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.

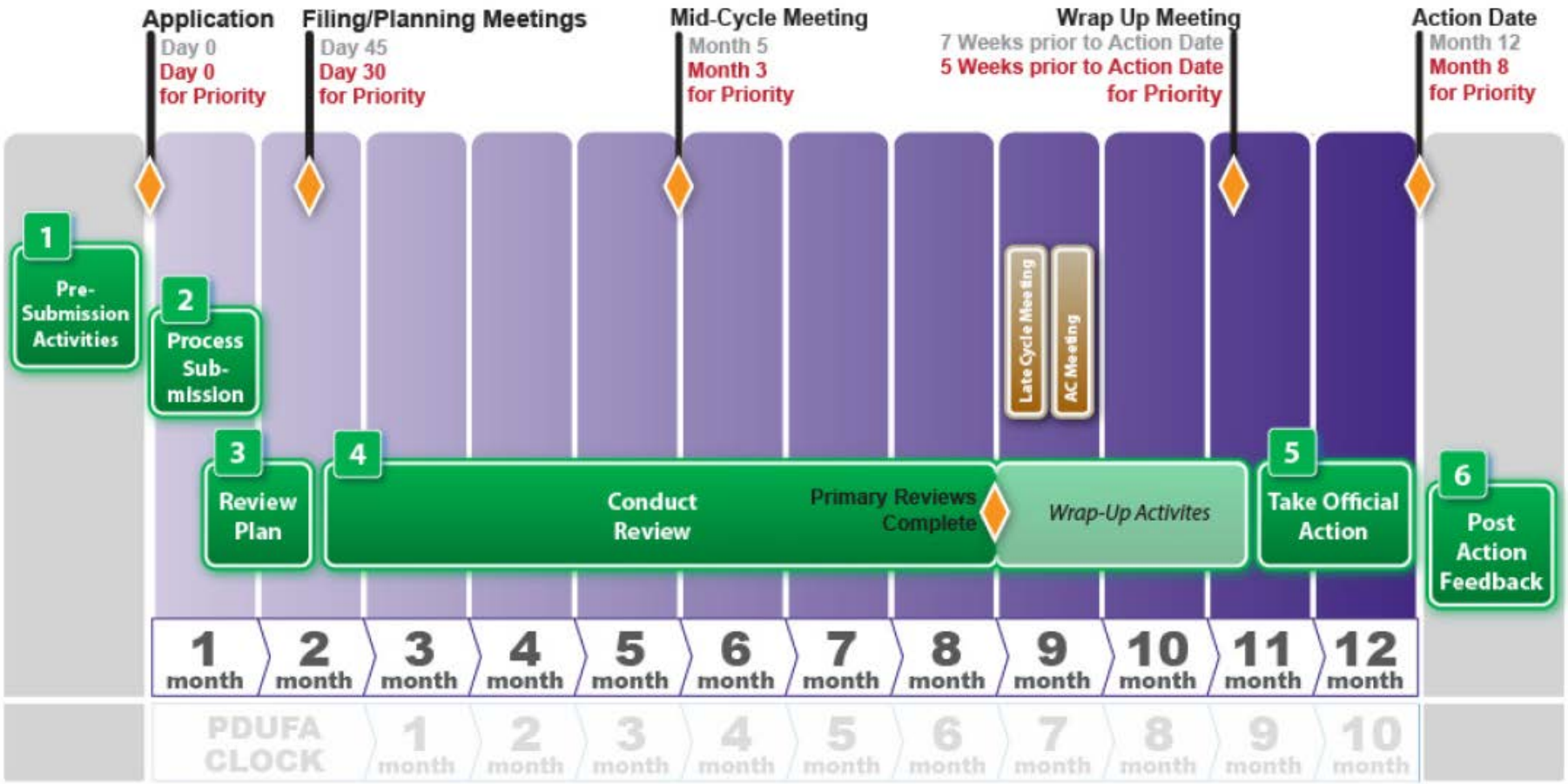
FDA DISCLAIMER

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

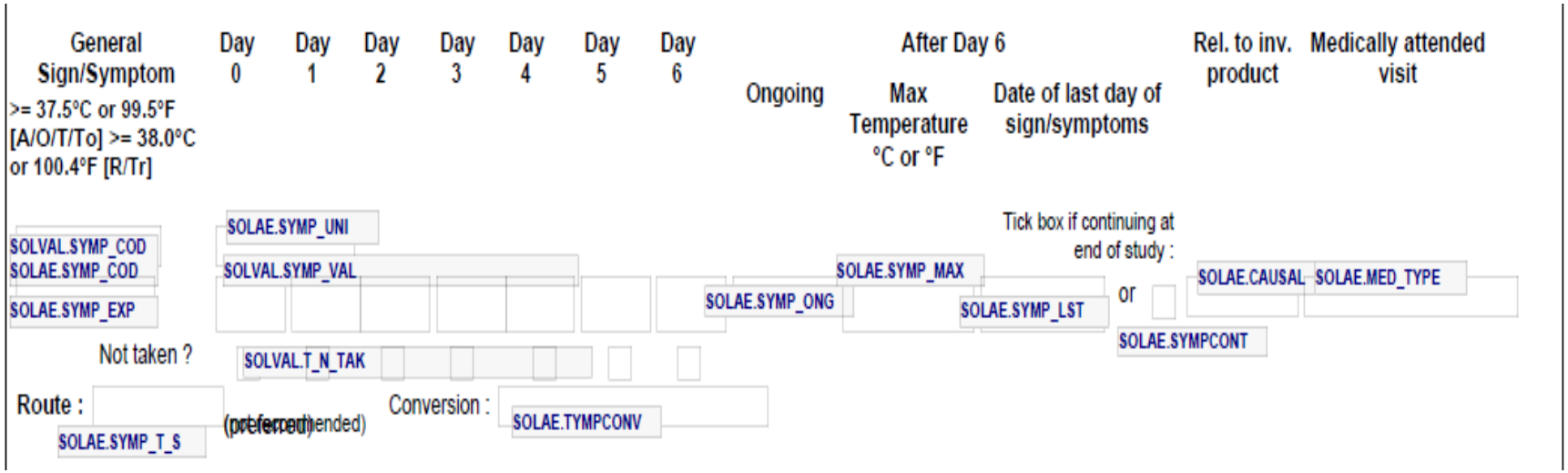
Complete this form and then enter details in the following forms.		
Solicited Systemic Reactions - Presence		
Did the subject experience any of the following reactions between Day 00 and Day 14 after the vaccination:		
1.	Headache?	◯ Yes ◯ No
2.	Malaise?	◯ Yes ◯ No
3.	Myalgia?	◯ Yes ◯ No
4.	Asthenia?	◯ 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)	☒	

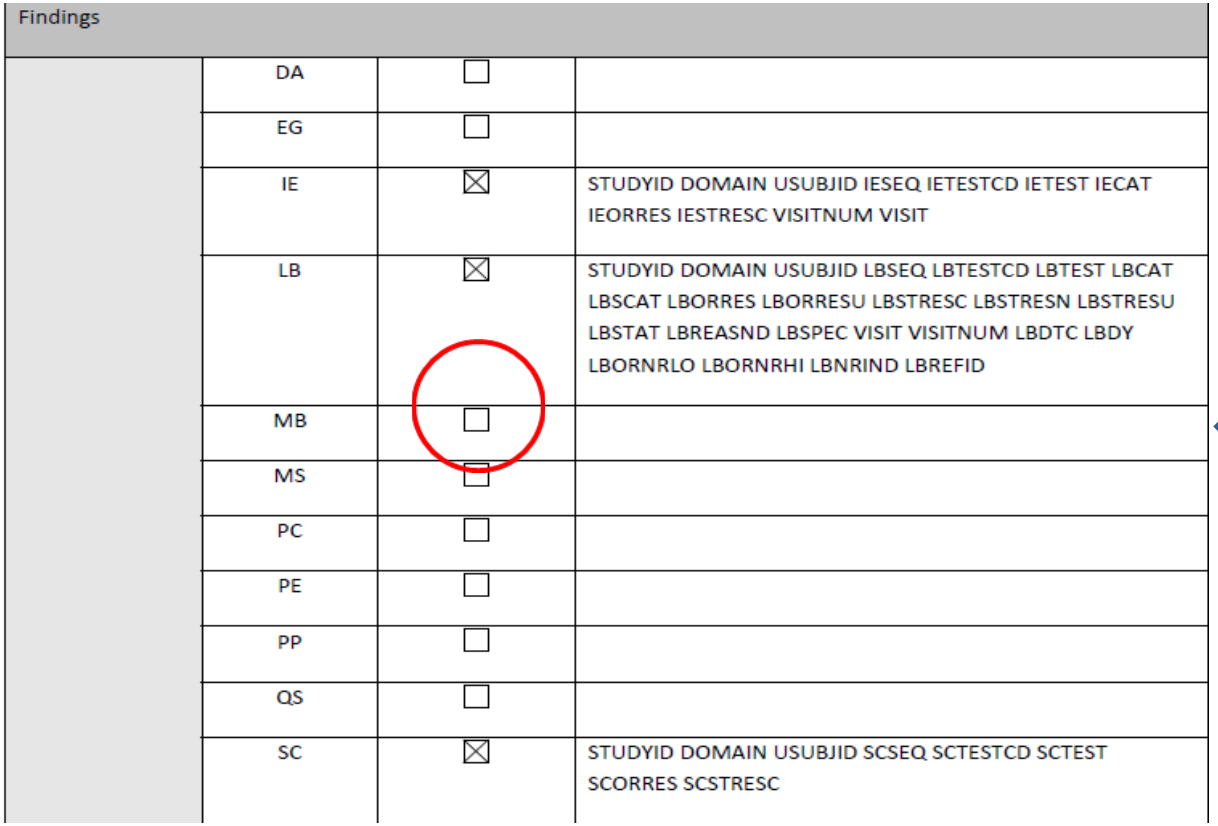
Discuss with review division before utilizing custom domains

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
	AE		1	INJECTION SITE SWELLING	Injection site sw...	Solicited	Administration site	General disorders and administration site conditions	Grade 2	N		None	Related
	AE		2	INJECTION SITE SWELLING	Injection site sw...	Solicited	Administration site	General disorders and administration site conditions	Grade 2	N		None	Related
	AE		3	INJECTION SITE SWELLING	Injection site sw...	Solicited	Administration site	General disorders and administration site conditions	Grade 1	N		None	Related
	AE		1	COUGH	Cough	Unsolicited	Systemic	Respiratory, thoracic and mediastinal disorders	Grade 1	N		None	Not related
	AE		1	DERMATITIS PHOTO CONTACT	Photosensitivity ...	Unsolicited	Systemic	Skin and subcutaneous tissue disorders	Grade 1	N		Health care provider cont. + med.	Not related
	AE		2	DERMATITIS	Dermatitis	Unsolicited	Systemic	Skin and subcutaneous tissue disorders	Grade 1	N		Health care provider cont. + med.	Not related
	AE		3	INJECTION SITE PAIN	Injection site pain	Solicited	Administration site	General disorders and administration site conditions	Grade 1	N		None	Related
	AE		4	HEADACHE	Headache	Solicited	Systemic	Nervous system disorders	Grade 1	N		None	Related
	AE		5	HEADACHE	Headache	Solicited	Systemic	Nervous system disorders	Grade 1	N		None	Related
	AE		6	MALAISE	Malaise	Solicited	Systemic	General disorders and administration site conditions	Grade 1	N		None	Related
	AE		7	MYALGIA	Myalgia	Solicited	Systemic	Musculoskeletal and connective tissue disorders	Grade 1	N		None	Related
	AE		1	COMMON COLD	Nasopharyngitis	Unsolicited	Systemic	Infections and infestations	Grade 2	N		Health care provider cont. + med.	Not related
	AE		2	PHARYNGITIS	Pharyngitis	Unsolicited	Systemic	Infections and infestations	Grade 2	N		Health care provider cont. + med.	Not related
	AE		3	TONSILLITIS	Tonsillitis	Unsolicited	Systemic	Infections and infestations	Grade 2	N		Health care provider cont. + med.	Not related
	AE		4	HEADACHE	Headache	Solicited	Systemic	Nervous system disorders	Grade 1	N		None	Related
	AE		5	HEADACHE	Headache	Solicited	Systemic	Nervous system disorders	Grade 2	N		Health care provider cont. + med.	Related
	AE		6	HEADACHE	Headache	Solicited	Systemic	Nervous system disorders	Grade 1	N		Health care provider cont. + med.	Related
	AE		7	MALAISE	Malaise	Solicited	Systemic	General disorders and administration site conditions	Grade 2	N		Health care provider cont. + med.	Related
	AE		8	MALAISE	Malaise	Solicited	Systemic	General disorders and administration site conditions	Grade 3	N		Health care provider cont. + med.	Related
	AE		9	MALAISE	Malaise	Solicited	Systemic	General disorders and administration site conditions	Grade 1	N		Health care provider cont. + med.	Related
	AE		10	ABDOMINAL PAIN	Abdominal pain	Unsolicited	Systemic	Gastrointestinal disorders	Grade 1	N		Health care provider cont. + med.	Not related
	AE		1	HEADACHE	Headache	Solicited	Systemic	Nervous system disorders	Grade 1	N		None	Related
	AE		2	MALAISE	Malaise	Solicited	Systemic	General disorders and administration site conditions	Grade 1	N		None	Related
	AE		3	RHINORRHEA					◆◆◆◆◆				
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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	SHIVE	Shiver	10040558	Chills	10008531	MODERATE	RECOVERE	1	2

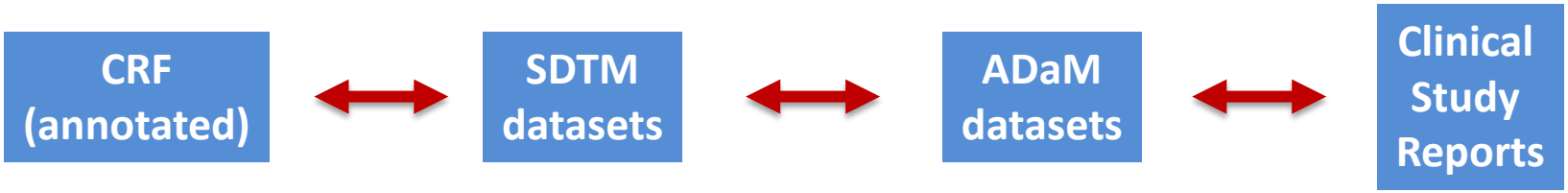
AETERM	AELLT	AELLTCD	AEDECOD	AEPTCD	AESEV	AEOUT	AESTDY	AEENDY
SHIVER	Shiver	10040558	Chills	10008531	SEVERE	RECOVERE	55	56
CHILLS	Chills	10008531	Chills	10008531	SEVERE	RECOVERE	55	56

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

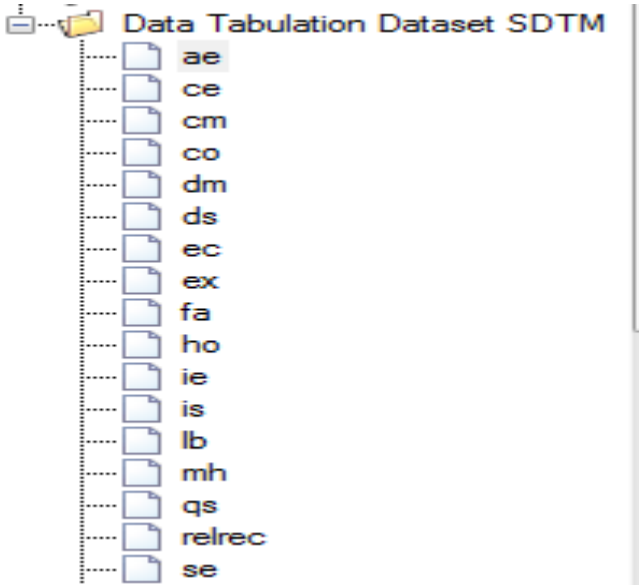
[redacted] DIARY CARD [redacted] WAS RECREATED BY STUDY COORDINATOR

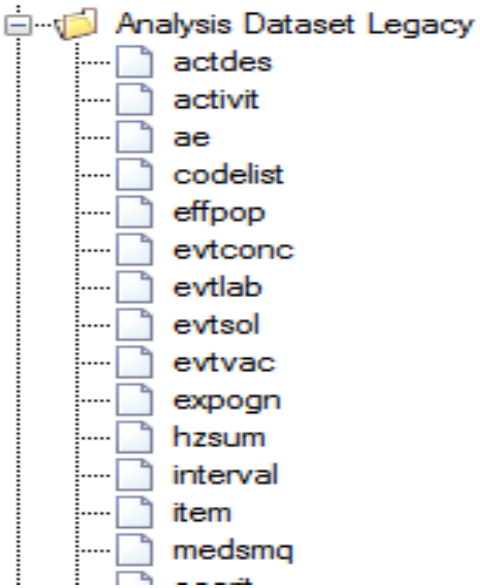
[redacted]

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.

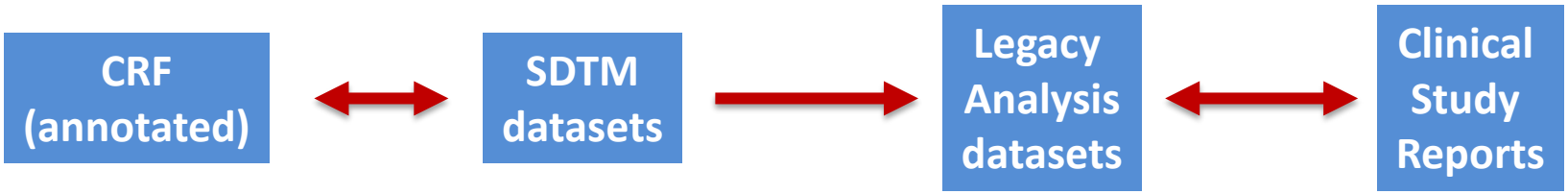
Death indicated in SDTM dataset, not present in Legacy analysis dataset

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

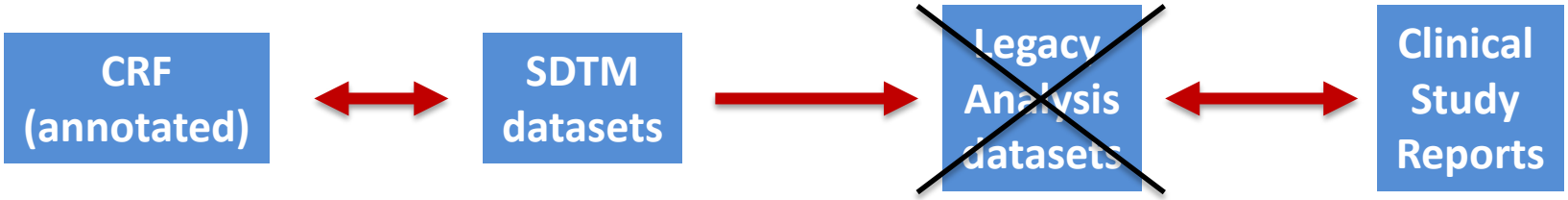
Data Traceability



- 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