection Data)	☒	

Discuss with review division before utilizing custom domains

Usage of DOMAINS for vaccine clinical study data

Reactogenicity should be captured in CE – not AE or custom

Events			
	AE	☒	STUDYID DOMAIN USUBJID AESEQ AETERM AEDECOD AECAT AESCAT AEBODSYS AESEV AESER AEACNOTH AEREL AEOUT AESCONG AESDISAB AESDTH AESHOSP AESLIFE AESMIE AESTDTC AEENDTC AESTDY AEENRF AEENDY VISIT VISITNUM
	CE	☐	
	DS	☒	STUDYID DOMAIN USUBJID DSSEQ DSTERM DSDECOD DSCAT

	SR	☒	Solicited Reaction Data STUDYID DOMAIN USUBJID SRSEQ SRTESTCD SRDECOD SRTEST SRCAT SRMETHOD SRORRES SRORRESU SRSTRESU SRSTRESN SRSTRESC VISIT VISITNUM SRDOSE SRDC SRDTC SRLSTDTC SRSTDTC SRENDTC SRPRES SRACN SROG SRTERM
		☐	

LB should only be used for study data from safety lab findings

Findings			
	DA	☐	
	EG	☐	
	IE	☒	STUDYID DOMAIN USUBJID IESEQ IETESTCD IETEST IECAT IEORRES IESTRESC VISITNUM VISIT
	LB	☒	STUDYID DOMAIN USUBJID LBSEQ LBTESTCD LBTEST LBCAT LBSCAT LBORRES LBORRESU LBSTRESC LBSTRESN LBSTRESU LBSTAT LBREASND LBSPEC VISIT VISITNUM LBDTC LBDY LBORNRLO LBORNRHI LBNRIND LBREFID
	MB	☐	
	MS	☐	
	PC	☐	
	PE	☐	
	PP	☐	
	QS	☐	
	SC	☒	STUDYID DOMAIN USUBJID SCSEQ SCTESTCD SCTEST SCORRES SCSTRESC

RT-PCR
PRNT
ELISA
Culture

From SDTMIG (version 3.2): "Laboratory test findings including, but is not limited to hematology, clinical chemistry and urinalysis data. This domain does not include microbiology or pharmacokinetic data, which are stored in separate domains."

LB should only be used for safety labs (and yet another submission)

IS (Immunogenicity Assessment Specimen)	☐	
LB (Laboratory Test Results)	☒	
MB (Microbiology Specimen)	☐	

Immunogenicity and Microbiology Specimen Domains are available for use in version 3.2

Technical Rejection Criteria for Study Data – published March 2, 2017

- The FDA may refuse to file (RTF) for NDAs and BLAs, or refuse to receive (RTR) for ANDAs, an electronic submission that does not have study data in conformance to the required standards specified in the FDA Data Standards Catalog

TS Missing

Trial Design			
	TA	☐	
	TE	☐	
	TI	☒	STUDYID DOMAIN USUBJID IETESTCD IETEST IECAT IEORRES IESTRESC VISITNUM VISIT TISEQ
	TS	☐	
	TV	☐	

According to **Technical Rejection Criteria for Study Data** - A Trial Summary (TS) dataset must be present for each study in module 4, sections 4.2.3.1, 4.2.3.2, 4.2.3.4 and in module 5, sections 5.3.1.1, 5.3.1.2, 5.3.3.1, 5.3.3.2, 5.3.3.3, 5.3.3.4, 5.3.4, 5.3.5.1, 5.3.5.2

*even if the study started prior to December 17, 2016

Other Technical Rejection Criteria for Study Data

- #1735 – the correct STF file-tags must be used for all standardized datasets in section 4.2 and section 5.3 (e.g., data-tabulations-dataset-sdtm, data-tabulations-dataset-send, and analysis-dataset-adam)
- #1736 – DM datasets and define.xml must be submitted in sections 4.2 and 5.3. ADSL dataset must be submitted in section 5.3
- #1737 – for each study in section 4.2 and 5.3, no more than one dataset of the same name should be submitted as new

Understanding where errors have occurred in SDTM datasets submitted to CBER and how to avoid them

1. Issues with data integrity
2. Issues with datasets that don't follow SDTM rules
3. Issues with data traceability

Understanding where errors have occurred in SDTM datasets submitted to CBER and how to avoid them

1. **Issues with data integrity**
2. Issues with datasets that don't follow SDTM rules
3. Issues with data traceability

Missing Data

STUDYID	DOMAIN	USUBJID	AESEQ	AETERM	AEDECOD	AECAT	AESCAT	AEBODSYS	AESEV	AESER	AEACN	AEACNOTH	AEREL
[redacted]	AE	[redacted]	7	INJECTION SITE PAIN	Injection site pain	Solicited	Administration site	General disorders and administration site conditions	Grade 1	N		None	Related
[redacted]	AE	[redacted]	1	INJECTION SITE SWELLING	Injection site sw...	Solicited	Administration site	General disorders and administration site conditions	Grade 2	N		None	Related
[redacted]	AE	[redacted]	2	INJECTION SITE SWELLING	Injection site sw...	Solicited	Administration site	General disorders and administration site conditions	Grade 2	N		None	Related
[redacted]	AE	[redacted]	3	INJECTION SITE SWELLING	Injection site sw...	Solicited	Administration site	General disorders and administration site conditions	Grade 1	N		None	Related
[redacted]	AE	[redacted]	1	COUGH	Cough	Unsolicited	Systemic	Respiratory, thoracic and mediastinal disorders	Grade 1	N		None	Not related
[redacted]	AE	[redacted]	1	DERMATITIS PHOTO CONTACT	Photosensitivity ...	Unsolicited	Systemic	Skin and subcutaneous tissue disorders	Grade 1	N		Health care provider cont. + med.	Not related
[redacted]	AE	[redacted]	2	DERMATITIS	Dermatitis	Unsolicited	Systemic	Skin and subcutaneous tissue disorders	Grade 1	N		Health care provider cont. + med.	Not related
[redacted]	AE	[redacted]	3	INJECTION SITE PAIN	Injection site pain	Solicited	Administration site	General disorders and administration site conditions	Grade 1	N		None	Related
[redacted]	AE	[redacted]	4	HEADACHE	Headache	Solicited	Systemic	Nervous system disorders	Grade 1	N		None	Related
[redacted]	AE	[redacted]	5	HEADACHE	Headache	Solicited	Systemic	Nervous system disorders	Grade 1	N		None	Related
[redacted]	AE	[redacted]	6	MALAISE	Malaise	Solicited	Systemic	General disorders and administration site conditions	Grade 1	N		None	Related
[redacted]	AE	[redacted]	7	MYALGIA	Myalgia	Solicited	Systemic	Musculoskeletal and connective tissue disorders	Grade 1	N		None	Related
[redacted]	AE	[redacted]	1	COMMON COLD	Nasopharyngitis	Unsolicited	Systemic	Infections and infestations	Grade 2	N		Health care provider cont. + med.	Not related
[redacted]	AE	[redacted]	2	PHARYNGITIS	Pharyngitis	Unsolicited	Systemic	Infections and infestations	Grade 2	N		Health care provider cont. + med.	Not related
[redacted]	AE	[redacted]	3	TONSILLITIS	Tonsillitis	Unsolicited	Systemic	Infections and infestations	Grade 2	N		Health care provider cont. + med.	Not related
[redacted]	AE	[redacted]	4	HEADACHE	Headache	Solicited	Systemic	Nervous system disorders	Grade 1	N		None	Related
[redacted]	AE	[redacted]	5	HEADACHE	Headache	Solicited	Systemic	Nervous system disorders	Grade 2	N		Health care provider cont. + med.	Related
[redacted]	AE	[redacted]	6	HEADACHE	Headache	Solicited	Systemic	Nervous system disorders	Grade 1	N		Health care provider cont. + med.	Related
[redacted]	AE	[redacted]	7	MALAISE	Malaise	Solicited	Systemic	General disorders and administration site conditions	Grade 2	N		Health care provider cont. + med.	Related
[redacted]	AE	[redacted]	8	MALAISE	Malaise	Solicited	Systemic	General disorders and administration site conditions	Grade 3	N		Health care provider cont. + med.	Related
[redacted]	AE	[redacted]	9	MALAISE	Malaise	Solicited	Systemic	General disorders and administration site conditions	Grade 1	N		Health care provider cont. + med.	Related
[redacted]	AE	[redacted]	10	ABDOMINAL PAIN	Abdominal pain	Unsolicited	Systemic	Gastrointestinal disorders	Grade 1	N		Health care provider cont. + med.	Not related
[redacted]	AE	[redacted]	1	HEADACHE	Headache	Solicited	Systemic	Nervous system disorders	Grade 1	N		None	Related
[redacted]	AE	[redacted]	2	MALAISE	Malaise	Solicited	Systemic	General disorders and administration site conditions	Grade 1	N		None	Related
[redacted]	AE	[redacted]	3	RHINORRHEA					◆◆◆◆◆				
◆◆◆◆◆◆			0						◆◆◆◆◆				
◆◆◆◆◆◆			0						◆◆◆◆◆				
◆◆◆◆◆◆			0						◆◆◆◆◆				
◆◆◆◆◆◆			0						◆◆◆◆◆				
◆◆◆◆◆◆			0						◆◆◆◆◆				
◆◆◆◆◆◆			0						◆◆◆◆◆				
◆◆◆◆◆◆			0						◆◆◆◆◆				
◆◆◆◆◆◆			0						◆◆◆◆◆				
◆◆◆◆◆◆			0						◆◆◆◆◆				
◆◆◆◆◆◆			0						◆◆◆◆◆				
◆◆◆◆◆◆			0						◆◆◆◆◆				
◆◆◆◆◆◆			0						◆◆◆◆◆				
◆◆◆◆◆◆			0						◆◆◆◆◆				
◆◆◆◆◆◆			0						◆◆◆◆◆				
◆◆◆◆◆◆			0						◆◆◆◆◆				
◆◆◆◆◆◆			0						◆◆◆◆◆				
◆◆◆◆◆◆			0						◆◆◆◆◆				
◆◆◆◆◆◆			0						◆◆◆◆◆				
◆◆◆◆◆◆			0						◆◆◆◆◆				
◆◆◆◆◆◆			0						◆◆◆◆◆				
◆◆◆◆◆◆			0						◆◆◆◆◆				
◆◆◆◆◆◆			0						◆◆◆◆◆				

Significant data were missing from this submission

Preferred Terms not consistently captured in the same System Organ Class

AETERM	Organ systems (SOC)
Conjunctivitis	EYE DISORDER or INFECTIONS AND INFESTATIONS
Respiratory infections; respiratory illness; bronchitis; COPD; ILI; influenza; many others	RESPIRATORY/PULMONARY/THORACIC or INFECTIONS AND INFESTATIONS
Hypertensive episodes	INVESTIGATIONS or VASCULAR DISORDERS or CARDIAC DISORDERS or NERVOUS SYSTEM DISORDERS
Phayingitis/sore throat	RESPIRATORY/PULMONARY/THORACIC or INFECTIONS AND INFESTATIONS
Fever and temp elevation	GENERAL CONDITIONS or ADMINISTRATION SITE REACTIONS or INVESTIGATIONS
Gastroenteritis	GASTROINTESTINAL DISORDERS or INFECTIONS AND INFESTATIONS

Sponsor submits preliminary datasets

- Approximately 2-4 months before the Action Due Date a sponsor informed CBER that they had accidentally submitted preliminary datasets to the BLA. There were no indicators that the datasets were preliminary or final.

- **Resulted in:**
  - **Multiple information requests**
  - **Resubmission of datasets**
  - **Creation of new datasets that show the differences between the preliminary and final datasets**
  - **Ultimately delayed approval**

Understanding where errors have occurred in SDTM datasets submitted to CBER and how to avoid them

1. Issues with data integrity
2. **Issues with datasets that don't follow SDTM rules**
3. Issues with data traceability

SDTM datasets should be validated prior to submission

CT0001	Value for AEACN not found in (ACN) CT codelist	Error	66
CT0002	Value for AESEV not found in (AESEV) CT codelist	Error	23662
CT0027	Value for AEOUT not found in (OUT) CT codelist	Error	2515
SD1082	AEACNOTH variable length is too long for actual data	Error	1
SD1082	AEBODSYS variable length is too long for actual data	Error	1
SD1082	AEDECOD variable length is too long for actual data	Error	1
SD0063	SDTM/dataset variable label mismatch	Warning	26
SD0065	USUBJID/VISIT/VISITNUM values do not match SV domain data	Warning	1357
SD0080	AE start date is after the latest Disposition date	Warning	360
SD0091	AEOUT is not 'FATAL', when AESDTH='Y'	Warning	50
SD1021	Unexpected character value in AETERM variable	Warning	126

- If data can not be corrected, a reasonable explanation must be provided in the SDRG
- Future submissions may be automatically delayed if significant validation errors occur

Deaths not indicated in AESDTH (permissible variable for results in death)

DOMAIN	AETERM	AEMODIFY	AEDECOD	AECAT	AEBODSYS	AESEV	AESER	AEACN	AEACNOTH	AERE	AEOUT	AESDTH	ESTDTC	AEENDTC	AESTDY	AEENDY	AEENRF
AE	SIGMOID V	SIGMOID V	VOLVULUS	ADVERSE E	GASTROINT	SEVERE	Y	DOSE NOT	PROC OR P	NONE	FATAL				27	32	
AE	RESPIRATO	RESPIRATO	RESPIRATO	ADVERSE E	RESPIRATO	SEVERE	Y	DOSE NOT	PROC OR P	NONE	FATAL				27	32	
AE	HYPOXIC R	HYPOXIC R	RESPIRATO	ADVERSE E	RESPIRATO	SEVERE	Y	DOSE NOT	HOSPITALI	NONE	FATAL				331	340	
AE	MELANOMA	MELANOMA	MALIGNANT	ADVERSE E	NEOPLASMS	SEVERE	Y	DOSE NOT	OTHER	NONE	FATAL				202	231	
AE	CEREBRAL	CEREBRAL	CEREBRAL	ADVERSE E	NERVOUS S	SEVERE	Y	DOSE NOT	HOSPITALI	NONE	FATAL				361	362	
AE	CONGESTIV	CONGESTIV	CARDIAC F	ADVERSE E	CARDIAC D	SEVERE	Y	DOSE NOT	OTHER	NONE	FATAL				190	190	
AE	LUNG CANC	LUNG CANC	LUNG NEOP	ADVERSE E	NEOPLASMS	MODERATE	Y	DOSE NOT	PHYSICIAN	NONE	FATAL				.	302	
AE	GUILLAIN	GUILLAIN	GUILLAIN-	ADVERSE E	NERVOUS S	SEVERE	Y	DOSE NOT	HOSPITALI	POSSIB	FATAL				228	231	
AE	MI	MI	MYOCARDIA	ADVERSE E	CARDIAC D	SEVERE	Y	DOSE NOT	HOSPITALI	NONE	FATAL				165	165	
AE	PNEUMONIA	PNEUMONIA	PNEUMONIA	ADVERSE E	INFECTION	SEVERE	Y	DOSE NOT	PROC OR P	NONE	FATAL				168	172	
AE	PANCREAS	PANCREAS	PANCREATI	ADVERSE E	NEOPLASMS	SEVERE	Y	DOSE NOT	AE WITHDR	NONE	FATAL				212	223	
AE	RESPIRATO	RESPIRATO	RESPIRATO	ADVERSE E	RESPIRATO	SEVERE	Y	DOSE NOT	HOSPITALI	NONE	FATAL				268	270	
AE	SEPSIS	SEPSIS	SEPSIS	ADVERSE E	INFECTION	SEVERE	Y	DOSE NOT	HOSPITALI	NONE	FATAL				133	133	
AE	EXACERBAT	EXACERBAT	IRRITABLE	ADVERSE E	GASTROINT	SEVERE	Y	DOSE NOT	PROC OR P	NONE	FATAL				131	133	
AE	INTRACRAN	INTRACRAN	HAEMORRHA	ADVERSE E	NERVOUS S	SEVERE	Y	DOSE NOT	HOSPITALI	NONE	FATAL				180	181	

- SDTMIG states - As long as no data was collected for Permissible variables, a sponsor is free to drop them and the corresponding descriptions from the Define-XML.
- The DTHFL (death flag) and DTHDTC (date/time of death) should also be utilized
- Ideally the DD (death details) domain in SDTMIG v3.2 should be utilized

Rule SD0088 states that "Subject Reference End Date/Time (RFENDTC) in DM should be populated for all randomized subjects, those where Planned Arm Code (ARMCD) is not equal to 'SCRNFAIL' or 'NOTASSGN'."

dm.xpt

	DOMAIN	SUBJID	RFSTDTC	RFENDTC	SITEID	INVID	COUNTRY
1	DM	[redacted]			[redacted]	[redacted]	[redacted]
2	DM		2014-02-				
3	DM		2014-03-	2014-08-3			
4	DM		2014-02-				
5	DM		2014-03-				
6	DM		2014-03-				
7	DM		2014-03-				
8	DM		2014-02-				
9	DM		2014-03-				
10	DM		2014-03-				

- This submission had 1424 warnings and applicant did not explain why the Subjects who were randomized had a null value.

Rule SD0080 states that "Start Date/Time of Adverse Event (AESTDTC) should be **less than or equal to** the Start Date/Time of the latest Disposition Event (DSSTDTC)."

	DOMAIN	USUBJID	DSDECOD	DSCAT	EPOCH	DSSTDTC
41	DS	[redacted]16	CONTINUIN	PROTOCOL	Vaccinat	2014-03-1

	DOMAIN	USUBJID	AEDECOD	AECAT	EPOCH	AESTDTC
3	AE	[redacted]16	Pallor	C	Vaccinat	2014-08-1

- Sponsor provided an explanation that "This trial was ongoing at the database lock and vital signs records were still collected after the latest disposition date."

AEs that become Serious AEs (SAEs)

AE is listed on more than one line even though it describes the same event can cause confusion (e.g. extra counts in the numerator and denominator).

AETERM	AELLT	AELLTCD	AEDECOD	AESOCCD	AESER	AESTDTC	AEENDTC	AESTDY	AEENDY	AEDUR
Sepsis	SEPSIS	10040047	SEPSIS	1002188	Y	[redacted]		241	242	P2D
Sepsis	SEPSIS	10040047	SEPSIS	1002188	N			240	240	P1D

According to SDTMIG (v 3.2) - The structure of the AE domain is one record per adverse event per subject.

- We prefer that the event be recorded or "collapsed" to the highest level of severity, causality, seriousness and outcome
- The FA domain should be utilized to provide the additional details for the AE

Use of LLT instead of PT for reactogenicity events

Table 13 Solicited general adverse events

Fatigue
Fever
Gastrointestinal symptoms †
Headache
Myalgia
Shivering

According to MedDRA - LLT 'shivering' maps to the PT of 'chills'. These terms should be combined on the diary card. Example below shows a subject who was in the 7 day diary card subset having chills documented as an unsolicited AE during the 7 days after vaccination.

5	SHIVER	Shiver	10040558	Chills	10008531	MODERATE	RECOVERE	[redacted]	1	2

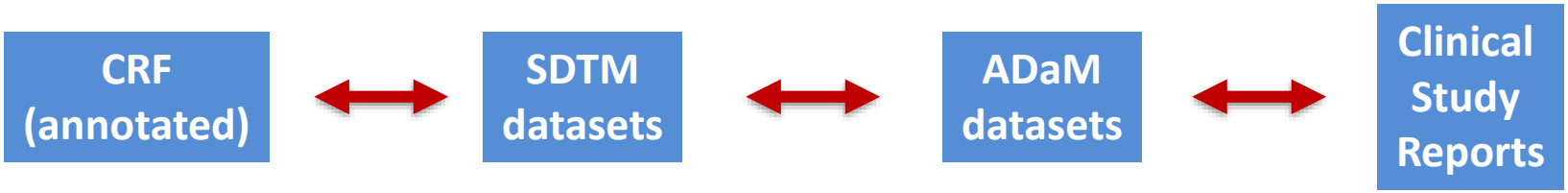
AETERM	AELLT	AELLTCD	AEDECOD	AEPTCD	AESEV	AEOUT	[redacted]	AESTDY	AEENDY
SHIVER	Shiver	10040558	Chills	10008531	SEVERE	RECOVERE		55	56
CHILLS	Chills	10008531	Chills	10008531	SEVERE	RECOVERE		55	56

This subject also had an AE that was duplicated because of use of two LLTs for "chills"

Understanding where errors have occurred in SDTM datasets submitted to CBER and how to avoid them

1. Issues with data integrity
2. Issues with datasets that don't follow SDTM rules
3. **Issues with data traceability**

Data Traceability



Data should be traceable from the collection documents (e.g. Diary Cards, CRF) to the raw datasets (SDTM) to the analysis datasets (ADaM) and to the Clinical Study Reports

Diary Card "Recreated" by Study Coordinator

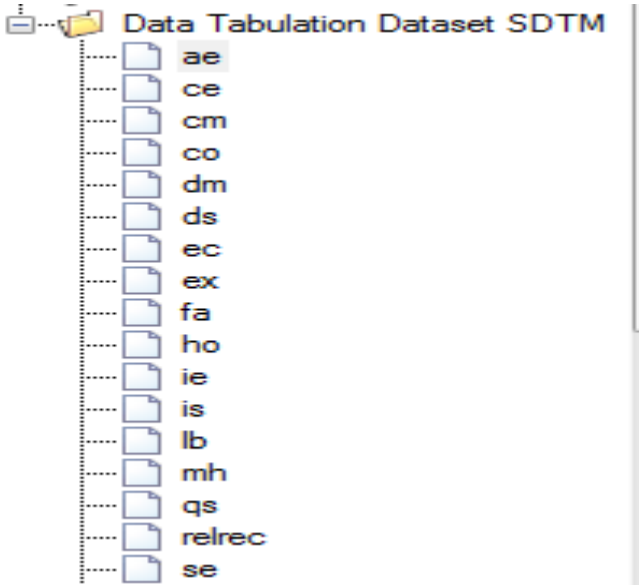
[redacted] DIARY CARD [redacted] WAS RECREATED BY STUDY COORDINATOR

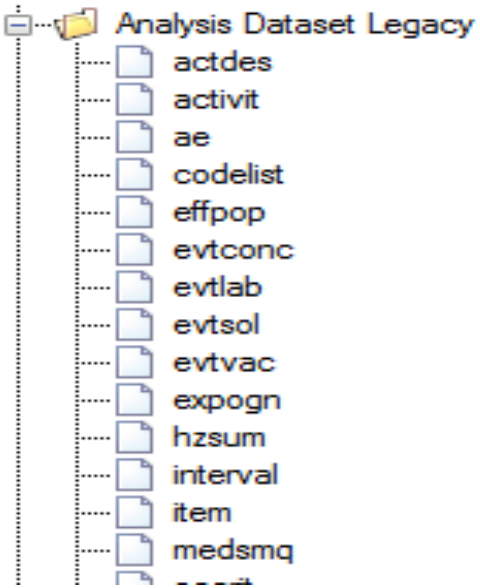
[redacted]

97.9	0	0	NO	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE
98.6	0	0	NO	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE
98.6	0	0	NO	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE
98.7	0	0	NO	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE
98.6	0	0	NO	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE
96.8	0	0	NO	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE
98.6	0	0	NO	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE
98.6	0	0	NO	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE

Diary Card was "recreated" 10 months after vaccination. It is unclear how temperature value were obtained. It is also unclear if a reactogenicity event Value of "none" means it did not occur or if it was not gathered.

Data submitted in SDTM format and analyses performed on the legacy data





- Analyses code (SAS) not compatible with the SDTM data.
- Significant effort for CBER to verify any calculations as a result.

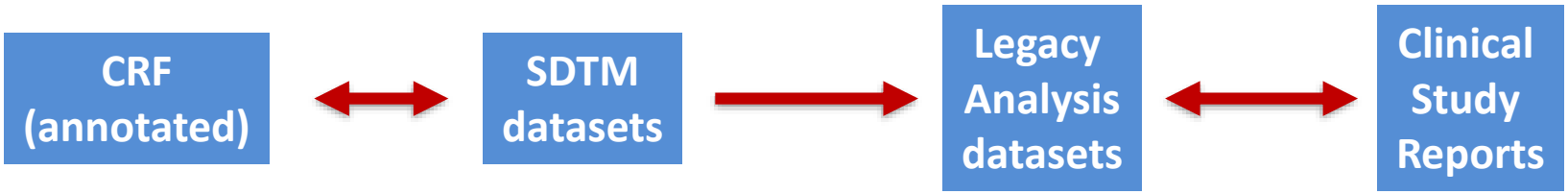
Death indicated in SDTM dataset, not present in Legacy analysis dataset

STUDYID	DOMAIN	USUBJID	AESEQ	AEGRPID	AESPID	AELNKID	AETERM	AEMODIFY	AELLT
[redacted]	AE	[redacted]	1		1		ATRIAL FIBRILLATION PAROXYSMAL	PAROXYSMAL ATRIAL FIBRILLATION	Paroxysmal atrial fibrillation
	AE		2	1	1-1		HYPOTENSION		Hypotension
	AE		3	1	1-2		DEATH	DEATH CAUSE UNKNOWN	Unknown cause of death

This subject was not identified in the analysis data set as having died

Reviewers had no way to reconcile thediscrepancy because the analysis was not in ADaM

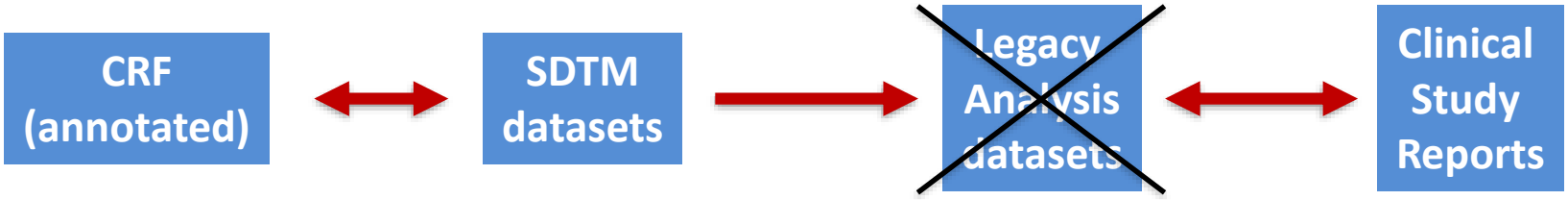
Data Traceability



- Data traceability is lost when legacy analysis datasets are submitted with SDTM datasets

  Significant effort for CBER to verify any calculations from the Legacy Analysis as a result.

Data Traceability



- Data traceability is lost when legacy analysis datasets are submitted with SDTM datasets

  Significant effort for CBER to verify any calculations from the Legacy Analysis as a result.

Take Home Recommendations

1. Communicate with your review team about data collection and dataset format early in product development
   - Submit the CBER Study Data Standardization Plan (SDSP) by the End of Phase 2 Meeting
2. Ensure data quality prior to submitting your BLA
   - Validate your SDTM and ADaM datasets prior to submission
   - Correct warnings and errors
   - Warnings/errors that cannot be corrected should be identified and a rationale provided in SDRG/ADRG

Take Home Recommendations

3. Provide a clear, traceable pathway from the primary collection documents (e.g. Diary Cards, CRF) to the raw datasets (SDTM) to the analysis datasets (ADaM).

4. CBER recommends submitting annotated CRFs with your clinical trial protocols.

5. Datasets should not have empty cells. It is unclear if an empty cell is a null result or data not collected.

Documents Referenced Today

- Guidance for Industry "Providing Regulatory Submissions in Electronic Format –Standardized Study Data"
- Study Data Technical Conformance Guide
- Technical Rejection Criteria for Study Data
- CBER Study Data Standardization Plan (SDSP) Checklist - Contact Regulatory Project Manager

Contact Information

CBER CDISC Contact:

CBER.CDISC@fda.hhs.gov

U.S. FOOD & DRUG ADMINISTRATION

Perspectives from CBER's Office of Compliance and Biologics Quality

Bioresearch Monitoring Experiences with Study Data Submissions to CBER

Bhanu Kannan
FDA Center for Biologics Evaluation and Research
Office of Compliance and Biologics Quality (OCBQ)
Division of Inspections and Surveillance
July 13, 2017

Agenda

- FDA Data Standard Requirements
- CBER Bioresearch Monitoring Inspections
- Study Data Collection and Submission
- CBER Experiences with Submitted Data
- Suggestions for Sponsors
- FDA resources

FDA Study Data Standard Requirements-1

- Why should submitted study data be standardized?
  - Helps streamline FDA review process
  - Enables consistent use of analysis tools

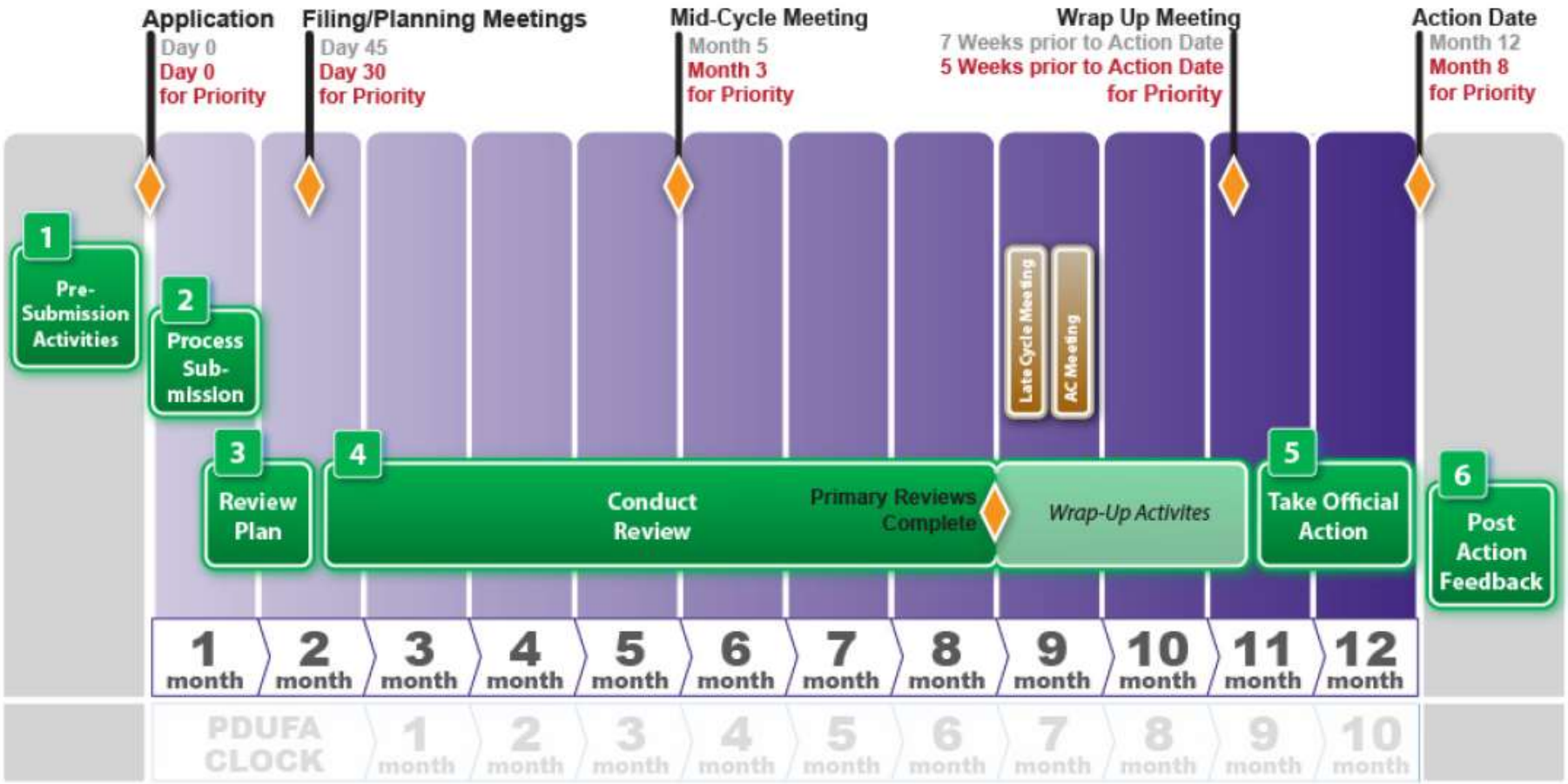
FDA Study Data Standard Requirements Resources Cited

- Guidance for Industry - Providing Regulatory Submissions in Electronic Format -Standardized Study Data
- CBER and CDER study data submissions link
- Factsheet-Study data standards

CBER Bioresearch Monitoring (BIMO) Branch

- Conduct pre-license and pre-approval data verification inspections
- Investigate complaints
- Answer questions about Good Clinical Practice (GCP)
- Help evaluate concerns about data integrity
  - Clinical investigators
  - Sponsor/Monitor/Contract Research Organizations /Sponsor Investigators
  - Institutional Review Boards
  - Good Laboratory Practice (GLP)/Nonclinical Lab

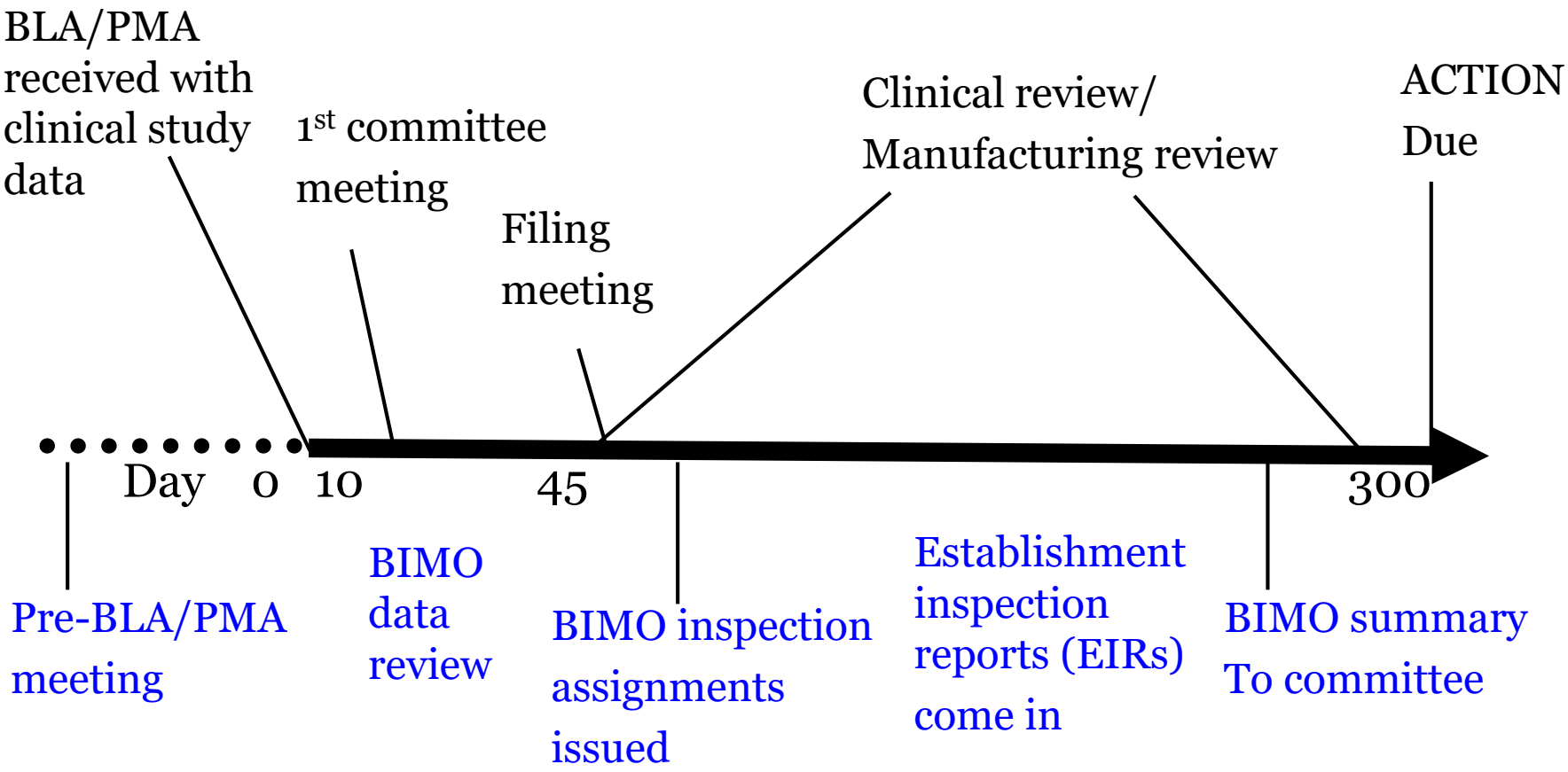
21st Century Review



From CDER's *21st Century Review Process Desk Reference Guide*

BLA Timeline-BIMO Review (10 month review period)

Priority (6 month) applications adjusted accordingly



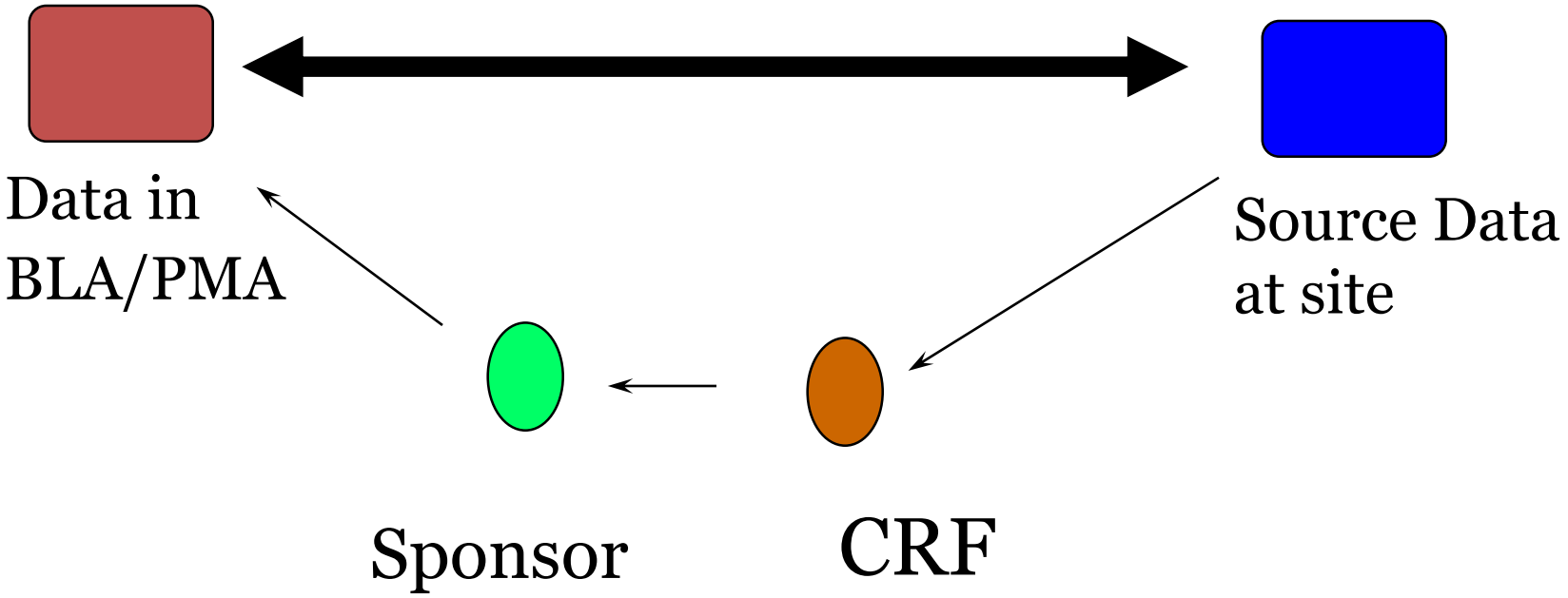
CBER BIMO site selection process for inspection-1

- BLA/sBLA/ANDA data tables
- Contents of the assignment-examples of data to be verified include
  - Adverse events
  - Protocol deviations
  - Subject eligibility
  - Blinding
  - Efficacy and Safety Endpoints

CBER BIMO site selection process for inspection-2

- Factors in site selection include, but not limited to
  - Subject distribution and disposition
  - Subject exclusions and discontinuation
  - Protocol deviations data
  - Inconsistent data for a site
    - Increased efficacy
    - Decreased incidence of adverse events
    - Randomization cannot be reconstructed
  - Inspection history of investigators
  - GCP problems reported by sponsor
  - Number of sub-investigators/satellite sites
  - Pending workloads in FDA geographic regions

Comparison of Data in BLA/PMA to Source During the Inspection



Challenges in data extraction from BLA data submissions for BIMO site selection

- SITEID variable was not included/available in all datasets except DM (Demography) dataset.
- Dataset submitted did not include standardized data variables. (see Slides 12 and 15)
- Protocol deviations submitted as pdf listings (see Slide 13)
- Subjects were not listed using standardized USUBJID variable. Instead subjects were listed under SUBJID/PID/PATIENT variable. (see Slide 14)
- Definition (Define) files were not user friendly and the definitions of dataset variables were not available. (see Slide 16)
- Critical endpoint data (rows of data) were missing. Possibly due to inadequate data validation by sponsor? (from previous talk)

More surprises if there were no Pre-BLA meetings!

CBER BIMO Experiences with Submitted Data-1

Data submitted as WELIM dataset instead of DV dataset for protocol deviations. Non-standardized variables were used.

	PID	CENTER	ELIM_V	ELIMCODE	ELI_TYPE
1	1	123	.		
2	2	123	1	111	AB
3	3	123	.		
4	4	123	.		
5	5	123	.		
6	6	456	.	112	AB
7	6	456	.	113	AB
8	6	456	.	114	AB
9	7	456	1	112	AB
10	8		1	112	AB
11	9	456	.	114	AB
12	10	456	.		

CBER BIMO Experiences with Submitted Data-2

Protocol deviations were submitted as pdf listings

Country	Site number	Issue category	Description of protocol deviation
Poland	111	Protocol deviation-Informed consent	On ICF there is incorrect date stated by parent, only year, no month and date for subject 12345
China	112	Protocol deviation-Other	In source documentation there is missing data on when the drug was returned, numbers of returned, DUNs and drug accountability (used / unused / lost vials).
United States	113	Protocol deviation-other	The normal ranges used in the local lab report did not consider the age difference. The ranges that were used in the report and transcribed into EDC reflect only the adult's range but not for the specific young age. It's the internal computer system issue of the study site because the normal range for different age group is actually available at the site, but just not on the lab reports.

The last row acknowledges potential issues in the integration of different computer systems used during data collection

CBER BIMO Experiences with Submitted Data-3

- Protocol deviation submitted in non-standard format and with incomplete data

STDYSITE	PATIENT	REASON 1	REASON 2
111	123456	Subject withdrawal, because it is unclear whether subject received the vaccine. Subject #123456 had the same randomization sticker on the source document. Undetermined which vaccine was received by wh	

- Incomplete information for a protocol deviation under REASON 1
- Instead of USUBJID the dataset included the variable PATIENT

CBER BIMO Experiences with Submitted Data-4

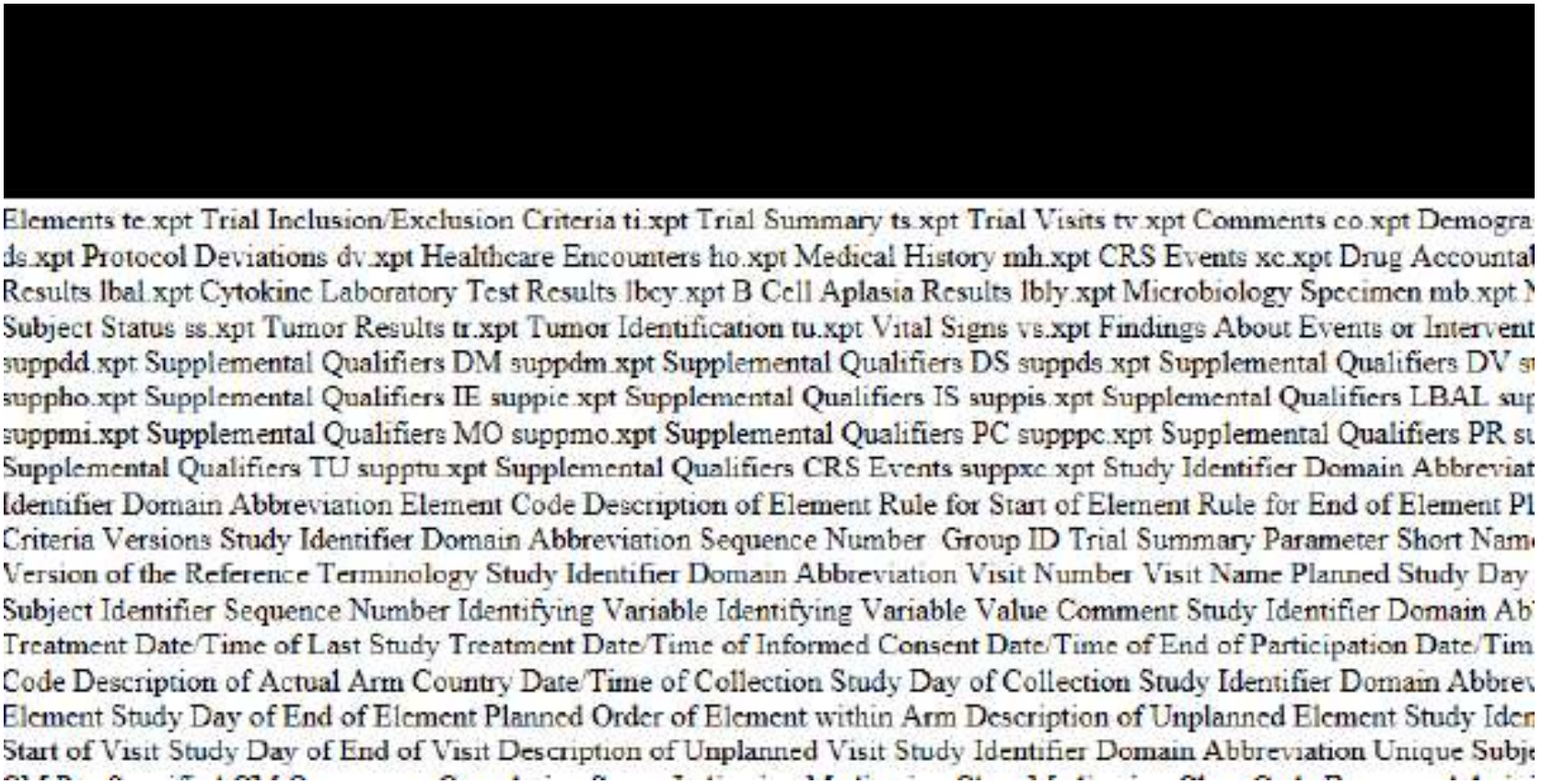
- Protocol deviations were submitted as "Comments" in COMMENTS (CO) dataset

RDOMAIN	USUBJID	COVAL
MB	100-5001-123456	No nasal culture swab received
QS	100-5001-123457	Based on the documentation provided, the subject can be considered immuno-competent.

- In another study-no corresponding definition submitted for a column variable in ADSL dataset-inadequate validation?

CBER BIMO Experiences with Submitted Data-5

Example of a Definition file that is not useful to the review:



Elements te.xpt Trial Inclusion/Exclusion Criteria ti.xpt Trial Summary ts.xpt Trial Visits tv.xpt Comments co.xpt Demogra
ds.xpt Protocol Deviations dv.xpt Healthcare Encounters ho.xpt Medical History mh.xpt CRS Events xc.xpt Drug Accountal
Results lbal.xpt Cytokine Laboratory Test Results lbcy.xpt B Cell Aplasia Results lbly.xpt Microbiology Specimen mb.xpt
Subject Status ss.xpt Tumor Results tr.xpt Tumor Identification tu.xpt Vital Signs vs.xpt Findings About Events or Intervent
suppdd.xpt Supplemental Qualifiers DM suppdm.xpt Supplemental Qualifiers DS suppds.xpt Supplemental Qualifiers DV s
suppho.xpt Supplemental Qualifiers IE suppie.xpt Supplemental Qualifiers IS suppis.xpt Supplemental Qualifiers LBAL sup
suppmi.xpt Supplemental Qualifiers MO suppmo.xpt Supplemental Qualifiers PC supppc.xpt Supplemental Qualifiers PR su
Supplemental Qualifiers TU supptu.xpt Supplemental Qualifiers CRS Events suppxc.xpt Study Identifier Domain Abbreviat
Identifier Domain Abbreviation Element Code Description of Element Rule for Start of Element Rule for End of Element Pl
Criteria Versions Study Identifier Domain Abbreviation Sequence Number Group ID Trial Summary Parameter Short Nam
Version of the Reference Terminology Study Identifier Domain Abbreviation Visit Number Visit Name Planned Study Day
Subject Identifier Sequence Number Identifying Variable Identifying Variable Value Comment Study Identifier Domain Ab
Treatment Date/Time of Last Study Treatment Date/Time of Informed Consent Date/Time of End of Participation Date/Tim
Code Description of Actual Arm Country Date/Time of Collection Study Day of Collection Study Identifier Domain Abbrev
Element Study Day of End of Element Planned Order of Element within Arm Description of Unplanned Element Study Iden
Start of Visit Study Day of End of Visit Description of Unplanned Visit Study Identifier Domain Abbreviation Unique Subje

CBER BIMO Experiences with Submitted Data-6

Examples of "Do's"

- A DV dataset and a good "definition" file

STUDYID	DOMAIN	USUBJID	DVDECOD	DVTERM	DVCAT
AB1-C11	DV	AB1-C11-101001	Informed Consent	Minor PD - Subject 101001 inadvertently dated the Data Privacy Consent Form with the incorrect year.	
AB1-C11	DV	AB1-C11-101001	Visit Schedule	Visit not performed as scheduled. Week 32 was not conducted within ± 14 days of expected visit date.	
AB1-C11	DV	AB1-C11-101002	Visit Schedule	Visit not performed as scheduled. Week 28 was not conducted within ± 14 days of expected visit date.	
AB1-C11	DV	AB1-C11-101002	Procedures/Tests	MINOR PD: Site shipped week 0 serum on 22May2016 and was logged out on shipping log. Sample was not receive	
AB1-C11	DV	AB1-C11-101002	Procedures/Tests	Minor PD: Site staff inadvertently did not capture subject 101002's temperature during their Screening Visit.	
AB1-C11	DV	AB1-C11-101002	Procedures/Tests	Partial Vital signs completed at visit Screening.	
AB1-C11	DV	AB1-C11-101003	Visit Schedule	Major PD- Subject 101003 had their Week 4 visit OOW.	
AB1-C11	DV	AB1-C11-101003	Visit Schedule	IP injection not administered as scheduled at visit Week 4.	Vaccine given outside protocol specified ...

DM (Demographics)

DM (Demographics) -- SPECIAL PURPOSE								dm.xpt
Name	Label	Key	Type	Length	Controlled Terms or Format	Origin	Role	Comment
STUDYID	Study Identifier	1	text	6	["AB1-C11"]	CRF Page 1	Identifier	AB1-C11
DOMAIN	Domain Abbreviation		text	2	["DM"]	Assigned	Identifier	
USUBJID	Unique Subject Identifier	2	text	15		Derived	Identifier	See Method (MT.CM.DM.USUBJID)
SUBJID	Subject Identifier for the Study		text	7		CRF Page 10	Topic	
RFSTDTC	Subject Reference Start Date/ Time		datetime		ISO 8601	CRF Page 12, 13, 14	Record Qualifier	
RFENDTC	Subject Reference End Date/Time		datetime		ISO 8601	CRF Page 42, 43, 44, 45	Record Qualifier	

Suggestions for Good Quality Data Submission

- Study specific data collection by sponsor
  - Sponsor develops protocol specific CRFs
- Advance discussions with CBER about esource data collection and/or data extraction from electronic data capture (EDC) systems and data integration
- Advance discussion of study data standardization plan (SDSP) including the domains and variables to be submitted early on during the study

Good quality data that comes through the FDA gateway could potentially avoid delay in our inspection site selection process

Information For Industry

Click for:

- CDER eData Team at: eDATA@fda.hhs.gov
- CBER CDISC Contact: CBER.CDISC@fda.hhs.gov
- Guidance for Industry: Computerized Systems Used in Clinical Investigations
- Guidance for Industry: Electronic Source data in Clinical Investigations
- Guidance for Industry: Providing Regulatory Submissions in Electronic Format – Standardized Study Data
- Study Data Technical Conformance Guide
- Technical Rejection Criteria for Study Data
- PDF of today's slides
- Email any remaining questions to us at: CDERSBIA@fda.hhs.gov

Open Q&A begins shortly – type in your questions now.

Click Here for Evaluation and Certificate

Learn about other resources from CDER Small Business & Industry Assistance:
Visit Our Website!