Getting from CDASH to ADaM

LPO Support Webinar

28 May 2019

NIH NATIONAL CANCER INSTITUTE

Upon completion of this webinar, you should be able to

- Identify the high level purpose of CDASH, SDTM and ADaM
- Explain the relationships between CDASH -> SDTM -> ADaM
  - ➢ And some potential pitfalls of not planning ahead for data handoffs
- Discuss ideas for proactively documenting cross-functional data requirements that will support an implementation of standards from data collection through analysis

High Level Purpose of CDASH, SDTM and ADaM

Efficiency and Reuse

- CDASH EDC specifications (Rave builds)
- SDTM dataset creation
- ADaM datasets = CSR TLF generation (One Proc Away)

Support Regulatory Review

- Traceability through the data lifecycle
- Predictability and Familiarity (where to find data)
- Supports review software

Data Aggregation

- Make data useful beyond a single study
- Learn more from the data

Requirements for FDA Submissions

- **SDTM is required for data tabulations in regulatory submissions**
  - Align data collection with SDTM Requirements as much as possible
    - Concept definitions
    - Use of terminology
    - Naming conventions
    - Organization of data by topic

CDASH is harmonized with SDTM in this way

- **ADaM is required for analysis data in regulatory submissions**
  - ADaM uses SDTM as its "source"
  - *If data collection is aligned with SDTM (e.g., CDASH), and SDTM can be produced more efficiently, ADaM will have quicker access to SDTM source and will be fully traceable back to data collection*

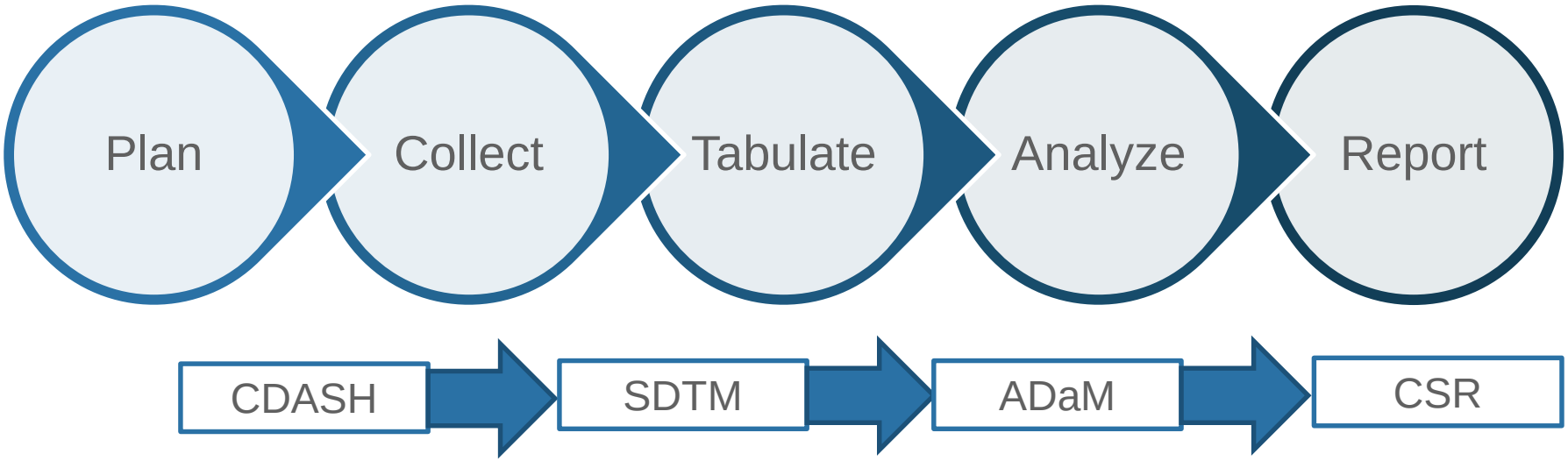
Traceability in the data is essential to FDA

Timeliness in preparing submission is essential to Sponsor

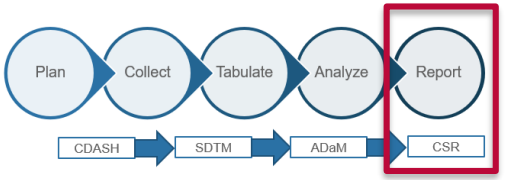
Data Lifecycle Connections

For timely preparation of traceable, standardized review datasets:

- Begin by planning for CDASH *in the protocol*
- Develop CDASH data collection instruments
- Tabulate more efficiently and effectively in SDTM
- Provide SDTM to ADaM in a timely manner for analysis and reporting



What are the data lifecycle connections?



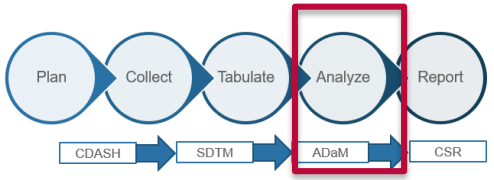
Clinical Study Report (TLFs)

- **Example CSR Table: All AEs by SOC**
- **Begin with the end in mind:** What data should be collected?
  - Perform the analysis described in the Protocol and SAP
  - Provide adequate safety information
  - Meet other regulatory and science requirements for this study
  - **Present the collected and analyzed data in a standard way**

Table 12. All Adverse Events Grouped by Body System

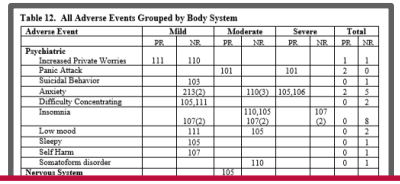
Adverse Event	Mild		Moderate		Severe		Total	
	PR	NR	PR	NR	PR	NR	PR	NR
Psychiatric								
Increased Private Worries	111	110					1	1
Panic Attack			101		101		2	0
Suicidal Behavior		103					0	1
Anxiety		213(2)		110(3)	105,106		2	5
Difficulty Concentrating		105,111					0	2
Insomnia		107(2)		110,105 107(2)		107 (2)	0	8
Low mood		111		105			0	2
Sleepy		105					0	1
Self Harm		107					0	1
Somatoform disorder				110			0	1
Nervous System			105					
Headache			109	106	109		3	1
Decrease in Vision		213					0	1
Dizziness		213					0	1
Gastrointestinal								
Vomiting	108						1	0
Abdominal Cramps/Pain		112				108	0	2
Nausea		111					0	1
Diarrhea		213					0	1
General								
Body Pain						106	0	1
Fatigue	109(2)	108	109	107			3	2
Respiratory, Thoracic, and Mediastinal								
Bronchial Disorder				106			0	1
Dyspnea		112					0	1
Pneumonia				213(2)			0	2
Metabolism and Nutrition								
Lack of appetite		108					0	1
Anemia/iron deficiency		109					0	1
Hypothyreosis				110			0	1
Musculoskeletal & Connective Tissue								
Leg cramps		109					0	1
Neck pain				109			0	1
Ear and Labyrinth								
Otitis media		109					0	1
Infections and Infestations								
Urinary Infection			107				1	0
Angina Tonsillaris				108			0	1
Injury, Poisonings and Procedural								
Injury to left arm				101			0	1

What are the data lifecycle connections?



ADaM should be One PROC Away from TLFs

- Example ADaM ADAE
  - Analysis data creates TLFs in Clinical Study Report
  - ADaM is specified (by FDA) as the standard for analysis datasets
- SAS: One Proc Away from TLF



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Low mood		111		105			0	2
Sleepy		105					0	1
Self Harm		107					0	1
Somatoform disorder				110			0	1
Nervous System			105					

5.2 Sample ADAE Variable Metadata

Table 5.2.1 Example of ADAE Variable Metadata

Dataset Name	Variable Name	Variable Label	Variable Type	Display Format	Codelist / Controlled Terms	Source / Derivation
ADAE	STUDYID	Study Identifier	text	$3		AE.STUDYID
ADAE	USUBJID	Unique Subject Identifier	text	$11		AE.USUBJID
ADAE	AESEQ	Sequence Number	integer	3.0		AE.AESEQ
ADAE	AETERM	Reported Term for the Adverse Event	text	$200		AE.AETERM
ADAE	AEDECOD	Dictionary-Derived Term	text	$200	MedDRA	AE.AEDECOD MedDRA Version 11.1
ADAE	AEBODSYS	Body System or Organ Class	text	$200	MedDRA	AE.AEBODSYS MedDRA Version 11.1
ADAE	TRTEMFL	Treatment Emergent Analysis Flag	text	$1	Y	If ADSL.TRTSDT <= ASTDT<=(ADSL.TRTEDT +14) then TRTEMFL='Y'
ADAE	PREFL	Pre-treatment Flag	text	$1	Y	If ASTDT < ADSL.TRTSDT then PREFL='Y'
ADAE	FUPFL	Follow-up Flag	text	$1	Y	If ASTDT > ADSL.TRTEDT+14 then FUPFL='Y'
ADAE	AESTDTC	Start Date/Time of Adverse Event	text	$10		AE.AESTDTC
ADAE	ASTDT	Analysis Start Date	integer	yymmdd10.		<Sponsor will insert derivation here>
ADAE	ASTDTF	Analysis Start Date Imputation Flag	text	$1	(DATEFL)	If start date is completely missing or missing the year then ASTDTF='Y' Else if start date has month missing then ASTDTF='M' Else if start date has day missing then ASTDTF='D'
ADAE	AEENDTC	End Date/Time of Adverse Event	text	$10		AE.AEENDTC
ADAE	AENDT	Analysis End Date	integer	yymmdd10.		<Sponsor will insert derivation here>

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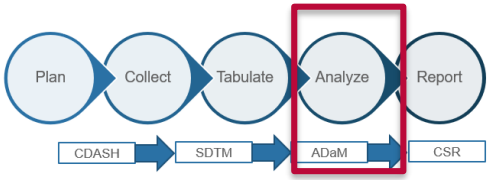
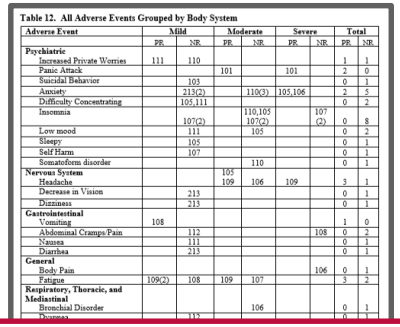


ADaM requires SDTM as its source

- Example ADaM ADAE
- **Begin with SDTM, which** is the required source for ADaM datasets
  - SDTM metadata has to be available before ADaM can be programmed
  - SDTM data has to be available before ADaM dataset can be created and TLFs produced for CSR



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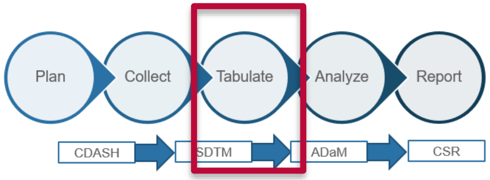

What are the data lifecycle connections?

SDTM is the source for ADaM

- Example SDTM: all AEs in AE.xpt
- It is important to be able to **prepare SDTM** datasets as **quickly and efficiently** as possible in order to program the analysis datasets (ADaM)

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SDTM AE.XPT

STUDTI	DOMAIN	USUBJID	AESEQ	AETERM	AELLT	ELLTCI	AEDECOD	AEPTCD	AEHLT	AEHLTCD	AEHLGT	EHLGTC	AEBODSYS	EBDSYC	AESOC	ESOCCI	AESER	AEACN	AEREL	ESCON	ESDISA	AESDTI	ESHOS	ESLIF	AESMI	AESTDTC	AEENDTC
DSS1234	AE	DSS1234-051-0	1	COMMON COLD	COMMON COLD	1E+07	NASOPHARYNGITIS	1002881	UPPER RESPIRATORY TRACT INFECTIONS	10046309	INFECTIONS - PATHOGEN UNSPECIFI	1002187	INFECTIONS AND INFESTATIONS	10021881	INFECTIONS AND INFESTATIONS	1E+07	N	NO ACTION TAKEN	NOT RELATED	N	N	N	N	N	N	2018-05-17	2018-05-28
DSS1234	AE	DSS1234-051-0	2	ARTERIOLAR NARROWIN	ARTERIAL DISORDI	1E+07	ARTERIOLAR DISORDI	10060963	NON-SITE SPECIFIC VASCULAR DISORDERS	10047067	VASCULAR DISORDERS NEC	10047066	CARDIAC DISORDERS		VASCULAR DISORDERS	1E+07	N	DOSE INTERRUPTED	POSSIBLY RELAT	N	N	N	N	N	N	2018-06-18	
DSS1234	AE	DSS1234-051-0	3	SEVERE CHEST PAIN	CHEST PAIN	1E+07	CHEST PAIN	10008479	PAIN AND DISCOMFORT NEC	10033372	GENERAL SYSTEM DISORDERS NEC	10018073	RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		GENERAL DISORDERS AND ADMINISTRATION SITE CONDITI	1E+07	Y	STUDY DRUG WITHDRAW	POSSIBLY RELAT	N	N	N	Y	Y	N	2018-07-01	2018-07-03
DSS1234	AE	DSS1234-073-0	1	ARTERIOLAR NARROWIN	ARTERIAL DISORDI	1E+07	ARTERIOLAR DISORDI	10060963	NON-SITE SPECIFIC VASCULAR DISORDERS	10047067	VASCULAR DISORDERS NEC	10047066	CARDIAC DISORDERS		VASCULAR DISORDERS	1E+07	N	DOSE INTERRUPTED	POSSIBLY RELAT	N	N	N	N	N	N	2018-06-18	
DSS1234	AE	DSS1234-051-0	1	COMMON COLD	COMMON COLD	1E+07	NASOPHARYNGITIS	1002881	UPPER RESPIRATORY TRACT INFECTIONS	10046309	INFECTIONS - PATHOGEN UNSPECIFI	1002187	INFECTIONS AND INFESTATIONS	10021881	INFECTIONS AND INFESTATIONS	1E+07	N	NO ACTION TAKEN	NOT RELATED	N	N	N	N	N	N	2018-05-17	2018-05-28
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DSS1234	AE	DSS1234-073-0	4	ARTERIOLAR NARROWIN	ARTERIAL DISORDI	1E+07	ARTERIOLAR DISORDI	10060963	NON-SITE SPECIFIC VASCULAR DISORDERS	10047067	VASCULAR DISORDERS NEC	10047066	CARDIAC DISORDERS		VASCULAR DISORDERS	1E+07	N	DOSE INTERRUPTED	POSSIBLY RELAT	N	N	N	N	N	N	2018-06-18	
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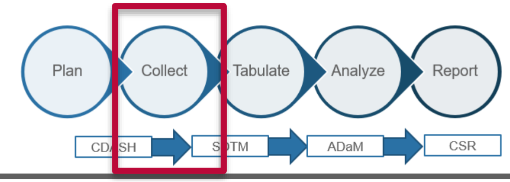
DSS1234	AE	DSS1234-051-01	1	COMMON COLD	COMMON COLD	1E+07	NASOPHARYNGITIS	1002881	UPPER RESPIRATORY TRACT INFECTIONS	10046309	INFECTIONS - PATHOGEN UNSPECIFI	1002187	INFECTIONS AND INFESTATIONS	10021881	INFECTIONS AND INFESTATIONS	1E+07	N	NO ACTION TAKEN	NOT RELATED	N	N	N	N	N	N	2018-05-17	2018-05-28
DSS1234	AE	DSS1234-051-01	2	ARTERIOLAR NARROWIN	ARTERIAL DISORDI	1E+07	ARTERIOLAR DISORDI	10060963	NON-SITE SPECIFIC VASCULAR DISORDERS	10047067	VASCULAR DISORDERS NEC	10047066	CARDIAC DISORDERS		VASCULAR DISORDERS	1E+07	N	DOSE INTERRUPTED	POSSIBLY RELAT	N	N	N	N	N	N	2018-06-18	
DSS1234	AE	DSS1234-051-01	3	SEVERE CHEST PAIN	CHEST PAIN	1E+07	CHEST PAIN	10008479	PAIN AND DISCOMFORT NEC	10033372	GENERAL SYSTEM DISORDERS NEC	10018073	RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		GENERAL DISORDERS AND ADMINISTRATION SITE CONDITI	1E+07	Y	STUDY DRUG WITHDRAW	POSSIBLY RELAT	N	N	N	Y	Y	N	2018-07-01	2018-07-03
DSS1234	AE	DSS1234-073-0	1	ARTERIOLAR NARROWIN	ARTERIAL DISORDI	1E+07	ARTERIOLAR DISORDI	10060963	NON-SITE SPECIFIC VASCULAR DISORDERS	10047067	VASCULAR DISORDERS NEC	10047066	CARDIAC DISORDERS		VASCULAR DISORDERS	1E+07	N	DOSE INTERRUPTED	POSSIBLY RELAT	N	N	N	N	N	N	2018-06-18	
DSS1234	AE	DSS1234-051-01	1	COMMON COLD	COMMON COLD	1E+07	NASOPHARYNGITIS	1002881	UPPER RESPIRATORY TRACT INFECTIONS	10046309	INFECTIONS - PATHOGEN UNSPECIFI	1002187	INFECTIONS AND INFESTATIONS	10021881	INFECTIONS AND INFESTATIONS	1E+07	N	NO ACTION TAKEN	NOT RELATED	N	N	N	N	N	N	2018-05-17	2018-05-28
DSS1234	AE	DSS1234-051-01	2	ARTERIOLAR NARROWIN	ARTERIAL DISORDI	1E+07	ARTERIOLAR DISORDI	10060963	NON-SITE SPECIFIC VASCULAR DISORDERS	10047067	VASCULAR DISORDERS NEC	10047066	CARDIAC DISORDERS		VASCULAR DISORDERS	1E+07	N	DOSE INTERRUPTED	POSSIBLY RELAT	N	N	N	N	N	N	2018-06-18	
DSS1234	AE	DSS1234-051-01	3	SEVERE CHEST PAIN	CHEST PAIN	1E+07	CHEST PAIN	10008479	PAIN AND DISCOMFORT NEC	10033372	GENERAL SYSTEM DISORDERS NEC	10018073	RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		GENERAL DISORDERS AND ADMINISTRATION SITE CONDITI	1E+07	Y	STUDY DRUG WITHDRAW	POSSIBLY RELAT	N	N	N	Y	Y	N	2018-07-01	2018-07-03
DSS1234	AE	DSS1234-073-0	1	ARTERIOLAR NARROWIN	ARTERIAL DISORDI	1E+07	ARTERIOLAR DISORDI	10060963	NON-SITE SPECIFIC VASCULAR DISORDERS	10047067	VASCULAR DISORDERS NEC	10047066	CARDIAC DISORDERS		VASCULAR DISORDERS	1E+07	N	DOSE INTERRUPTED	POSSIBLY RELAT	N	N	N	N	N	N	2018-06-18	
DSS1234	AE	DSS1234-051-01	1	COMMON COLD	COMMON COLD	1E+07	NASOPHARYNGITIS	1002881	UPPER RESPIRATORY TRACT INFECTIONS	10046309	INFECTIONS - PATHOGEN UNSPECIFI	1002187	INFECTIONS AND INFESTATIONS	10021881	INFECTIONS AND INFESTATIONS	1E+07	N	NO ACTION TAKEN	NOT RELATED	N	N	N	N	N	N	2018-05-17	2018-05-28
DSS1234	AE	DSS1234-051-01	1	ARTERIOLAR NARROWIN	ARTERIAL DISORDI	1E+07	ARTERIOLAR DISORDI	10060963	NON-SITE SPECIFIC VASCULAR DISORDERS	10047067	VASCULAR DISORDERS NEC	10047066	CARDIAC DISORDERS		VASCULAR DISORDERS	1E+07	N	DOSE INTERRUPTED	POSSIBLY RELAT	N	N	N	N	N	N	2018-06-18	
DSS1234	AE	DSS1234-051-01	3	SEVERE CHEST PAIN	CHEST PAIN	1E+07	CHEST PAIN	10008479	PAIN AND DISCOMFORT NEC	10033372	GENERAL SYSTEM DISORDERS NEC	10018073	RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		GENERAL DISORDERS AND ADMINISTRATION SITE CONDITI	1E+07	Y	STUDY DRUG WITHDRAW	POSSIBLY RELAT	N	N	N	Y	Y	N	2018-07-01	2018-07-03
DSS1234	AE	DSS1234-073-0	1	ARTERIOLAR NARROWIN	ARTERIAL DISORDI	1E+07	ARTERIOLAR DISORDI	10060963	NON-SITE SPECIFIC VASCULAR DISORDERS	10047067	VASCULAR DISORDERS NEC	10047066	CARDIAC DISORDERS		VASCULAR DISORDERS	1E+07	N	DOSE INTERRUPTED	POSSIBLY RELAT	N	N	N	N	N	N	2018-06-18	

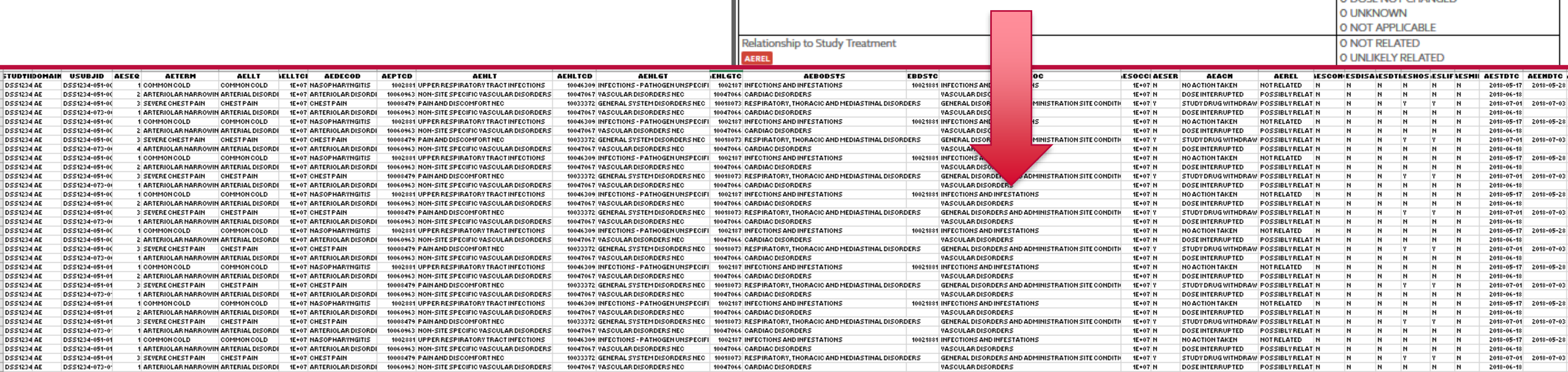


What are the data lifecycle connections?

CDASH is harmonized with SDTM

- Example eCRF to collect AEs
- In order to prepare SDTM data in a timely manner, **Begin by ensuring data collection** is harmonized with SDTM concepts and meets all SDTM and FDA requirements for AE data.

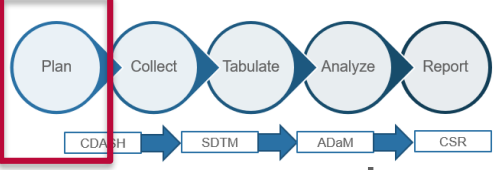
Were any adverse events experienced? NOT SUBMITTED AEYN	O Yes O No
Adverse Event Category: *Defaulted* AECAT	**Sponsor Defined**
Adverse Event Subcategory: *Defaulted* AESCAT	**Sponsor Defined**
What is the adverse event identifier? AESPID	________________
What is the adverse event term? AETERM	________________
Start Date AESTDTC AESTDAT	__/___/____
Is the adverse event ongoing? AEENRF / AEENRTPT AEENTPT AEONGO	O Yes O No
End Date AEENDTC AEENDAT	__/___/____
What is the severity of the adverse event? AESEV	O MILD O MODERATE O SEVERE
Was the adverse event serious? AESER	O Yes O No
Was the adverse event associated with a congenital anomaly or birth defect? AESCONG	O Yes O No
Did the adverse event result in disability or permanent damage? AESDISAB	O Yes O No
Did the adverse event result in death? AESDTH	O Yes O No
Death Date DS.DSSTDTC DM.DTHDTC DM.DTHDAT	__/___/____
Did the adverse event result in initial or prolonged hospitalization of the subject? AESHOSP	O Yes O No
Was the adverse event life threatening? AESLIFE	O Yes O No
Did the adverse event require intervention to prevent permanent impairment or damage due to the use of a medical device? SUPPAE.QVAL WHERE QNAM = "AESINTV" AESINTV	O Yes O No
Was the adverse event a medically important event not covered by other serious criteria? AESMIE	O Yes O No
Action Taken with Study Treatment AEACN	O DRUG WITHDRAWN O DOSE REDUCED O DOSE INCREASED O DOSE NOT CHANGED O UNKNOWN O NOT APPLICABLE
Relationship to Study Treatment AEREL	O NOT RELATED O UNLIKELY RELATED



What are the data lifecycle connections?

Protocol should support CDASH and SDTM requirements, too

- Example Protocol AE Section
- In order to harmonize data collection with SDTM (and by extension ADaM), **begin by** thinking about data standardization when we are writing /reviewing the protocol
  - Ensure language is harmonized with SDTMIG AE and other FDA requirements
  - ➢ Including text that allows the creation of a standardized data collection instrument (concepts aligned to SDTM)



Panacea Protocol
Protocol 292

Version 1.1
04 September 2014

Panacea Protocol

Protocol Number: 292

Principal Investigator: Dr. Heal

IND Sponsor: CDISC Education

Draft or Version Number: 1.1

04 September 2014

4 SAFETY REPORTING

4.1 Adverse Events

The investigator will ensure that all untoward medical occurrence (adverse event) that occurs after the first dose of study medication, that may or may not have a causal relationship with study medication, and that are observed by the investigator or reported by the subject are captured in the subject's medical record and are entered into the study data collection system.

The investigator must provide as much detail as possible about the adverse event as required by the data collection system and must minimally provide:

- Adverse event description
- Dates of start and end of the adverse event
- Severity of the adverse event
- Determination of whether the adverse event is
- Any action taken due to the adverse event.

Were any adverse events experienced? NOT SUBMITTED AETN	O Yes O No
Adverse Event Category: *Defaulted* AECAT	Sponsor Defined
Adverse Event Subcategory: *Defaulted* AESCAT	Sponsor Defined
What is the adverse event identifier? AESPID	_____
What is the adverse event term? AETERM	_____
Start Date AESTDTC AESTDAT	__/___/____
Is the adverse event ongoing? AEENRF / AEENRTPT AENTPT AEONGO	O Yes O No
End Date AEENDTC AEENDAT	__/___/____
What is the severity of the adverse event? AESEV	O MILD O MODERATE O SEVERE
Was the adverse event serious? AESER	O Yes O No
Was the adverse event associated with a congenital anomaly or birth defect? AESCONG	O Yes O No
Did the adverse event result in disability or permanent damage? AESDISAB	O Yes O No
Did the adverse event result in death? AESDTH	O Yes O No
Death Date DLDSTDTC DM.DTHDTC DM.DTHDAT	__/___/____
Did the adverse event result in initial or prolonged hospitalization of the subject? AESHOSP	O Yes O No
Was the adverse event life threatening? AESLIFE	O Yes O No
Did the adverse event require intervention to prevent permanent impairment or damage due to the use of a medical device? SUPPAE.QVAL WHERE QNAM = 'AESINTV' AESINTV	O Yes O No
Was the adverse event a medically important event not covered by other serious criteria? AESMIE	O Yes O No
Action Taken with Study Treatment AEACN	O DRUG WITHDRAWN O DOSE REDUCED O DOSE INCREASED O DOSE NOT CHANGED O UNKNOWN O NOT APPLICABLE
Relationship to Study Treatment AEREL	O NOT RELATED O UNLIKELY RELATED O POSSIBLY RELATED O RELATED
Outcome AEOUT	O RECOVERING / RESOLVING O NOT RECOVERED / NOT RESOLVED O RECOVERED / RESOLVED O RECOVERED / RESOLVED WITH SEQUELAE O FATAL

What Happens if we DO NOT Begin With the End in Mind?

- Preparing SDTM data becomes very complex, time-consuming and error-prone when we don't begin with the end in mind
  - This is called "legacy data conversion" and should be avoided
- How to avoid legacy data conversion
  - **Best**: Implement CDASH and collaborate continuously with SDTM programmers to build a mapping specification
  - At least: build a mapping specification **before you create the study database** so that *you* understand where the data will go in SDTM
- But, how do organizations produce SDTM data if they DO NOT plan for it during data collection?

Complex/Time-Consuming Legacy Data Conversion

There are multiple steps involved in LDC
We will focus on what happens in Steps 2-3

- Minimum steps involved in legacy data conversion:
- Step 1: Create SDTM Trial Design data (TI, TV, TS, TE/TA at a minimum)
- **Step 2: Review the data**
- **Step 3: Annotate the CRF**
- Step 4: Map the data to SDTM and validate
- Step 5: Create Define.xml
- Step 6: Validate the whole package (SDTM and Define.xml)

Complex/Time-Consuming Legacy Data Conversion

- **STEP 2:** Review and understand the legacy data
- **Inputs**: Legacy datasets, DMP, Legacy CRF, DTS, Protocol
  - Identify potential issues and problems, e.g., missing or inconsistent data
  - Identify natural keys
  - Identify where important, required data, such as Demographics, Exposure, Adverse Events and Disposition are in the legacy data
  - Identify collected relationships (RELREC)
  - Review use of Controlled terminology
  - Decide on standard units for tests

Ideally, the people who conducted the study will still be available to answer questions in case the available documentation and data are not 100% clear

Complex/Time-Consuming Legacy Data Conversion

- **STEP 3:** Annotate the legacy CRF for SDTM
- **Inputs**: Legacy datasets, DMP, Legacy CRF, DTS, Protocol
  - Can be very complex and time consuming
  - Requires knowledge of the data handling conventions for that study (e.g., DMP)
  - Should involve data managers, biostatisticians and others who are familiar with the study data (*may or may not be available*)
  - Usually there is not a 1:1 relationship between the legacy CRF and an SDTM domain
- Output: The annotated CRF will be the specification for all downstream activities including creating the SDTM datasets from the legacy data

Steps 2 and 3 can take **several months** to **2+ years**

What makes legacy data conversion so complex?

- Missing data that SDTM requires or expects, e.g.,
  - Informed Consent Date
  - Dates of first and last exposure to IP
  - Disposition of participants (when and how did they finish the study)
- Data that goes into one SDTM domain have been collected throughout many CRFs
- Data that goes into a single SDTM variable may have been collected using multiple different *questions*
- Individual questions may have collected multiple SDTM concepts
  - Sometimes these have to be manually reviewed and individual values mapped to the correct SDTM variable - this is especially true if the collected value is free text

What makes legacy data conversion so complex?

- Individual legacy CRFs often have many different kinds of data mixed together making traceability to SDTM difficult
- Controlled Terminologies used to collect data may or may not match required SDTM terminology
  - ➢ May not even be mappable without losing or adding meaning
- Individual data collection fields may look like an SDTM variable, but may have a different definition from the SDTM variable to which they will be mapped
  - E.g., Adverse Event Action Taken
    - SDTM AEACN is limited to action taken *with the study treatment*
    - ➢ Collected data may have other concepts mixed in (what else did you do?)
- What else can go wrong?
  - You may not find out until you start doing a legacy data conversion

Legacy Data Conversion - **To Be Avoided**

- Difficult for anyone to do even if they are an expert in the standards
- Can delay the submission timeline significantly (months to years)
- Can increase the submission preparation budget significantly (multiple $millions depending on time, complexity and volume)
- Will often result in a less-than ideal set of review data which can potentially delay the review process or put it at risk

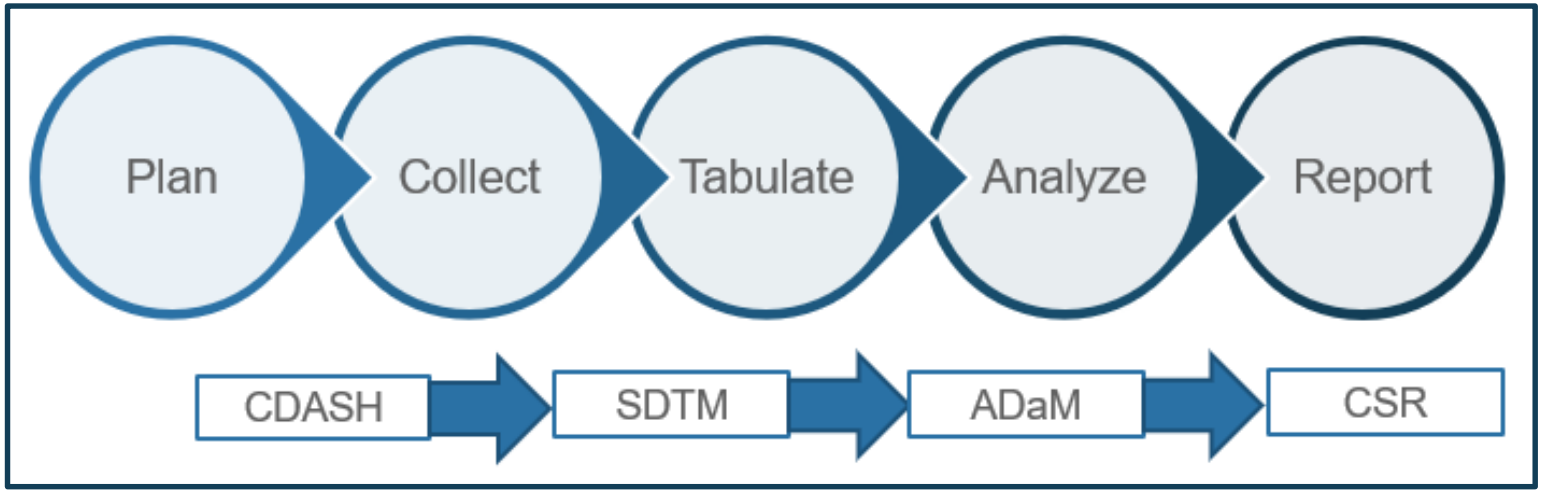
Requirement for standards should NOT come as a shock to any Sponsor organization.

FDA has been keeping industry informed and aware of data standards requirements since ~2004 through multiple Federal Register notices, many public presentations and public meetings, and online resources.

We knew about FDA requirements for more than a decade before the requirement became enforceable in 2016.

Purpose of **CDASH**

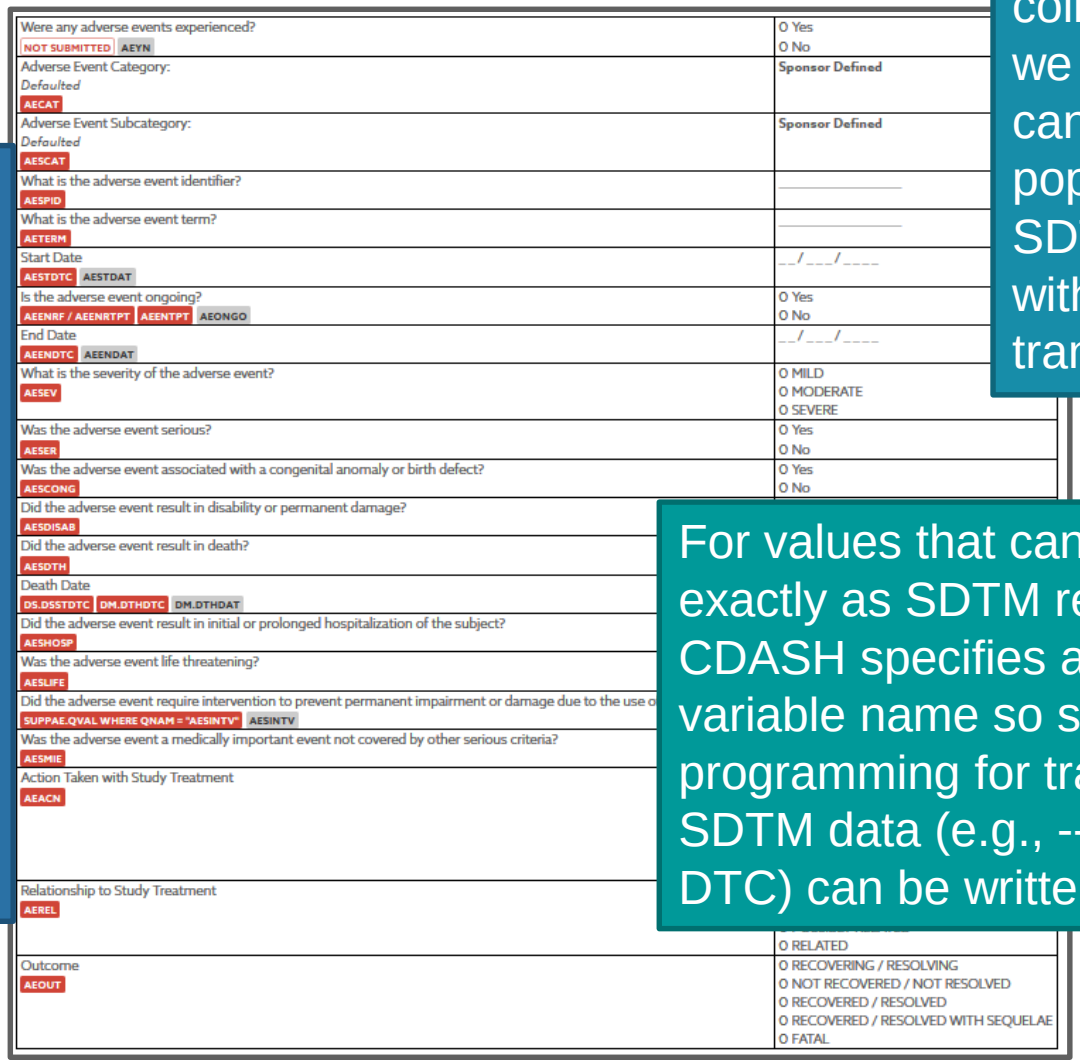
- Allow the creation of user-friendly data collection forms that
  - Align data collection with SDTM in a way that makes creation of SDTM tabulations more efficient
    - ➢ AVOID costly, complex, error-prone legacy data conversion
  - Support clear traceability throughout the entire data lifecycle



How CDASH is Aligned with SDTM

CDASH specifies a minimum set of fields:

- Logical set to have a valid record
- Target what is required for regulatory requirements including SDTM



Were any adverse events experienced? NOT SUBMITTED AEYN	O Yes O No
Adverse Event Category: *Defaulted* AECAT	**Sponsor Defined**
Adverse Event Subcategory: *Defaulted* AESCAT	**Sponsor Defined**
What is the adverse event identifier? AESPID	_____
What is the adverse event term? AETERM	_____
Start Date AESTDTC AESTDAT	__/___/____
Is the adverse event ongoing? AEENRF / AEENRTPT AEENTPT AEONGO	O Yes O No
End Date AEENDTC AEENDAT	__/___/____
What is the severity of the adverse event? AESEV	O MILD O MODERATE O SEVERE
Was the adverse event serious? AESER	O Yes O No
Was the adverse event associated with a congenital anomaly or birth defect? AESCONG	O Yes O No
Did the adverse event result in disability or permanent damage? AESDISAB	
Did the adverse event result in death? AESDTH	
Death Date DS.DSSTDTC DM.DTHDTC DM.DTHDAT	
Did the adverse event result in initial or prolonged hospitalization of the subject? AESHOSP	
Was the adverse event life threatening? AESLIFE	
Did the adverse event require intervention to prevent permanent impairment or damage due to the use o SUPPAE.QVAL WHERE QNAM = "AESINTV" AESINTV	
Was the adverse event a medically important event not covered by other serious criteria? AESMIE	
Action Taken with Study Treatment AEACN	
Relationship to Study Treatment AEREL	O RELATED
Outcome AEOUT	O RECOVERING / RESOLVING O NOT RECOVERED / NOT RESOLVED O RECOVERED / RESOLVED O RECOVERED / RESOLVED WITH SEQUELAE O FATAL

CDASH variable uses the target SDTM variable name for data collection if what we are collecting can directly populate the SDTM variable without transformation

For values that cannot be collected exactly as SDTM requires them, CDASH specifies a similar standard variable name so standard programming for transformation to SDTM data (e.g., --DAT/--TIM to --DTC) can be written

How CDASH is Aligned with SDTM

CDASH specifies standard wording (with controlled flexibility) for the data collection questions to keep the meaning of each question aligned with the meaning of the target SDTM variable

Were any adverse events experienced? NOT SUBMITTED AEYN	O Yes O No
Adverse Event Category: *Defaulted* AECAT	**Sponsor Defined**
Adverse Event Subcategory: *Defaulted* AESCAT	**Sponsor Defined**
What is the adverse event identifier? AESPID	_____
What is the adverse event term? AETERM	_____
Start Date AESTDTC AESTDAT	__/___/____
Is the adverse event ongoing? AEENRF / AEENRTPT AEENTPT AEONGO	O Yes O No
End Date AEENDTC AEENDAT	__/___/____
What is the severity of the adverse event? AESEV	O MILD O MODERATE O SEVERE
Was the adverse event serious? AESER	O Yes O No
Was the adverse event associated with a congenital anomaly or birth defect? AESCONG	O Yes O No
Did the adverse event result in disability or permanent damage? AESDISAB	O Yes O No
Did the adverse event result in death? AESDTH	O Yes O No
Death Date DS.DSSTDTC DM.DTHDTC DM.DTHDAT	__/___/____
Did the adverse event result in initial or prolonged hospitalization of the subject? AESHOSP	O Yes O No
Was the adverse event life threatening? AESLIFE	O Yes O No
Did the adverse event require intervention to prevent permanent impairment or damage due to the use of a medical device? SUPPAE.QVAL WHERE QNAM = "AESINTV" AESINTV	O Yes O No
Was the adverse event a medically important event not covered by other serious criteria? AESMIE	O Yes O No
Action Taken with Study Treatment AEACN	O DRUG WITHDRAWN O DOSE REDUCED O DOSE INCREASED O DOSE NOT CHANGED O UNKNOWN O NOT APPLICABLE
Relationship to Study Treatment AEREL	O NOT RELATED O UNLIKELY RELATED O POSSIBLY RELATED O RELATED
Outcome AEOUT	O RECOVERING / RESOLVING O NOT RECOVERED / NOT RESOLVED O RECOVERED / RESOLVED O RECOVERED / RESOLVED WITH SEQUELAE O FATAL

CDASH specifies using the same standardized value lists that are required for the target SDTM variables

How CDASH Addresses Data Collection Needs

Birth Date BRTHDTC BRTHDD BRTHMO BRTHYR BRTHDAT	__/___/____
Sex SEX	O Male O Female
Do you consider yourself Hispanic/Latino or not Hispanic/Latino? ETHNIC	O Hispanic or Latino O Not Hispanic or Latin O Not Reported
Which of the following five racial designations best describes you? More than one choice is acceptable. RACE	☐ American Indian ☐ Asian ☐ Black or African ☐ Native Hawaiian ☐ White

CDASH allows the display of synonyms for controlled terms to make data collection user friendly.
e.g., Male/Female instead of M/F.

For convenience, CDASH allows us to mix topics on one form, even though they have to be split out into multiple SDTM domains when the data are tabulated. Standardized OID naming supports getting data to the right SDTM domain.

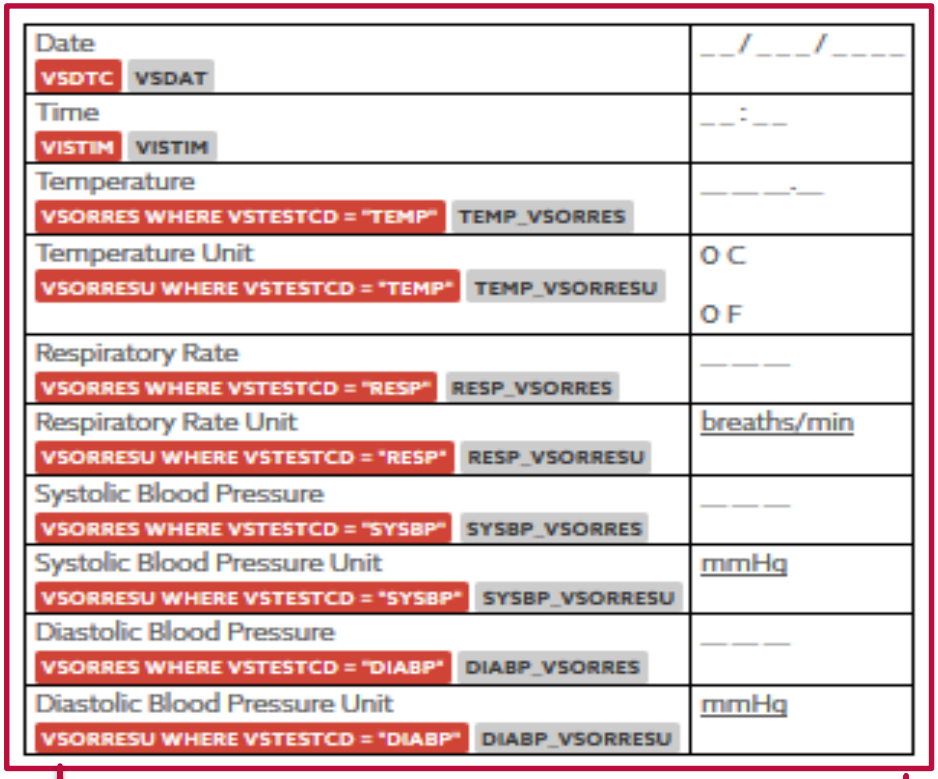
Defaulted DSCAT	**PROTOCOL MILESTONE**
Defaulted DSTERM DSDECOD	**INFORMED CONSENT OBTAINED**
What was the Informed Consent date? DSSTDTC DSSTDAT	__/___/____
What was the Informed Consent time? DSSTDTC DSSTTIM	__:__

Purpose of **SDTM**

- Provide a **standard way to present <u>all of the collected data</u>** to a reviewer
  - All data collected from all sources: eCRF/CRF/EDC, ePRO/eCOA, Core lab, Wearables, Genetic, Other Biomarkers, etc.
- Provide enough **predictability** in the organization, format and content that FDA (and other consumers) can
  - Find what they are looking for in the data
  - Create and use standards-based software (review tools, dashboards)
  - Aggregate data across studies to gain new information
    - E.g., looking at safety *across Sponsors* for IP in the same drug class
- **Provide the source** for ADaM (analysis datasets)
  - Anything presented in ADaM must have a source record in SDTM

CDASH to SDTM Vital Signs Example

CDASH: study-level Rave form metadata is aligned with SDTM variables and CT, and traceable through standard transposition programming



STUDYID	DOMAIN	USUBJID	VSSEQ	VSTESTCD	VSTEST	VSPOS	VSORRES	VSORRESU	VSSTRESC	VSSTRESN	VSSTRESU	VSDTC	VSDY
ABC	VS	ABC-001-001	1	SYSBP	Systolic Blood Pressure	Sitting	154	mmHg	154	154	mmHg	1999-06-19T08:45	1
ABC	VS	ABC-001-001	2	SYSBP	Systolic Blood Pressure	Sitting	152	mmHg	152	152	mmHg	1999-06-19T09:00	1
ABC	VS	ABC-001-001	3	DIABP	Diastolic Blood Pressure	Sitting	44	mmHg	44	44	mmHg	1999-06-19T08:45	1
ABC	VS	ABC-001-001	4	DIABP	Diastolic Blood Pressure	Sitting	48	mmHg	48	48	mmHg	1999-06-19T09:00	1
ABC	VS	ABC-001-001	5	PULSE	Pulse Rate	Sitting	72	beats/min	72	72	beats/min	1999-06-19	1
ABC	VS	ABC-001-001	6	TEMP	Temperature		34.7	C	34.7	34.7	C	1999-06-19T08:45	1
ABC	VS	ABC-001-001	7	TEMP	Temperature		36.2	C	36.2	36.2	C	1999-06-19T09:00	1
ABC	VS	ABC-001-001	10	SYSBP	Systolic Blood Pressure	Sitting	95	mmHg	95	95	mmHg	1999-07-21	33
ABC	VS	ABC-001-001	11	DIABP	Diastolic Blood Pressure	Sitting	44	mmHg	44	44	mmHg	1999-07-21	33
ABC	VS	ABC-001-001	12	TEMP	Temperature		97.16	F	36.2	36.2	C	1999-07-21	33

SDTM programming adds in derived and assigned submission variables, protocol concepts and standardized results for ALL data

Purpose of **ADaM**

- Provide a standard framework for presenting data used in the analysis
  - Standard Subject Level Analysis file (ADSL)
  - Standard framework for construction of analysis data files to support TLFs in CSR
- Provide clear traceability back to the collected data
  - 1:1 traceability with SDTM variables when data/meaning are the same
  - Metadata-level traceability
    - Imputation rules are applied when an SDTM value is missing or incomplete, and those rules are described in metadata
    - Calculation algorithms are included in metadata and point to SDTM source
      - Derived values use SDTM source in the calculation
      - Other complex computations (e.g., summary data) also use SDTM source

SDTM to ADaM Examples

STUDYID	DOMAIN	USUBJID	VSSEQ	VSTESTCD	VSTEST	VSPOS	VSORRES	VSORRESU	VSSTRESC	VSSTRESN	VSSTRESU	VSSTAT	VISITNUM	VISIT
ABC	VS	ABC-001-001	1	SYSBP	Systolic Blood Pressure	Sitting	120	mmHg	120	120	mmHg		1	SCREENING
ABC	VS	ABC-001-001	2	DIABP	Diastolic Blood Pressure	Sitting	44	mmHg	44	44	mmHg		1	SCREENING
ABC	VS	ABC-001-001	3	SYSBP	Systolic Blood Pressure	Sitting	116	mmHg	116	116	mmHg		2	RUN-IN
ABC	VS	ABC-001-001	4	DIABP	Diastolic Blood Pressure	Sitting	44	mmHg	44	44	mmHg		2	RUN-IN
ABC	VS	ABC-001-001	5	SYSBP	Systolic Blood Pressure	Sitting	114	mmHg	114	114	mmHg		3	WEEK 0
ABC	VS	ABC-001-001	6	DIABP	Diastolic Blood Pressure	Sitting	44	mmHg	44	44	mmHg		3	WEEK 0
ABC	VS	ABC-001-001	7	SYSBP	Systolic Blood Pressure	Sitting	118	mmHg	118	118	mmHg		4	WEEK 2
ABC	VS	ABC-001-001	8	DIABP	Diastolic Blood Pressure	Sitting	44	mmHg	44	44	mmHg		4	WEEK 2
ABC	VS	ABC-001-001	9	SYSBP	Systolic Blood Pressure	Sitting	126	mmHg	126	126	mmHg		4	WEEK 2 UNSCHEDULED
ABC	VS	ABC-001-001	10	DIABP	Diastolic Blood Pressure	Sitting	80	mmHg	80	80	mmHg		4.1	WEEK 2 UNSCHEDULED
ABC	VS	ABC-001-001	11	SYSBP	Systolic Blood Pressure	Sitting	122	mmHg	122	122	mmHg		5	WEEK 4
ABC	VS	ABC-001-001	12	DIABP	Diastolic Blood Pressure	Sitting	44	mmHg	44	44	mmHg		5	WEEK 4
ABC	VS	ABC-001-001	13	SYSBP	Systolic Blood Pressure	Sitting						NOT DONE	6	WEEK 8
ABC	VS	ABC-001-001	14	DIABP	Diastolic Blood Pressure	Sitting						NOT DONE	6	WEEK 8
ABC	VS	ABC-001-001	15	SYSBP	Systolic Blood Pressure	Sitting	134	mmHg	134	134	mmHg		7	WEEK 12
ABC	VS	ABC-001-001	16	DIABP	Diastolic Blood Pressure	Sitting	44	mmHg	44	44	mmHg		7	WEEK 12

SDTM VS.xpt is all Vital Signs “as collected” (no imputations) and is the source for all ADaM analysis datasets that use VS results

PARAM	AVISIT	AVISITN	VISITNUM	VSSEQ	ABLFL	AVAL	BASE	CHG	DTYPE	ADY	WTARGFL
Systolic BP (mmHg)	Screening	-4	1	1		120	114	.		-3	
Systolic BP (mmHg)	Run-In	-2	2	3		116	114	.			
Systolic BP (mmHg)	Week 0	0	2	5	Y	114	114	0			
Systolic BP (mmHg)	Week 2	2	4	7		118	114	4			
Systolic BP (mmHg)	Week 2	2	4.1	9		126	114	12			
Systolic BP (mmHg)	Week 4	4	5	11		122	114	8			Y
Systolic BP (mmHg)	Week 8	8	5	11		122	114	8	LOCF	53	Y
Systolic BP (mmHg)	Week 8	8	4.1	9		126	114	12	WOCF	39	Y
Systolic BP (mmHg)	Week 12	12	7	13		134	114	20		83	1	Y

For missing Week 8 SYSBP, LOCF from Week 4, WOCF from Unscheduled visit

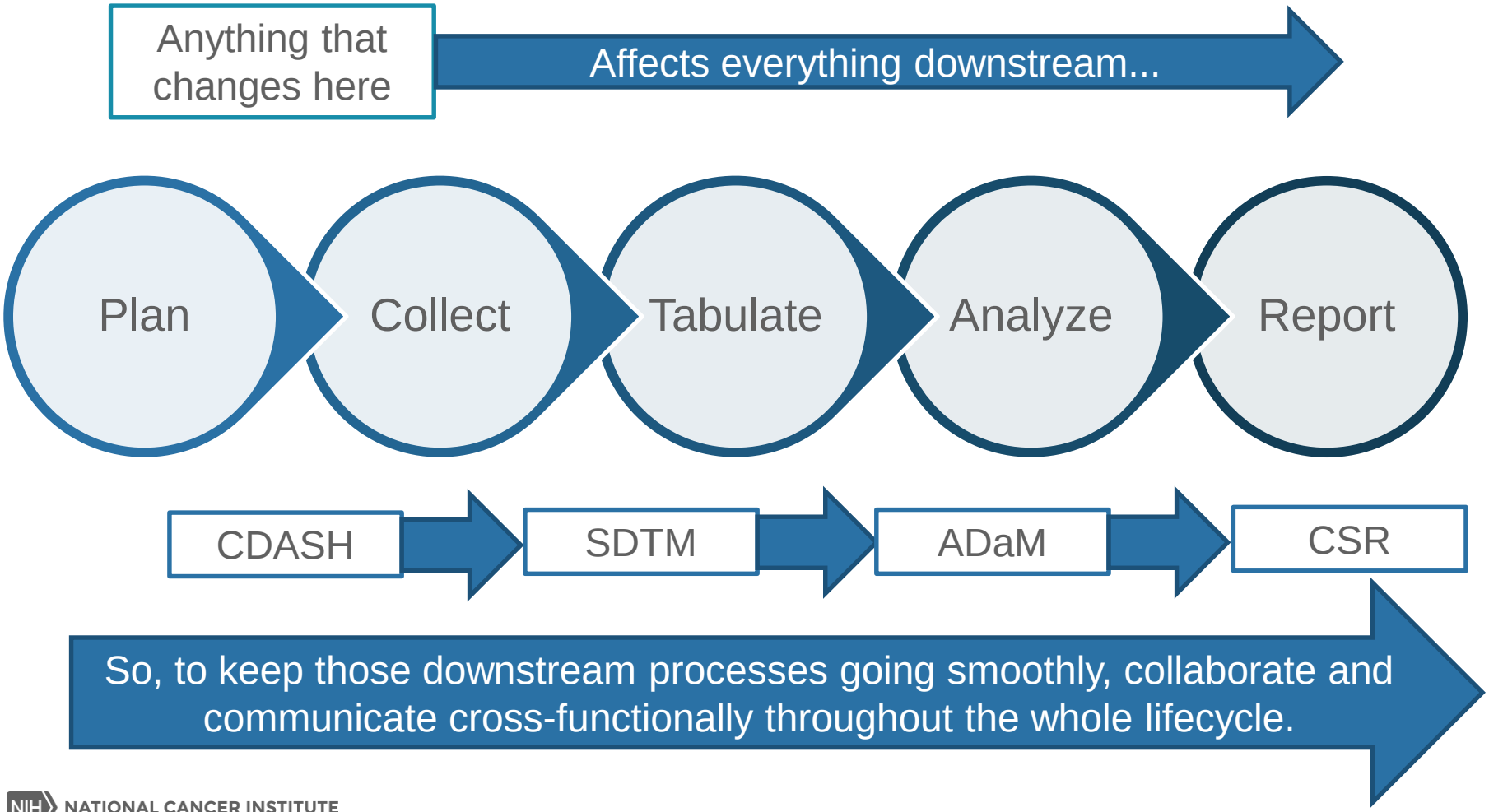
ADaM can manipulate data to meet analysis needs: imputations (LOCF, WOCF), standardized analysis visits, additional baseline values, analysis-specific parameters…

CDASH - SDTM - ADaM are Complementary Standards

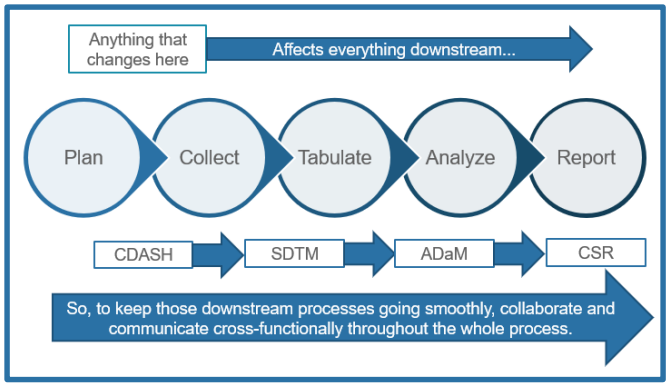
CDASH	SDTM	ADaM
• Designed for data collection • Provides data collection metadata (e.g., standard questions with controlled flexibility) • User friendly • Addresses site-facing aspects of standardization • Supports traceability to SDTM (and to ADaM)	• Designed for familiar, predictable data to support review • Provides “normalized” tabulation metadata • Includes all collected data, plus other variables that support review of data • No imputations allowed • Source is CDASH + all other collected data • Links data collection to analysis (should be transparently traceable)	• Standard framework/ metadata for presenting analysis data • Enough data to produce CSR TLFs • Imputations and other rules can be applied • Source is SDTM (multiple SDTM domains might be source for a single ADaM dataset) • Completes the thread of traceability through variables, values and metadata

Each standard has it’s own unique purpose, supporting a different part of the data lifecycle while keeping them connected. Using all three as intended provides clearly traceable data flow from collection through reporting.

Data Lifecycle: Begin with the End in Mind



Connections: Lifecycle Mapping



Partial DM Mapping Example

FormOID	VariableOID	DataDictionaryNam	ControlTyp	PreText	SDTM Variable	SDTM Transformation Logic	CT SUBSET USED IN STUDY	Define.xml Origin	Define.xml Comment	Used in AdaM Dataset
DM	SITEID		Text	Site	DM_SITEID	DM_SITEID		CRF (DM CRF)		SITEID in all datasts
DM	SUBJID		Text	Participant	DM_SUBJID	DM_SUBJID,		CRF (DM CRF)		
					USUBJID	USUBJID in all domains = STUDYID-SITEID-SUBJID (except when subject was in prior study; then use STUDYID-SITEID-SUBJID from first study)		Derived	USUBJID in all domains = STUDYID-SITEID-SUBJID (except when subject was in prior study; then use STUDYID-SITEID-SUBJID from first study)	USUBJID in all datasets
DM	BRTHYY		DateTime	Birth Year	DM_BRTHDTC	populate with collected portion of date with no imputations		CRF (DM CRF)		Create standardized BRTHDT in SAS format using collected DM_BRTHDTC and imputing 01 July.
DM	AGE		Text	N/A	DM_AGE	Derive Age in defaulted Age Unit by calculating DM_ICDTC - DM_BRTHDTC using 01 July in calculation		Derived	DM_ICDTC - DM_BRTHDTC (with 01 July imputed in the calculation to obtain a valid Age value)	
DM	AGEU	AGEU_YEARS	DropDownList	N/A	DM_AGEU	Default to YEARS	AGEU_YEARS	Derived	Defaulted to Years	
DM	SEX	SEX_1	DropDownList	Sex	DM_SEX	Populate with collected value (CDISC Submission Value from SEX_1 codelist)	SEX_1	CRF (DM CRF)		SEX in all datasets, translate M=0, F=1 in SEXN variable

Summary: **Begin With the End in Mind**

- For each study:
  - **Review** the protocol with standardization in mind
  - **Collaborate** cross-functionally (at least with SDTM and ADaM programmers)
    - (Starting from a GLIB mapping) create a detailed mapping and programming specification and eCRF annotations **for the study**
    - Proactively provide study level data handling conventions to the SDTM programmers (EDC derivations, SECs, coding, value-level Origin)
  - **Maintain** and share documentation to handle updates (typically from protocol amendments)
    - Continuous collaboration with SDTM and ADaM programmers
      - Update the mapping specification
      - Update the annotated eCRF and data handling conventions

Q&A

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