FDA Submission Process

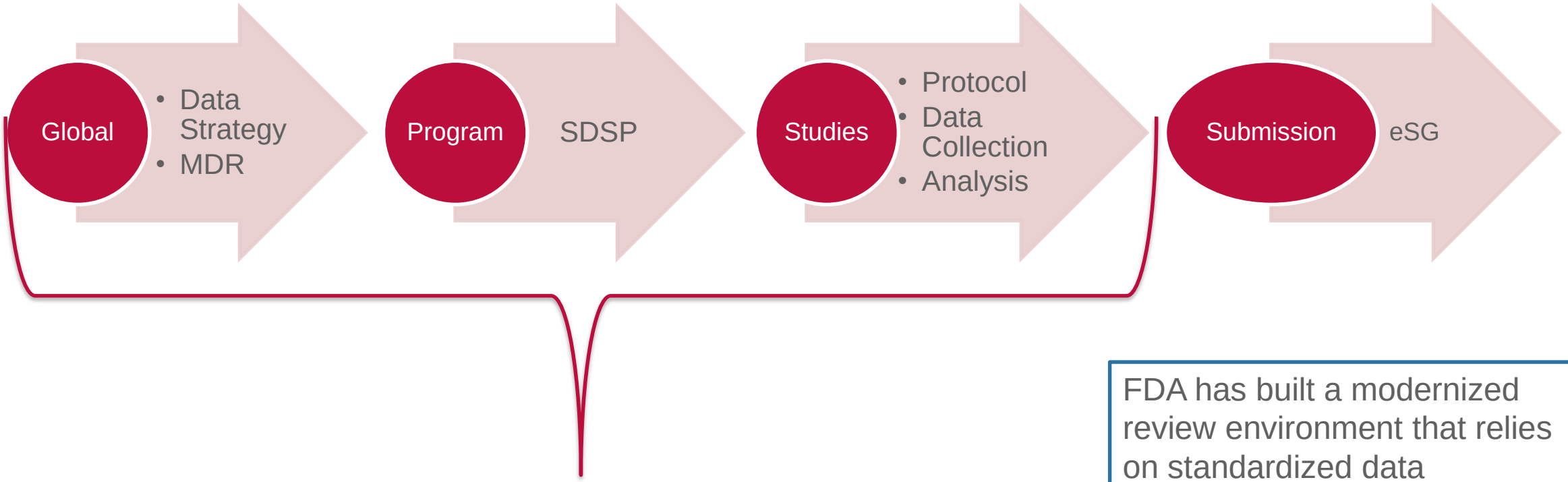
LPO Webinar

22 May 2019

NIH NATIONAL CANCER INSTITUTE

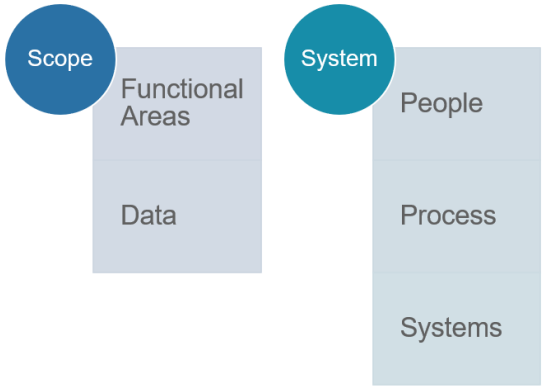
Upon completion of this webinar, you should be able to:

- Understand the overall process of preparing for a standardized submission to FDA
- Explain the basic documentation required for study data in a Submission
- Describe the electronic Common Technical Document and where to put study data
- Understand how to set up an account for the Electronic Submission Gateway (eSG)
- Access Helpful (URL) Resources When You Need Them

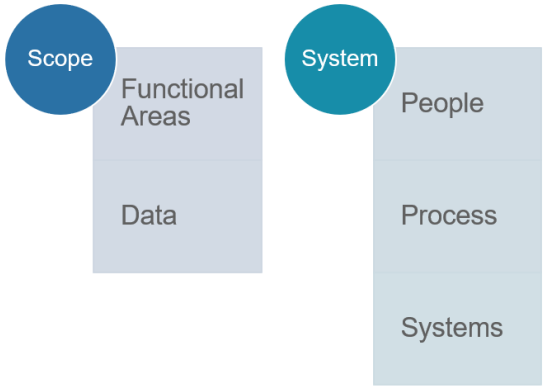


Upfront preparation for Submission is essential
The further upstream, the better!

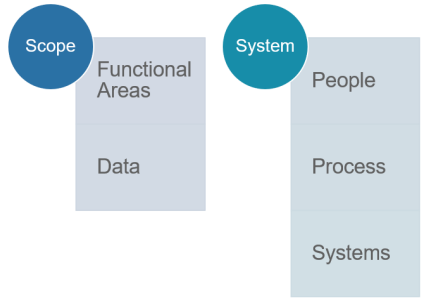
FDA has built a modernized review environment that relies on standardized data



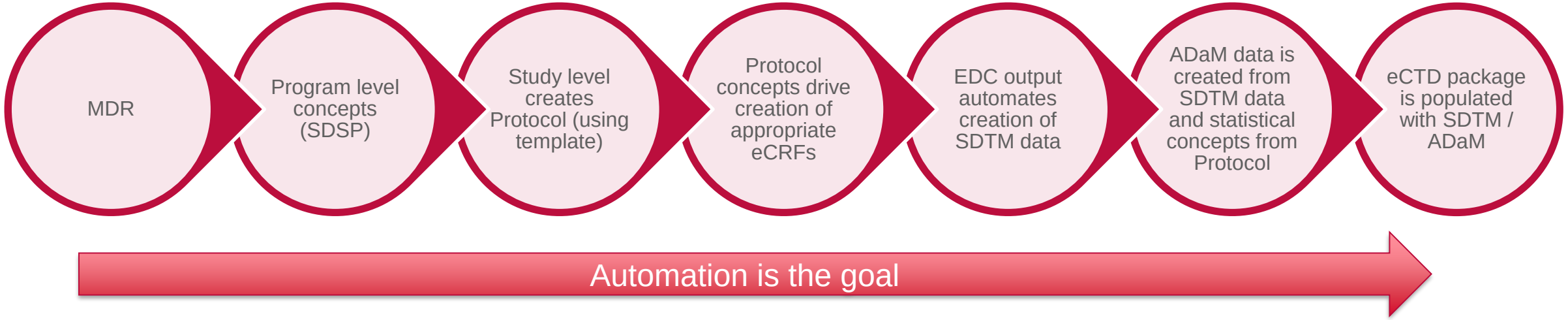
- Establish a Global, Cross-Functional **Data Strategy** and Documentation
  - Appropriate Scope: Focus on the data you need to support your internal and external data consumers and data-driven processes
    - Identify functional areas that have touchpoints and handoffs that are data driven
    - Data: Ensure each functional area has the data they need
      - in a useful format
      - when they need it
  - Data Lifecycle Documentation: Ensure all data consumers have a common understanding of the individual data concepts
    - Ideally the documentation will be centralized and available to cross-functional teams
    - Documentation can show what the data look like for each functional area



- Establish a workable cross-functional **Governance System**
  - Team of people who commit to
    - Remaining knowledgeable about the requirements (standards, Agency requirements, etc.)
    - Reviewing and dispositioning internal requests (custom domains, NSVs, codelist extensions and custom codelists)
  - Appropriate processes and procedures, with systematic training to align with Data Strategy
  - Technologies: Identify technologies to support your Data Strategy
    - Which systems are needed? How do they interconnect / exchange data?
    - Begin with the end in mind: Ensure that the interconnections and the final products (e.g., SDTM, ADaM) are ‘built in’ from the start either through technology or by procedure.
    - Strive for automation



- One of the technologies that can support a Data Strategy is an Metadata Repository (MDR)
- Can be simple
  - E.g., Global ALS with appropriate governance processes in place
- Or robust technological solution to support automation
  - E.g., MDR to house all standards, with automated connections between systems and governance



FDA Requirements Related to Standardized Submissions

BINDING Guidance

Providing Regulatory Submissions In Electronic Format — Standardized Study Data

Guidance for Industry

Technical specifications associated with this guidance are provided as separate, stand-alone documents and are updated periodically. These are:

- **Data Standards Catalog**
- **Study Data Technical Conformance Guide**
- **FDA Specific SEND Validation Rules**
- **FDA Specific SDTM Validation Rules**

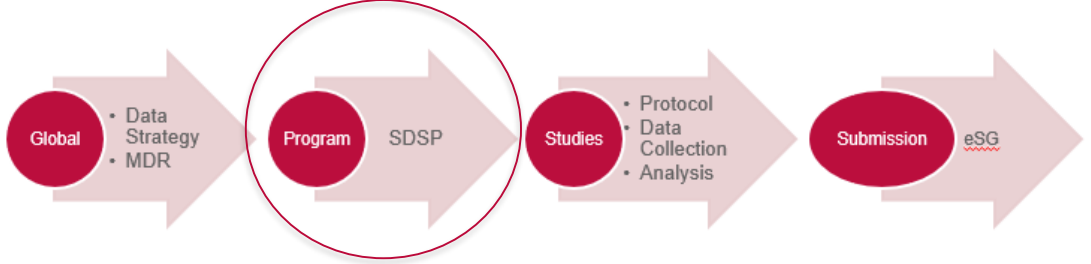
To make sure you have the most recent versions, please check:

http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm

Standardization Requirements Related to Submissions

- **Relevant quotes from (binding) Guidance:**
  - *"Sponsors and applicants may use established FDA-sponsor meetings (e.g., pre-IND and end-of-phase 2) to discuss the **study data standardization plan**…related to NDAs and BLAs."*
  - *"When planning a study (including the design of **case report forms**, **data management systems**, and statistical analysis plans), the sponsor or applicant must determine which FDA-supported standards to use…"*
  - "*The **use of controlled terminology** standards, also known as vocabularies, is an important component of study data standardization and **is** a **critical** component of achieving semantically interoperable data exchange. It is the expectation that sponsors or applicants will use the controlled terminologies maintained by external organizations as the standard. Examples of controlled terminology standards include:*
    - *The National Drug File (NDF) — Reference Terminology for drug classifications*
    - *CDISC Controlled Terminology*
    - *Medical Dictionary for Regulatory Activities (MedDRA)*

Submission: Stages of Preparation



- At the beginning of a **new program**
  - Start from a global standard (MDR)
  - Review current requirements from FDA: https://www.fda.gov/industry/fda-resources-data-standards/study-data-standards-resources
  - As you develop novel concepts for data collection, determine where they go in SDTM (develop custom domains, custom variables, custom codelists)
  - **Write your Study Data Standardization Plan**
    - Referenced in Technical Conformance Guide Section 2.1
    - SDSP Template and Examples: https://www.phuse.eu/css-deliverables

Study Data Standardization Plan

- **Study Data Standardization Plan (SDSP)**
  - Program level plan for standardization
    - Template created by PhUSE (with FDA participation)
  - Review at EOP2 meeting or other typical meetings between Sponsor and FDA
- What to include in the SDSP:
  - Sponsor Information
  - Description of Product, Indication(s), Patient Population
  - List of **completed** studies / standards used (non-clinical and clinical)
  - List of **planned** studies / standards (non-clinical and clinical)
  - Other details requested by FDA
    - May need more detail about Domains, etc.

1. General Sponsor Information

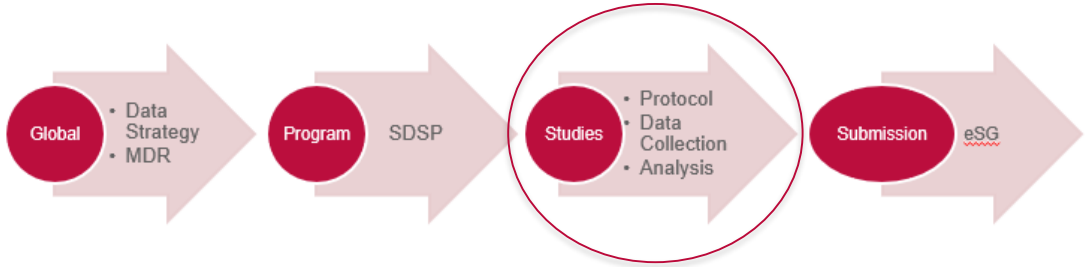
Name of Product	SuperDrug
Indication(s)	Hypertension
IND	054321
Sponsor Name	ABC Pharma
Sponsor Contact	Joe Smith
Sponsor Contact Email	Joe.Smith@abcpharma.com

3. List of Completed Studies and Standards

A. Nonclinical

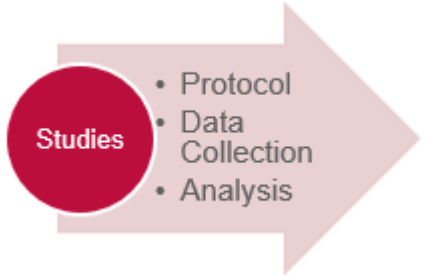
Study ID	Brief Title	Study Type	Exchange Standards	Terminology Standards
XYZ1	One month toxicity study in the Cynomolgus monkey	Repeat Dose Toxicity	SEND 3.0 Define.xml v.2.0	CDISC SEND Terminology 2014-06-27
XYZ2	One month toxicity study in the Han Wistar rat	Repeat Dose Toxicity	SEND 3.0 Define.xml v.2.0	CDISC SEND Terminology 2014-06-27

Submission: Stages of Preparation



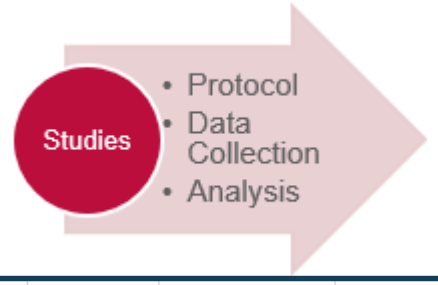
- At the start of each **new project/study**
  - Start from global standards (MDR)
  - Reference your Program level SDSP
  - Review current requirements from FDA: https://www.fda.gov/industry/fda-resources-data-standards/study-data-standards-resources
  - Use data collection structures that will support SDTM preparation (CDASH)
  - Create an end to end mapping from data collection to SDTM (and ADaM) in collaboration with SDTM programmers
  - Consider starting validation processes during the study to identify and resolve issues early

Create End to End Mapping Before Study Starts



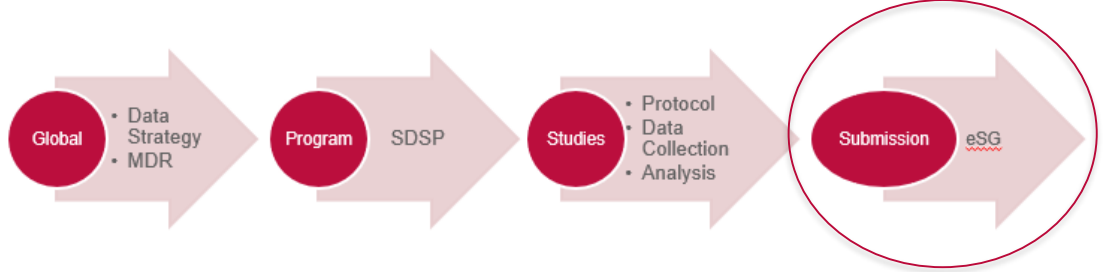
FormOID	FieldOID	VariableOID	DataDictionaryName	CodingDictionary	ControlType	PreText	SDTM Variable	SDTM Transformation Logic	CT SUBSET USED IN STUDY	Define.xml Origin	Define.xml Comment	Used in AdaM Dataset
CM	CMSPID	CMSPID			Text	What is the (concomitant) [medication/treatment/therapy] identifier?	CMSPID			CRF		
CM	CMTRT	CMTRT			LongText	What was the (concomitant) [medication/treatment/therapy] (name/term)?	CMTRT			CRF		
CM	CMOCCUR	CMOCCUR	NY		DropDownList	Did the subject take [pre-specified (concomitant) medication/treatment/therapy/dose]?; Has the subject taken [pre-specified (concomitant) medication/treatment/therapy/dose]?	CMOCCUR		NY_1	CRF		
CM	CMINGRD	CMINGRD			LongText	What were the active ingredients?	CMINGRD			CRF		
CM	CMINDC	CMINDC			LongText	For what indication, was the (concomitant) [medication/treatment/therapy] taken?	CMINDC			CRF		
CM	CMAENO	CMAENO			Text	What was the identifier for the adverse event(s) for which the (concomitant) [medication/treatment/therapy] was taken?		Create RELREC between CM and AE		CRF		
CM	CMMHNO	CMMHNO			Text	What was the identifier for the medical history event(s) for which the (concomitant) [medication/treatment/therapy] was taken?		Create RELREC between CM and MH				
CM	CMDOSE	CMDOSE			Text	What was the individual dose (of the concomitant [medication/treatment/therapy] per administration)?	CMDOSE					
CM	CMDSTXT	CMDSTXT			LongText	What was the individual dose of the (concomitant) [mediation/treatment/therapy]?	CMDOSE, CMDOSTXT	Parse out numeric values into CMDOSE and non-numeric values into CMDOSTXT				

Create End to End Mapping Before Study Starts



FormOID	FieldOID	VariableOID	DataDictionaryName	CodingDictionary	ControlType	PreText	SDTM Variable	SDTM Transformation Logic	CT SUBSET USED IN STUDY	Define.xml Origin	Define.xml Comment	Used in AdaM Dataset
CM	CMDOSFRQ	CMDOSFRQ	CMDOSFRQ		DropDownList	What was the frequency of the (concomitant) [medication/treatment/therapy]?	CMDOSFRQ		CMDOSFRQ_5			
CM	CMROUTE	CMROUTE	CMROUTE		SearchList	What was the route of administration of the (concomitant) [medication/treatment/therapy]?	CMROUTE		CMROUTE_9			
CM	CMSTDAT	CMSTDAT			DateTime	What was the (concomitant) [medication/treatment/therapy/dose] start date?	CMSTDTC	Concatenate CMSTDAT with CMSTTIM, Reformat as ISO 8601				
CM	CMSTTIM	CMSTTIM			DateTime	What was the (concomitant) [medication/treatment/therapy/dose] start time?	CMSTDTC	Concatenate CMSTDAT with CMSTTIM, Reformat as ISO 8601				
CM	CMPRIOR	CMPRIOR	NY		DropDownList	Was the (concomitant) [medication/treatment/therapy] given/taken prior to [CMSTTPT]?; Was the (concomitant) [medication/treatment/therapy] given/taken prior to study start?	CMSTRTPT	If CMPRIOR = Y, CMSTRTPT = BEFORE				
CM	CMONGO	CMONGO	NY		DropDownList	Was the (concomitant) [medication/treatment/therapy] ongoing?	CMENRTPT	If CMONGO = Y, CMENRTPT = ONGOING				
CM	CMENDAT	CMENDAT			DateTime	What was the (concomitant) [medication/treatment/therapy/dose] end date?	CMENDTC	Concatenate CMENDAT with CMENTIM, Reformat as ISO 8601				
CM	CMENTIM	CMENTIM			DateTime	What was the [medication/treatment/therapy/dose] end time?	CMENDTC	Concatenate CMENDAT with CMENTIM, Reformat as ISO 8601				
CM	CMDECOD	CMDECOD		WHO-Drug	LongText	Data Element Concomitant Meds Dictionary or Standardized Term does not have Preferred Question Text	CMDECOD			Assigned	Populated using Preferred name	
CM	CMCLAS	CMCLAS		WHO-Drug	LongText	Data Element Concomitant Meds Class Description does not have Preferred Question Text	CMCLAS			Assigned	Populated using ATC4	

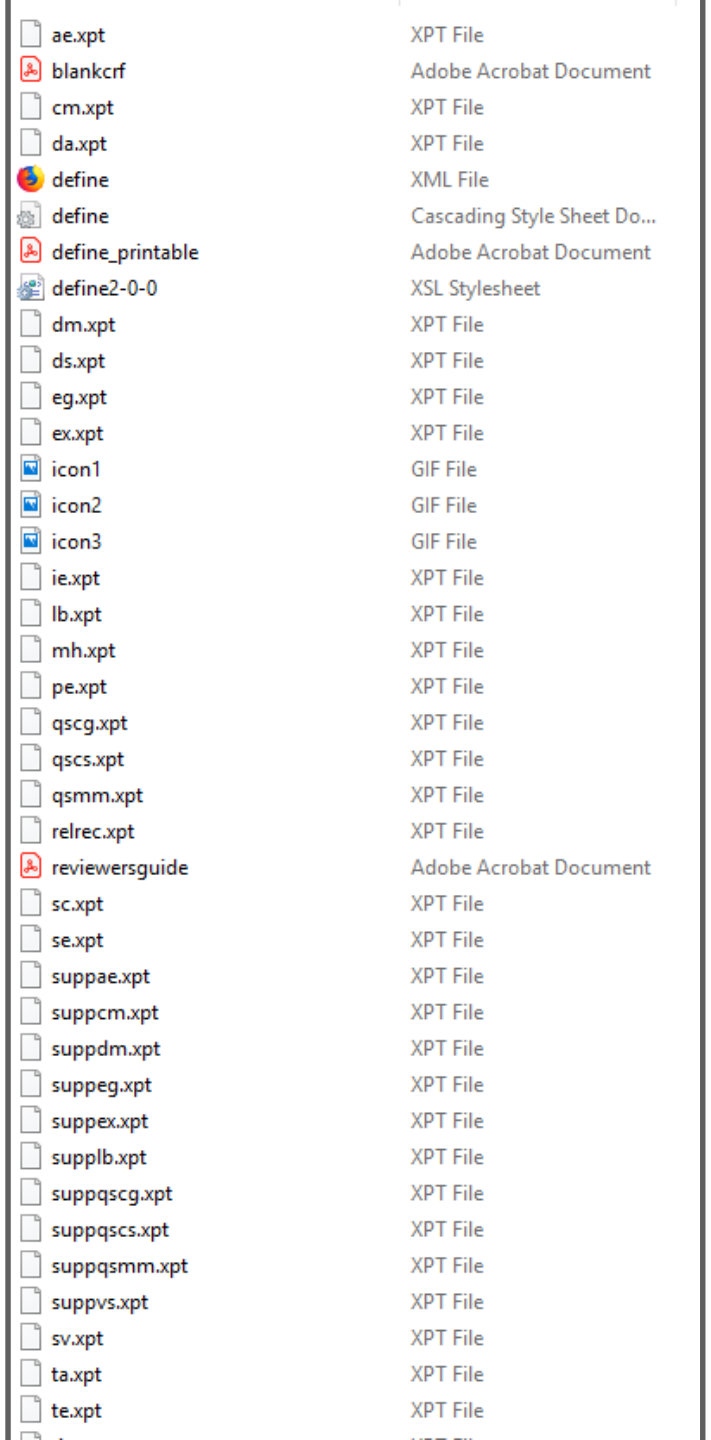
Submission: Stages of Preparation



- After the data have been collected
  - Ensure final mapping documentation is complete/correct
  - Send all data to SDTM programmers with SDTM-annotated blank CRF
  - Send all codelists that were used in the study
  - Communicate other important data handling conventions to SDTM Programmers
  - Participate in validation activities to support SDTM preparation
- Study teams and programmers assemble the SDTM and ADaM data and documentation, perform analysis, and write the Clinical Study Reports

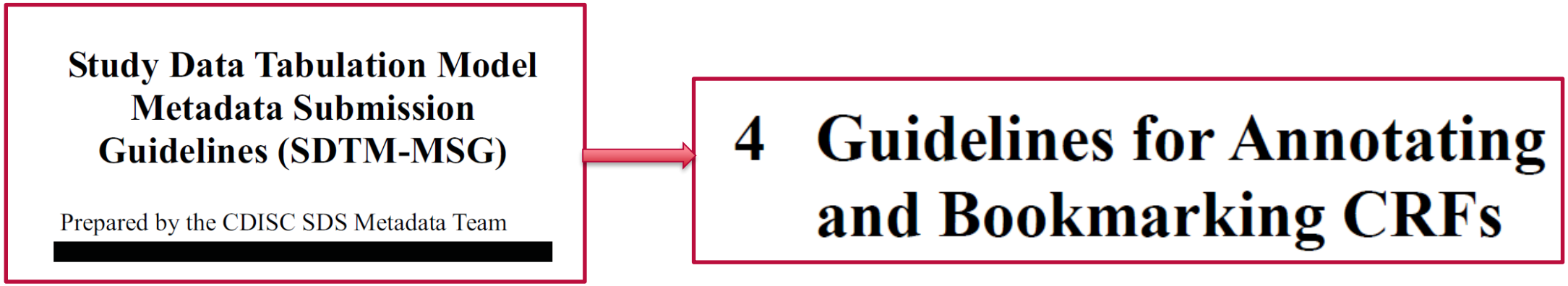
Submission Data and Documentation

One set per study in Module 5 Tabulations

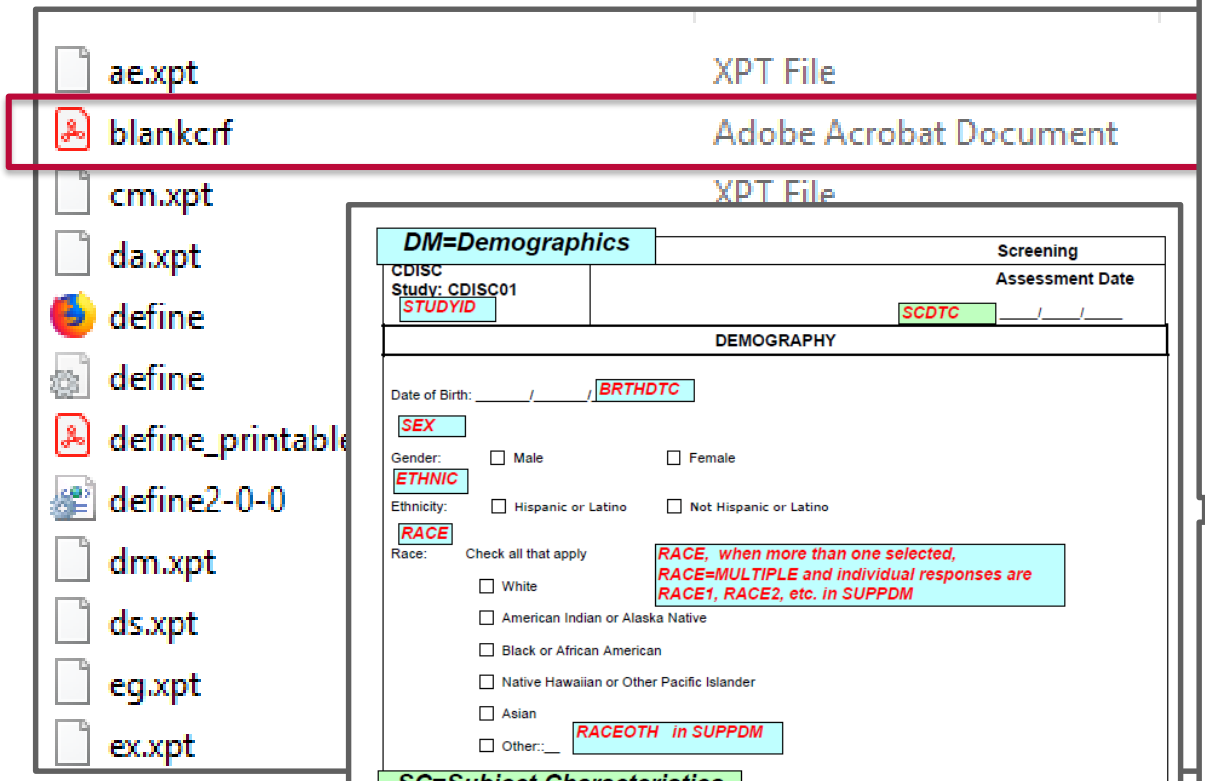


Study Documentation that is Required in Addition to SDTM Datasets

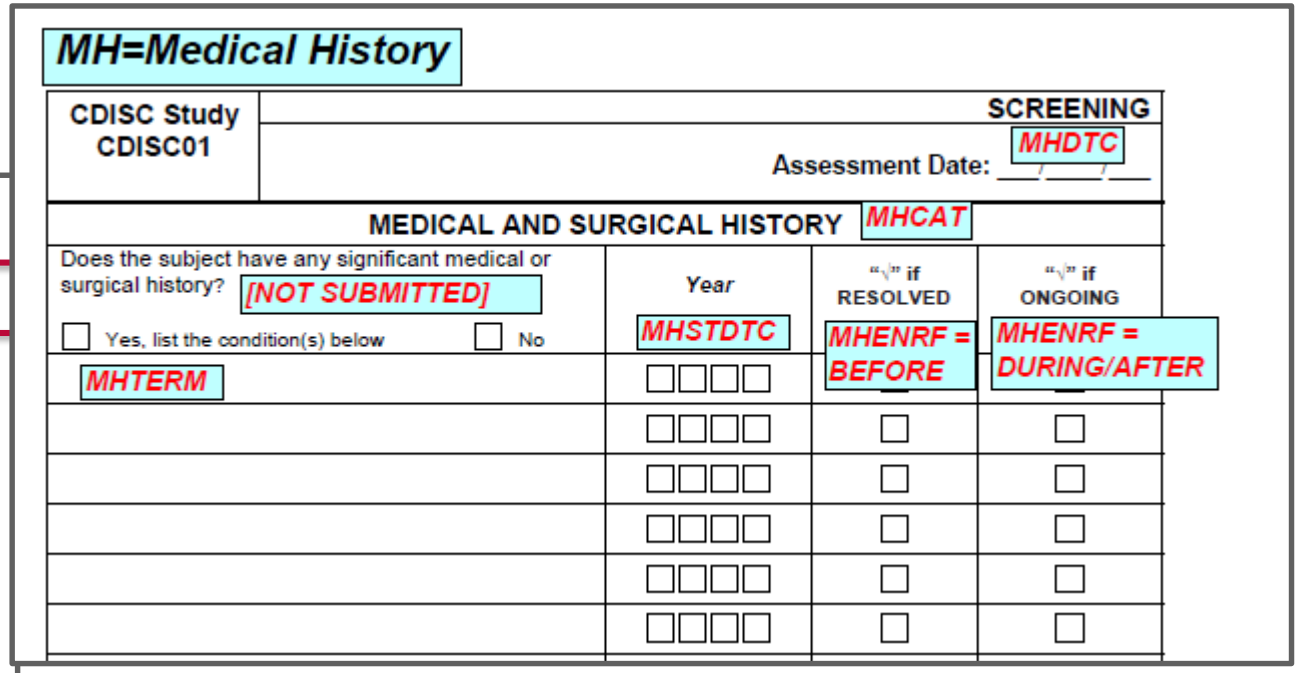
- **Annotated CRFs** should be created for their intended purpose
  - Annotations for study database programmers would have the CDASH annotation
  - Annotations for SDTM programmers would have both CDASH and SDTM annotations
  - Annotations for ADaM programmers need **SDTM annotations**
    - This one is also required in the eCTD to accompany the SDTM tabulations for the study
    - Current conventions for annotation are described in CDISC Metadata Submission Guidelines found in the Downloads section at https://www.cdisc.org/standards/foundational/sdtmig "MSG for SDTMIG" (zip file)

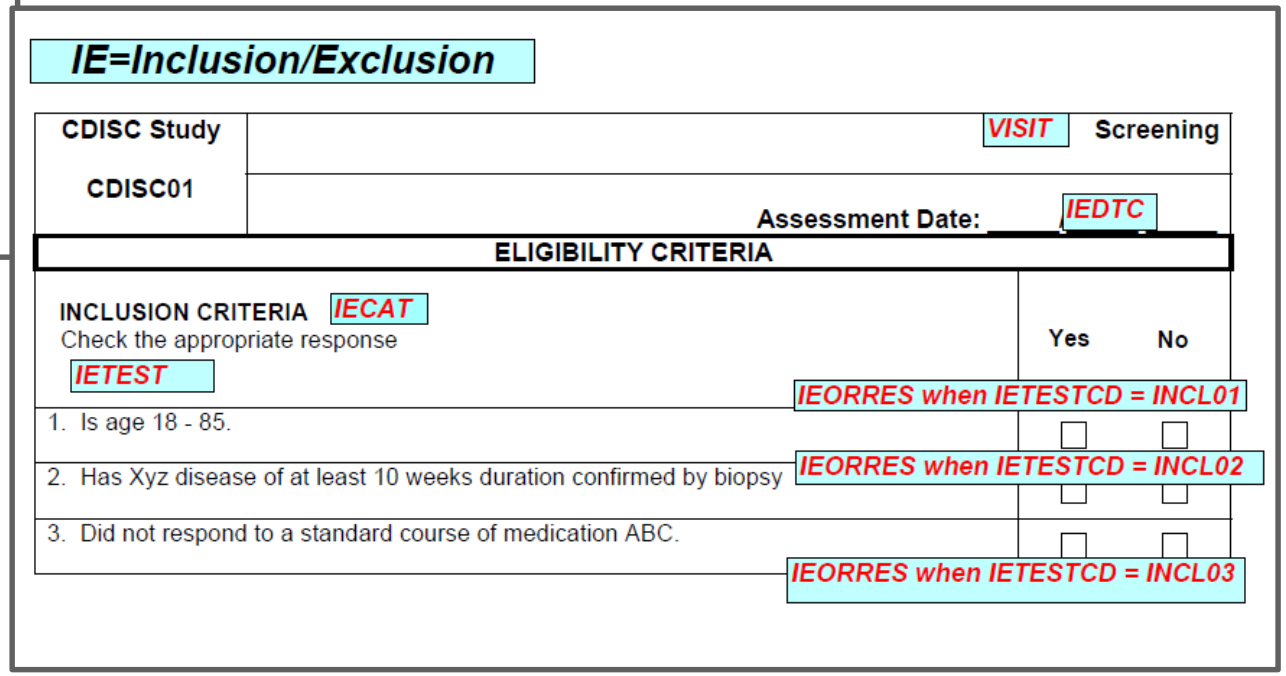


Submission Data and Documentation



- Blank
- Annotated for SDTM

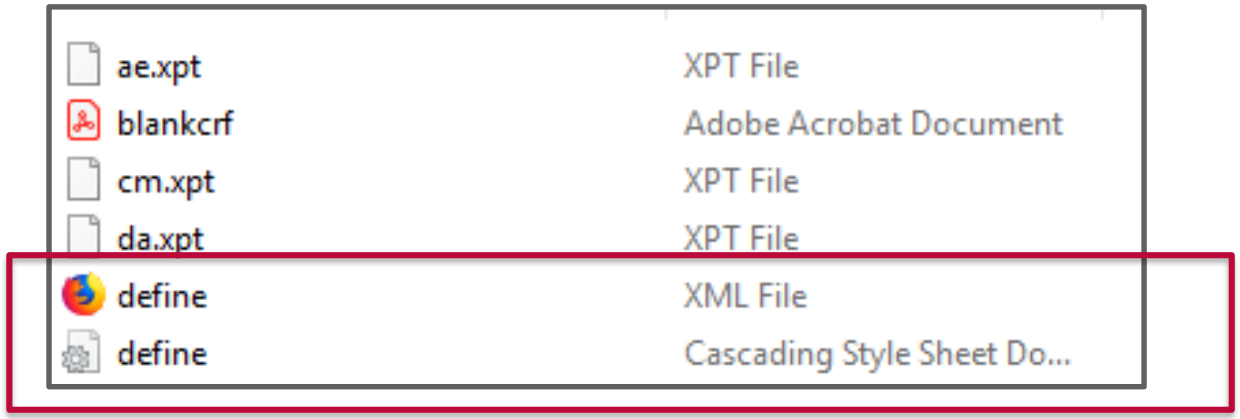




Study Documentation that is Required in Addition to SDTM Datasets

- **Define.xml** - the metadata for your SDTM data
  - Follows the ODM Define-XML standard
    - https://www.cdisc.org/standards/data-exchange/define-xml
  - Create one Define.xml per study (one each for SEND, SDTMIG and ADaM data)
  - Test it (can you open and navigate)
  - Validate it along with your SDTM datasets

Submission Data and Documentation



- XML file with the study metadata
- One per study (one each for SEND, SDTM and ADaM)
- Style Sheet to make Define.xml human readable and navigable

define.xml

```
<?xml version="1.0" encoding="UTF-8"?>
<?xml-stylesheet type="text/xsl" href="define2-0-0.xsl"?>
<!-- ************************************************************************** -->
<!-- File: define.xml  -->
<!-- Date: 2011-10-31  -->
<!-- Author: CDISC SDS Metadata Team  -->
<!-- Description: This is an example define.xml document of the Metadata Submission  -->
<!--    Guideline(SDTM-MSG).                                                       -->
<!--    This document complies with the Case Report Tabulation Data Definition     -->
<!--    Specification Version 1.0.0 and has a corresponding style sheet reference  -->
<!-- Release Notes:                                                               -->
<!--  1. If the define.xml includes a style sheet reference and is available in the  -->
<!--      same folder as the define.xml file, a browser application will format the  -->
<!--      output to mirror the data definition document layout as described within   -->
<!--      define.xml specification.                                                  -->
<!--  2. The resulting HTML presentation and the availability and usability of       -->
<!--      functions will vary depending upon which browser application used.         -->
<!-- ************************************************************************** -->

<ODM xmlns="http://www.cdisc.org/ns/odm/v1.2" xmlns:xsi="http://www.w3.org/2001/XMLSchema-instance" xmlns:xlink="http://www.w3.org/1999/xlink" xmlns:def="http://www.cdisc.org/ns/def/v1.0"
xsi:schemaLocation="http://www.cdisc.org/ns/odm/v1.2 http://www.cdisc.org/schema/def/v1.0/define1-0-0.xsd" FileOID="Studycdisc01" ODMVersion="1.2" FileType="Snapshot"
CreationDateTime="2011-06-15T11:00:46">
    <Study OID="cdisc01">
        <GlobalVariables>
            <StudyName>CDISC01</StudyName>
            <StudyDescription>CDISC Test Study</StudyDescription>
            <ProtocolName>CDISC01</ProtocolName>
        </GlobalVariables>
        <MetaDataVersion OID="CDISC.SDTMIG.3.1.2.SDTM.1.2" Name="Study CDISC01, Data Definitions" Description="Study CDISC01, Data Definitions" def:DefineVersion="1.0.0" def:StandardName="CDISC SDTM"
def:StandardVersion="3.1.2">
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            </def:AnnotatedCRF>
            <def:SupplementalDoc>
                <def:DocumentRef leafID="ReviewersGuide"/>
            </def:SupplementalDoc>
            <def:leaf ID="blankcrf" xlink:href="blankcrf.pdf">
                <def:title>Annotated Case Report Form</def:title>
            </def:leaf>
            <def:leaf ID="ReviewersGuide" xlink:href="reviewersguide.pdf">
                <def:title>Reviewers Guide</def:title>
            </def:leaf>
            <def:ComputationMethod OID="COMPMETHOD.QTCB">QTcB = QT interval / square root of (60 / heart rate)</def:ComputationMethod>
            <def:ComputationMethod OID="COMPMETHOD.QTCF">QTcF = QT interval / cubic root of (60 / heart rate)</def:ComputationMethod>
            <def:ValueListDef OID="ValueList.DA.DATESTCD">
```

WITHOUT a Style Sheet - it's just XML

- Annotated Case Report Form
- Reviewers Guide
- Datasets
- Value Level Metadata
- Computational Algorithms
- Controlled Terms

WITH a Style Sheet it is readable and can be used to navigate the data, SDRG and the CRF

Datasets for Study CDISC01

Dataset	Description	Class	Structure	Purpose	Keys	Location
TA	Trial Arms	Trial Design	One record per planned Element per Arm	Tabulation	STUDYID, ARMCD, TAETORD	ta.xpt
TE	Trial Elements	Trial Design	One record per planned Element	Tabulation	STUDYID, ETCD	te.xpt
TI	Trial Inclusion/Exclusion Criteria	Trial Desig			ETESTCD	ti.xpt
TS	Trial Summary	ial Desig	value		SPARMCD, TSSEQ	ts.xpt
TV	Trial Visits		sit per Arm	Tabulation	STUDYID, VISITNUM, ARMCD	tv.xpt
DM	Demographics			Tabulation	STUDYID, USUBJID	dm.xpt
SE	Subject Elements	rpose	nent per subject	Tabulation	STUDYID, USUBJID, SESTDTC, SEENDTC, TAETORD, ETCD	se.xpt
SV	Subject Visits	ecial Purpose	One record per actual visit per subject	Tabulation	STUDYID, USUBJID, SVSTDTC, VISITNUM	sv.xpt
CM	Concomitant Medications	Interventions	One record per recorded medication occurrence or constant-dosing interval per subject	Tabulation	STUDYID, USUBJID, CMSTDTC, CMENDTC, CMCAT, CMTRT, CMDOSTXT, CMDOSU, CMINDC, CMDOSFRQ	cm.xpt
EX	Exposure	Interventions	One record per constant dosing interval per subject	Tabulation	STUDYID, USUBJID, EXSTDTC, EXENDTC, EXTRT, EXDOSE	ex.xpt
AE	Adverse Events	Events	One record per adverse event per subject	Tabulation	STUDYID, USUBJID, AEDECOD, AESTDTC	ae.xpt
DS	Disposition	Events	One record per disposition status or protocol milestone per subject	Tabulation	STUDYID, USUBJID, DSSTDY, DSSTDTC, DSCAT, DSDECOD	ds.xpt
MH	Medical History	Events	One record per medical history event per subject	Tabulation	STUDYID, USUBJID, MHCAT, MHTERM, MHDTC, MHSTDTC	mh.xpt
DA	Drug Accountability	Findings	One record per drug accountability finding per subject	Tabulation	STUDYID, USUBJID, DATESTCD, DADTC	da.xpt
EG	ECG Test Results	Findings	One record per ECG observation per visit per subject	Tabulation	STUDYID, USUBJID, EGTESTCD, EGDTC, VISITNUM	eg.xpt
IE	Inclusion/Exclusion Criteria Not Met	Findings	One record per inclusion/exclusion criterion not met per subject	Tabulation	STUDYID, USUBJID, IETESTCD	ie.xpt
LB	Laboratory Tests Results	Findings	One record per analyte per visit per subject	Tabulation	STUDYID, USUBJID, LBCAT, LBMETHOD, LBTESTCD, LBDTC, VISITNUM	lb.xpt
PE	Physical Examination	Findings	One record per body system or abnormality	Tabulation	STUDYID, USUBJID, PETESTCD, PEDTC,	pe.xpt

Click on links to navigate

To dataset

To variable level metadata for the dataset

Demographics Dataset (DM)						dm.xpt
Variable	**Label**	**Type**	**Controlled Terms or Format**	**Origin**	**Role**	**Comment**
STUDYID	Study Identifier	text		Protocol	IDENTIFIER	
DOMAIN	Domain Abbreviation	text		Assigned	IDENTIFIER	
USUBJID	Unique Subject Identifier	text		Derived	IDENTIFIER	Concatenation of STUDYID.SUBJID
SUBJID	Subject Identifier for the Study	text		CRF Page 3	TOPIC	
RFSTDTC	Subject Reference Start Date/Time	date	ISO8601	Derived	RECORD QUALIFIER	For safety subjects equal to first date/time of study drug. Null for screen failures.
RFENDTC	Subject Reference End Date/Time	date	ISO8601	Derived	RECORD QUALIFIER	For safety subjects = termination date. Null for screen failures.
SITEID	Study Site Identifier	text		CRF Page 3	RECORD QUALIFIER	
BRTHDTC	Date/Time of Birth	date	ISO8601	CRF Page 6	RECORD QUALIFIER	
AGE	Age	integer		Derived	RECORD QUALIFIER	Screening Date - Birth date
AGEU	Age Units	text		Derived	VARIABLE QUALIFIER	Defaulted to YEARS
SEX	Sex	text	SEX	CRF Page 6	RECORD QUALIFIER	
RACE	Race	text	RACE	CRF Page 6		
ETHNIC	Ethnicity	text	ETHNIC	CRF Page 6		
ARMCD	Planned Arm Code	text	ARMCD	Derived	QUALIFIER	based on Randomization Number. See Note 2.1
ARM	Description of Planned Arm	text	ARM	Derived	SYNONYM QUALIFIER	From description of arm in TRIAL ARM (TA) based on Randomization Number
COUNTRY	Country	text	ISO3166	Assigned	RECORD QUALIFIER	
Supplemental Qualifier Dataset (SUPPDM)						

Click on links to navigate to value list used in this study

Computational Algorithms (COMPMETHOD.QTCB)	
Reference Name	**Computation Method**
COMPMETHOD.QTCB	QTcB = QT interval / square root of (60 / heart rate)
Computational Algorithms (COMPMETHOD.QTCF)	
Reference Name	**Computation Method**
COMPMETHOD.QTCF	QTcF = QT interval / cubic root of (60 / heart rate)

Go to the top of the define.xml

Date of document generation(2011-06-15T11:00:46)

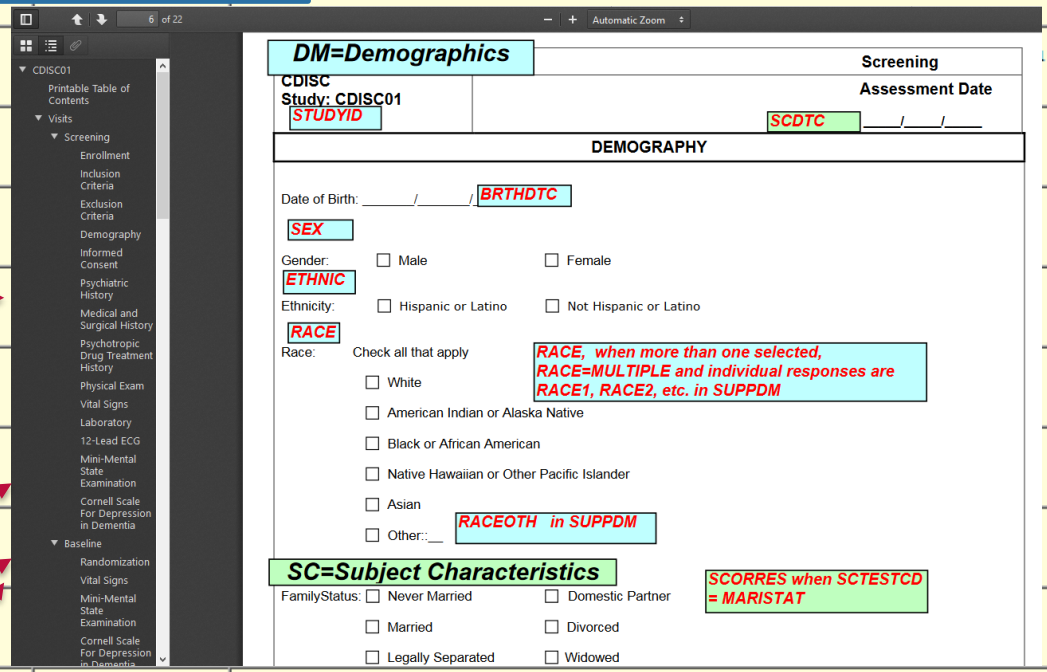
Controlled Terminology (Code Lists)	
ACN, Reference Name (ACN)	
Code Value	**Code Text**
DOSE NOT CHANGED	DOSE NOT CHANGED
DOSE REDUCED	DOSE REDUCED
DRUG INTERRUPTED	DRUG INTERRUPTED
DRUG WITHDRAWN	DRUG WITHDRAWN
AEENRF, Reference Name (AEENRF)	
Code Value	**Code Text**
AFTER	AFTER
AEREL, Reference Name (AEREL)	
Code Value	**Code Text**
NOT RELATED	NOT RELATED
POSSIBLY RELATED	POSSIBLY RELATED
RELATED	RELATED
AESEV, Reference Name (AESEV)	
Code Value	**Code Text**
MILD	MILD
MODERATE	MODERATE

Demographics Dataset (DM) — dm.xpt

Variable	Label	Type	Controlled Terms or Format	Origin	Role	Comment
STUDYID	Study Identifier	text		Protocol	IDENTIFIER	
DOMAIN	Domain Abbreviation					
USUBJID	Unique Subject Identifier					tenation of STUDYID.SUBJID
SUBJID	Subject Identifier for the Study					
RFSTDTC	Subject Reference Start Date/Time	date	ISO8601	Derived		
RFENDTC	Subject Reference End Date/Time	date	ISO8601	Derived		
SITEID	Study Site Identifier	text		CRF Page 3		
BRTHDTC	Date/Time of Birth	date	ISO8601	CRF Page 6		
AGE	Age	integer		Derived		
AGEU	Age Units	text		Derived		
SEX	Sex	text	SEX	CRF Page 6		
RACE	Race	text	RACE	CRF Page 6		
ETHNIC	Ethnicity	text	ETHNIC	CRF Page 6	RECORD QUALIFIER	
ARMCD	Planned Arm Code	text	ARMCD	Derived	RECORD QUALIFIER	Derived from arm code in TRIAL ARM (TA) based on Randomization Number. See Note 2.1
ARM	Description of Planned Arm	text	ARM	Derived	SYNONYM QUALIFIER	From description of arm in TRIAL ARM (TA) based on Randomization Number
COUNTRY	Country	text	ISO3166	Assigned	RECORD QUALIFIER	

Supplemental Qualifier Dataset (SUPPDM)

Click on page number to open that aCRF page



Value Level Metadata (ValueList.DA.DATESTCD)

Source Variable	Value	Label	Type	Controlled Terms or Format	Origin	Comment
DATESTCD	DISPAMT	Dispensed Amount	integer		CRF Page 19	
DATESTCD	RETAMT	Returned Amount	integer		CRF Page 19	

Value Level Metadata (ValueList.EG.EGTESTCD)

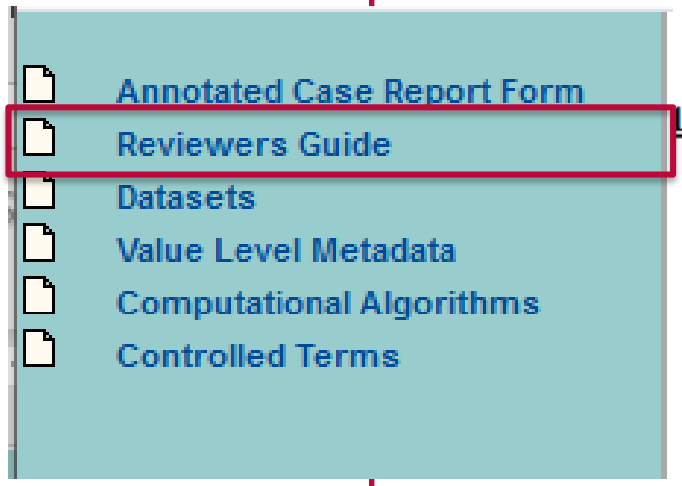
Source Variable	Value	Label	Type	Controlled Terms or Format	Origin	Comment
EGTESTCD	INTP	Interpretation	text	NABCLIN	CRF Page 12	
EGTESTCD	PRMEAN	Summary (Mean) PR Duration	integer		CRF Page 12	
EGTESTCD	QRSDUR	Summary (Mean) QRS Duration	integer		CRF Page 12	
EGTESTCD	QTCB	QTcB - Bazett's Correction Formula	float		DERIVED	See Computational Method: COMPMETHOD.QTCB
EGTESTCD	QTCF	QTcF - Fridericia's Correction Formula	float		DERIVED	See Computational Method: COMPMETHOD.QTCF
EGTESTCD	QTMEAN	Summary (Mean) QT Duration	integer		CRF Page 12	
EGTESTCD	VRMEAN	Summary (Mean) Ventricular Rate	integer		CRF Page 12	

Value Level Metadata (ValueList.PE.PETESTCD)

Source Variable	Value	Label	Type	Controlled Terms or Format	Origin	Comment
PETESTCD	PE01	Appearance/Skin	text		CRF Page 10	
PETESTCD	PE02	Head/Neck (Including Thyroid)	text		CRF Page 10	
PETESTCD	PE03	Eyes-Ears-Nose-Throat	text		CRF Page 10	
PETESTCD	PE04	Cardiovascular	text		CRF Page 10	
PETESTCD	PE05	Pulmonary	text		CRF Page 10	
PETESTCD	PE06	Abdomen	text		CRF Page 10	
PETESTCD	PE07	Neurological	text		CRF Page 10	
PETESTCD	PE08	Musculoskeletal	text		CRF Page 10	
PETESTCD	PE09	Other	text		CRF Page 10	

Value Level Metadata (ValueList.SC.SCTESTCD)

Source				Controlled Terms		



Navigate directly to a section or document using the navigation pane

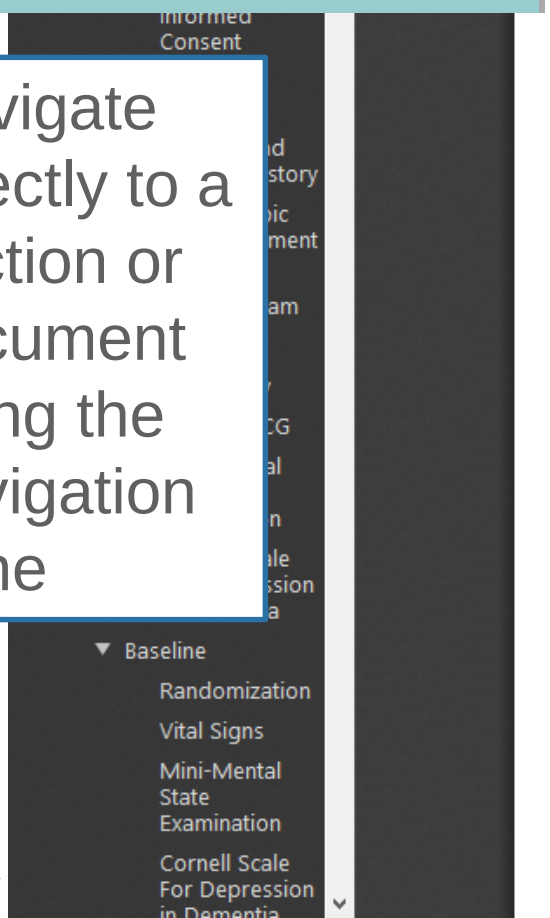
1.0 SDTM VALIDATION CRITERIA

Table 1. Sample Error Explanations

Domain	*Error Message*	*Explanation*
EX	**High Severity:** This subject is not found in the EX domain.	Subjects assigned to an ARMCD but who are missing exposure data did not take study medication.
VS, LB, EG, DA	No Baseline result	**Not an error:** The subjects without Baseline result flags are Screen Failures.
LB	Missing units on value	**Not an error:** Qualitative tests in LB have no standardized numeric results or units.
CM	Start date expected when end date provided	**Not an error:** Start date is unknown.

- Annotated Case Report Form
- Reviewers Guide
- Datasets
- Value Level Metadata
- Computational Algorithms
- Controlled Terms

Navigate directly to a section or document using the navigation pane



DM=Demographics

Screening

CDISC
Study: CDISC01
STUDYID

Assessment Date
SCDTC ____/____/____

DEMOGRAPHY

Date of Birth: _____/_____/_____ BRTHDTC

SEX

Gender: ☐ Male ☐ Female

ETHNIC

Ethnicity: ☐ Hispanic or Latino ☐ Not Hispanic or Latino

RACE

Race: Check all that apply

RACE, when more than one selected, RACE=MULTIPLE and individual responses are RACE1, RACE2, etc. in SUPPDM

- ☐ White
- ☐ American Indian or Alaska Native
- ☐ Black or African American
- ☐ Native Hawaiian or Other Pacific Islander
- ☐ Asian
- ☐ Other::__ RACEOTH in SUPPDM

SC=Subject Characteristics

SCORRES when SCTESTCD = MARISTAT

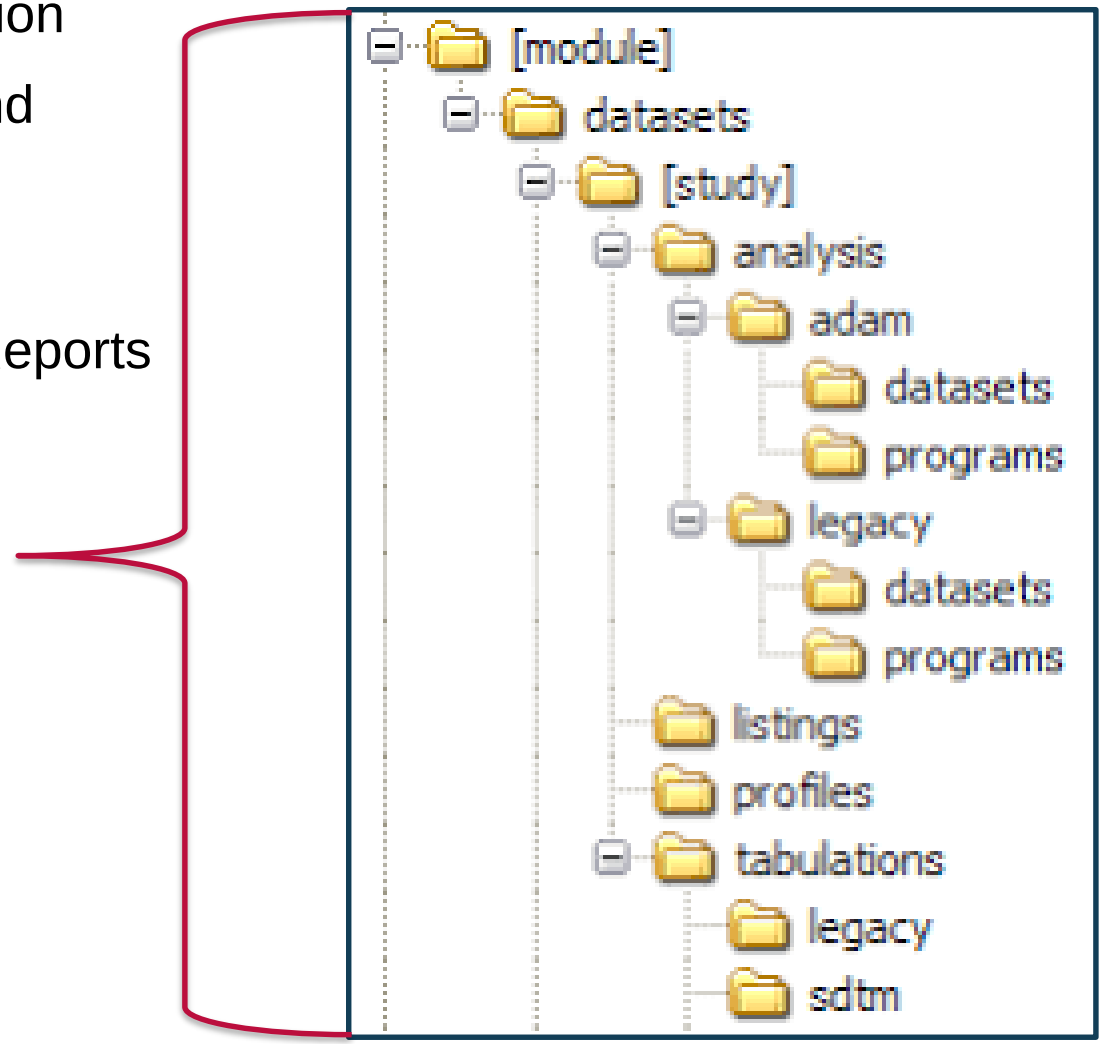
FamilyStatus: ☐ Never Married ☐ Domestic Partner ☐ Married ☐ Divorced ☐ Legally Separated ☐ Widowed

Submission Process: eCTD

- Just like we are required to organize data using Data Standards, the overall submission has to be assembled using a specific folder structure called Common Technical Document
  - https://www.fda.gov/drugs/electronic-regulatory-submission-and-review/electronic-common-technical-document-ectd
  - eCTD has a very specific, detailed Table of Contents (TOC) which can be found on the FDA website
  - https://www.fda.gov/media/76444/download
- **Regulatory Operations** group prepares the documentation and assembles it into the eCTD (very specific, detailed TOC/folder structure for electronic files)

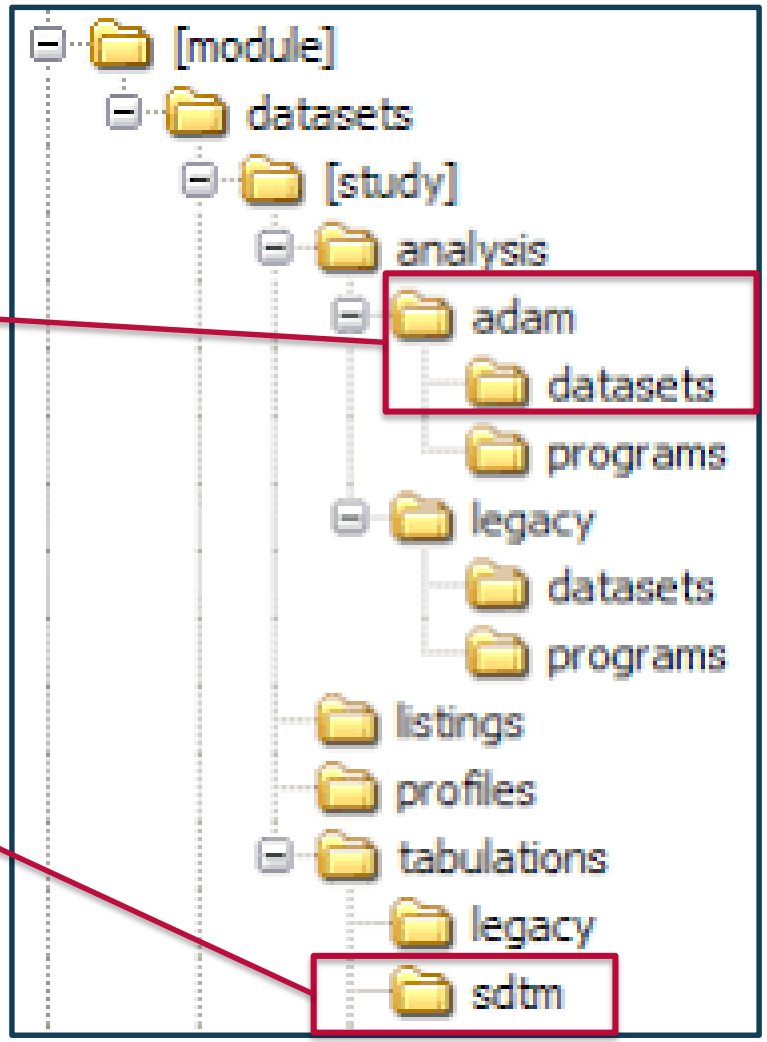
Submission Process: eCTD

- Module 1: Administrative Information
- Module 2: Quality, Non-Clinical and Clinical Summaries
- Module 3: Quality (CMC)
- Module 4: Non-Clinical Studies (Reports and Data)
- **Module 5: Clinical Studies (Reports and Data)**



Submission Process: eCTD Module 5 Data and Metadata

- What data (and associated documentation) should be in Module 5 for each study
  - Analysis Data files
    - ADaM datasets (SAS XPT) - sufficient to support the TLFs in the CSR
    - Define.xml
    - Analysis Data Reviewer's Guide
  - Clinical Data Tabulations
    - SDTM datasets (SAS XPT)
    - Define.xml
    - Blank annotated CRF (SDTM annotation)
    - Study Data Reviewer's Guide



Submission Process: Establish eSG Account

- Submission is done through FDA's electronic Submission Gateway (eSG)
- It is a lengthy process to establish an account (so start early)
- Requirements for using the eSG:
  - Request WebTrader account from FDA
  - Letter of Non-repudiation - eCopy and hard copy
    - To authorize electronic signatures **for your organization -** only has to be done once if you include the entire organization (not limited to individuals)
  - Obtain a Digital Certificate
    - Allows 2-way communication with FDA to ensure no unauthorized access

https://www.fda.gov/industry/create-esg-account/setting-webtrader-account-checklist

Submission Process: Establish eSG Account

- Perform three tests
  - Connection test: To confirm you can send a file (simple PDF or Word file)
  - Load test: Minimum 2GB *after compression* to ensure your connection is stable
    enough to send large files (recommended 7.5 GB to test realistic size of eCTD)
  - Submit example eCTD: To confirm you can create a valid eCTD
- After successful tests, obtain permission to use the eSG for production

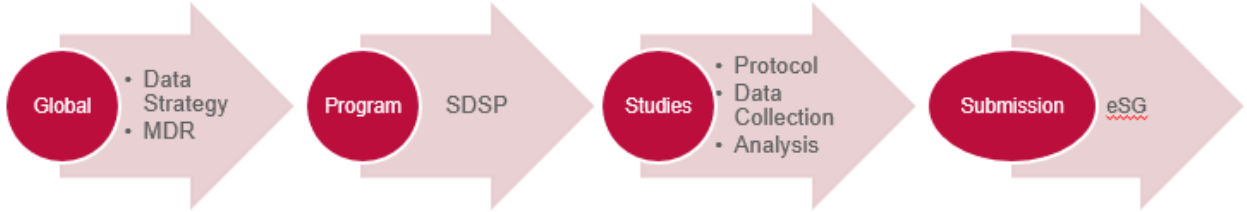
Perform these tests one at a time and confirm each was successful before you go to the next one

https://www.fda.gov/industry/create-esg-account/setting-webtrader-account-checklist

Submission Process: Suggestions for eSG Account

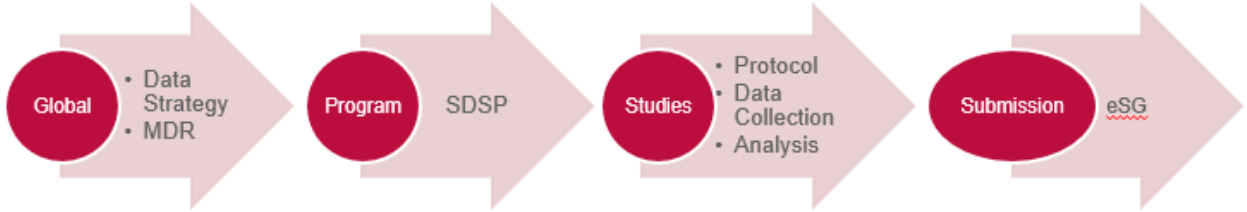
- Start early if you don’t already have an eSG account (minimum 3-4 months)
- Assign a permanent computer as your eSG interface
  - Must maintain a very specific Java configuration for FDA eSG
  - Can be a virtual machine
- Create an ESG account for each group that has submission responsibility
  - Depends on how siloed the Reg Ops group is
  - Don’t have to share passwords
  - People using it know exactly what’s going in - can track what’s going into the eSG

Best Practices



- Establish a Cross-functional, formal governance team / process
  - Stay aware of
    - published (and developing) CDISC standards
    - Published FDA (and PMDA) guidelines and requirements
  - Regularly review and disposition internal needs for
    - Custom domains
    - Custom variables (and associated variable naming fragments)
    - Custom codelists / extended codelists
- Strategically involve team members in **volunteer** activities
  - CDISC teams - keep up with what's new and what's coming in the future, have a voice in how the standards evolve
  - PhUSE teams - handling implementation challenges, developing communication documentation (FDA / SDRG)

Best Practices



- Strategic planning and end to end implementation will make everything go more smoothly
  - CDASH Implementation!
- Begin with the end in mind
  - Build an MDR of concepts that are tied to your analyses (CDASH Implementation!)
  - Build into each concept the set of SDTM variables that are needed to support analysis
  - Connect those SDTM variables to the CDASH collection metadata so you know where they will go in SDTM before you ever start collecting data (this is what CDASH is for!)
  - Validate data throughout the process so it's ready at Submission time
  - Communicate effectively and continuously with your adjacent functional areas (especially SDTM programming)

Helpful Resources

- Electronic Common Technical Document (eCTD)
  - https://www.fda.gov/drugs/electronic-regulatory-submission-and-review/electronic-common-technical-document-ectd
  - TOC: https://www.fda.gov/media/76444/download
- Electronic Submission Gateway (ESG)
  - https://www.fda.gov/industry/electronic-submissions-gateway/about-esg
  - https://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/CreateanESGAccount/ucm114659.htm
  - https://www.fda.gov/industry/electronic-submissions-gateway/esg-submission-process-high-level-technical-validation
  - https://www.fda.gov/drugs/electronic-regulatory-submission-and-review/submit-ectd-or-standardized-data-sample-fda

Helpful Resources

- FDA Webpage to Support Electronic Submissions
  - https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/default.htm
- PhUSE team that answers questions from FDA help desk email
  - https://www.phusewiki.org/wiki/index.php?title=SDTM_FAQ_Team_Responses
- PhUSE Templates
  - Data Reviewers Guides and Study Data Standardization Plan Templates and **Examples**
    - https://www.phuse.eu/css-deliverables
    - SDSP Guide: https://www.phuse.eu/documents/sop/wp/phuse-wp002-sdsp-sponsor-implementation-guide-v1-8408.pdf

Q&A

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