SDTM-MSG v2.0

16-April-2021

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History

- SDTM-MSG v1.0:

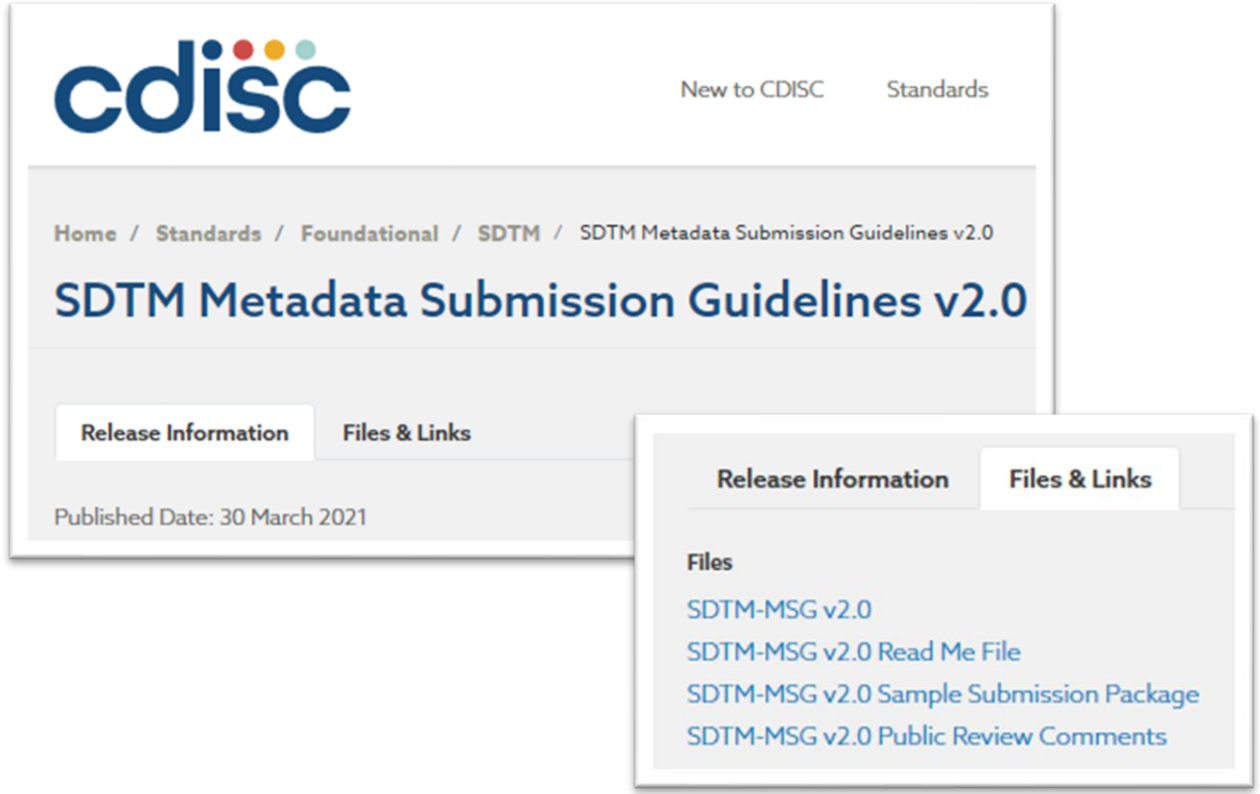
  30-Dec-2011

- SDTM-MSG v2.0 DRAFT:

  18-Sep-2020 for public review

- SDTM-MSG v2.0 Final:

  30-Mar-2021



https://www.cdisc.org/standards/foundational/sdtm/sdtm-metadata-submission-guidelines-v2-0

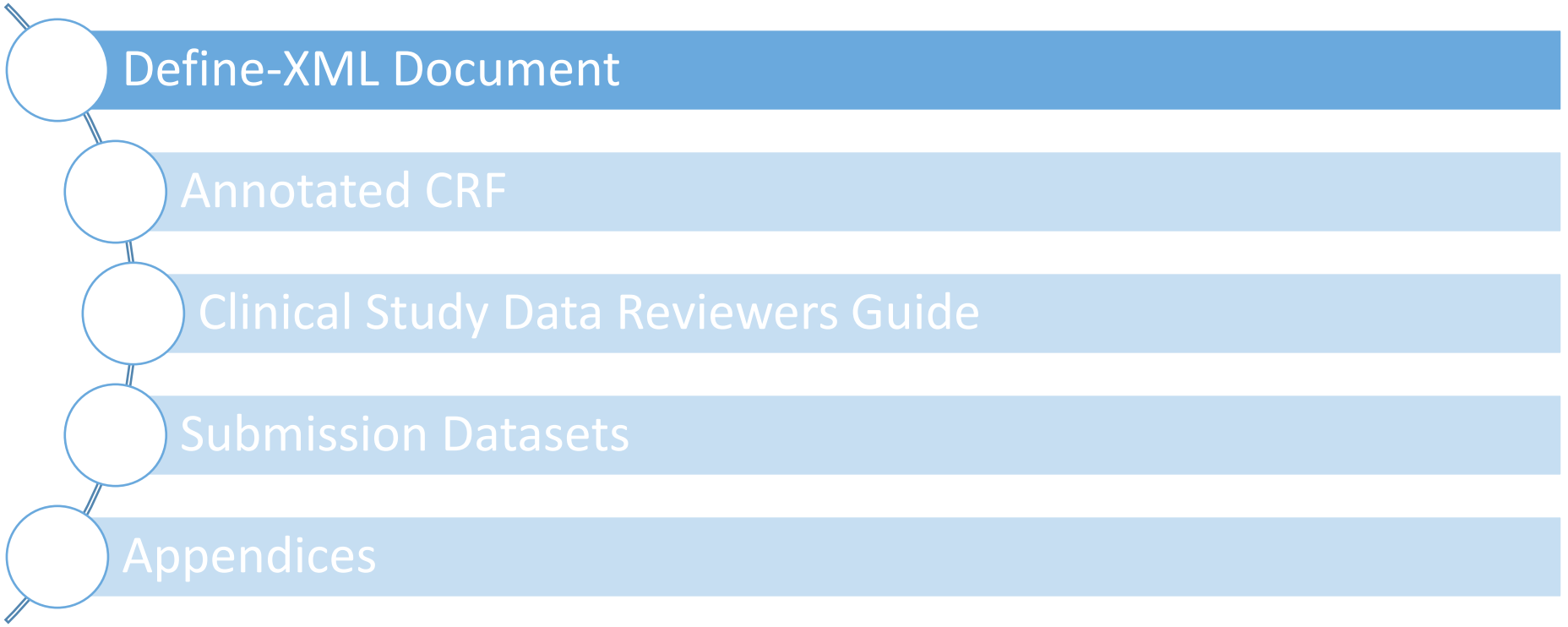
Content

- Guidance for preparing the components of the ICH eCTD M5 Clinical Study Reports ‘sdtm’ folder
- Sample Submission Package including
  - Datasets (*.xpt / *.xml)
  - aCRF
  - Study Data Reviewer’s Guide
- Public Review Comments

➢ **MSG related to SDTM v1.7 / SDTMIG v3.3, Define-XML v2.1, and SDTM Terminology 2020-03-27**

Organization of Document

- Introduction
- Define-XML Document
  - Explanation of metadata definition portion of the submission datasets
- Annotated CRF
  - Guidelines for annotating CRFs according to SDTM specifications
- Clinical Study Data Reviewers Guide
  - Preparation of cSDRG
- Submission Datasets
  - Outline of SDTM datasets contained in the sample submission
- Appendices
  - Additional background material


Define-XML Document
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Appendices

Define-XML Document

- Version 1.0 of the MSG explained the Define-XML document in great detail

V1.0

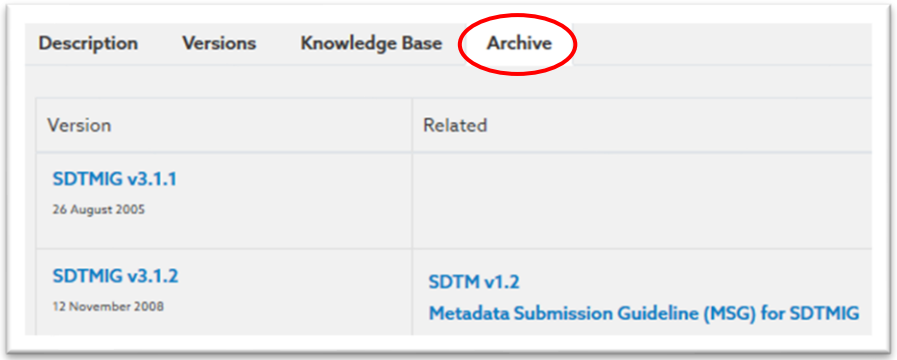
3 DEFINE.XML
3.1 Introduction
3.2 Dataset-Level Metadata
3.2.1 Organization
3.2.2 Content
3.3 Variable-Level Metadata
3.3.1 Organization
3.3.2 Content
3.4 Value-Level Metadata
3.5 Controlled Terminology
3.5.1 Define.xml
Table 3.5.1.1 - Controlled Terminology Metadata
3.5.2 CDISC Controlled Terminology
3.6 Stylesheets for the Define.xml
3.7 Define.xml Schema Validation

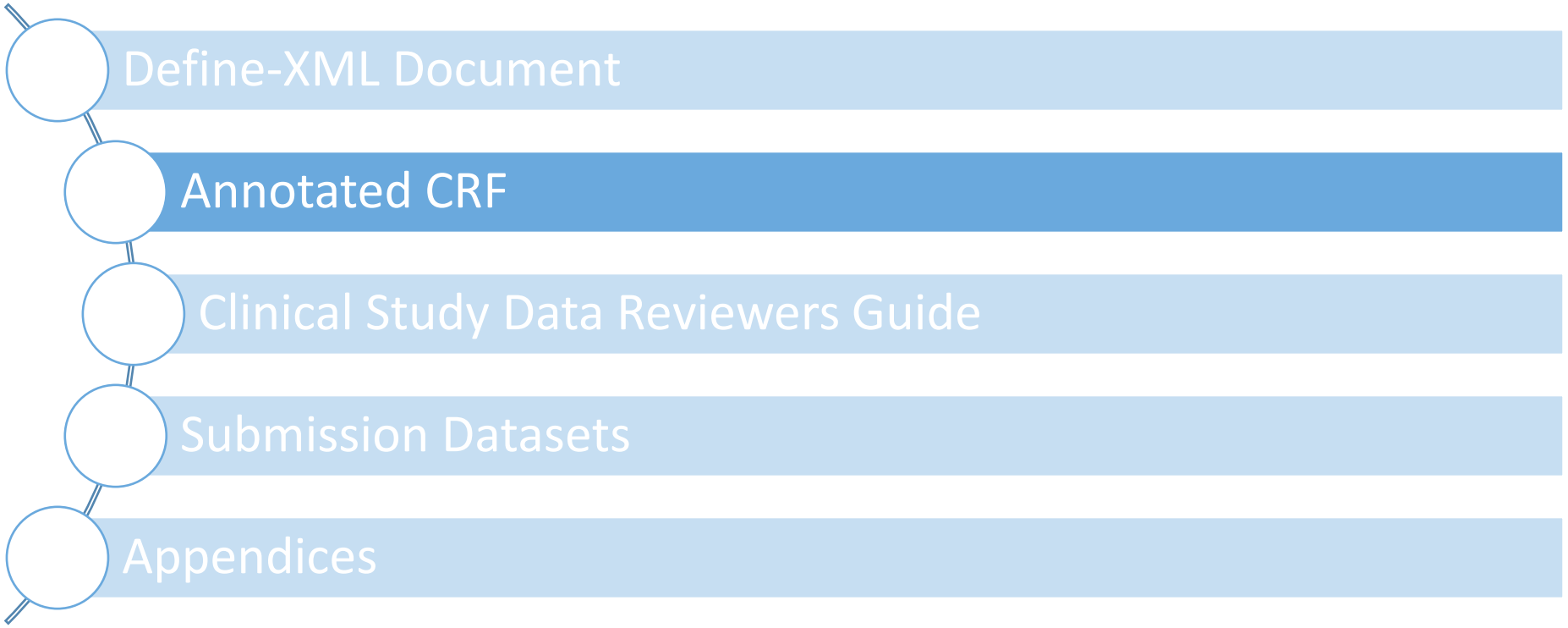
V2.0

2 DEFINE-XML DOCUMENT.....

- Source: https://www.cdisc.org/standards/foundational/sdtmig/

  => Archive

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Annotated CRF

- acrf.pdf is the current filename suggested by FDA and PMDA.

Basic Principles for Annotations

- CRF annotations should be searchable (i.e., text based).
- Annotations should reflect the data that were intended to be submitted within the SDTM.
- If data were intended to be collected but none actually were, it is not necessary to re-annotate the acrf.pdf. The fact that no data were collected will be indicated in the Define-XML document using the “HasNoData” attribute for datasets and variables. This can also be further described in the Clinical Study Data Reviewer’s Guide.
- Dual bookmarking and table of contents are recommended.

Annotated CRF

Basic Principles for Annotations

- General Note: Operational / Administrative Variable Names

  Annotations should only contain annotations for the tabulation datasets.

  Annotations representing sponsors' internal variables (e.g., system or collection variable names), while normally needed by the sponsor for data management, should not be included on the acrf.pdf if these variable names are not part of a regulatory submission.

Annotated CRF

Annotating Unique CRF Pages

- Sponsors can include either the entire CRF casebook or just the unique forms.
- It is recommended that sponsors include and annotate unique forms only. Bookmarking will represent the form as many times as needed to reflect how the data were intended for collection (all visits would be bookmarked and linked to the corresponding unique form).
- Sponsors who choose to submit the entire CRF rather than unique forms are responsible for determining the approach for their submission that best allows the reviewer to understand multiple occurrences of a given page.

Annotated CRF

Annotating Unique CRF Pages

- General Note: Unique Pages

  It is the sponsor's decision to determine what pages are considered unique. The following are some general guidelines that can be used in that determination:

  If a CRF page has a data collection point that is added, removed, or otherwise differs (e.g., allowable values are changed) from other instances of the CRF page, then the page is considered to be unique.

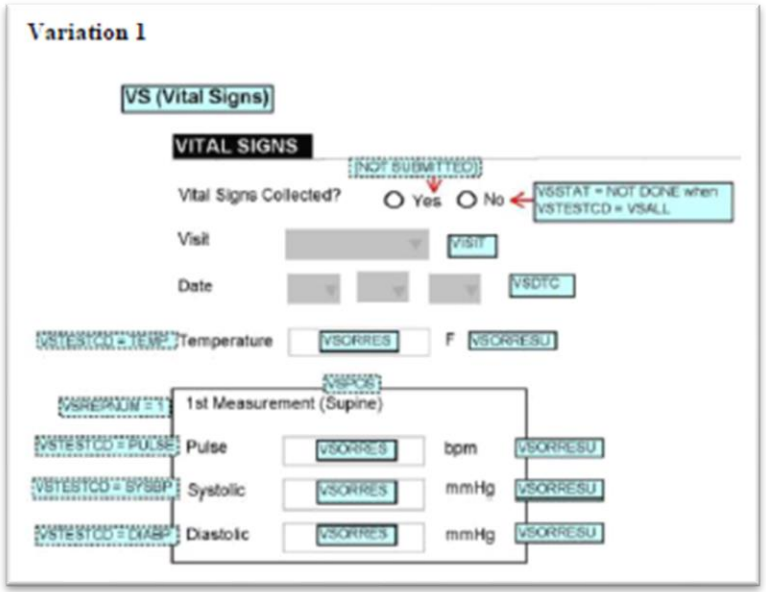
  Minor rearrangements of the CRF page not affecting data collection would generally not affect uniqueness.

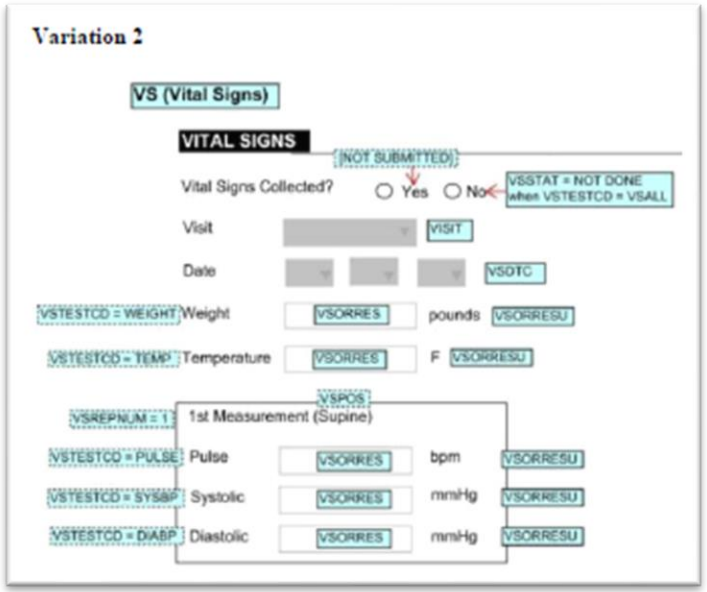
  Instructional (or operational) information on the CRF page not affecting data collection generally would not affect uniqueness.

Annotated CRF

Annotating Unique CRF Pages

- Partial CRF annotations should be avoided. Fully annotation of CRF pages is recommended.





- Recommendation to use dashed annotation borders for annotations which do not represent collected data
  (e.g., VSPOS or VSREPUM pre-printed on CRF page, [NOT SUBMITTED]).

Annotated CRF

Annotating Unique CRF Pages

- General Note: Annotating Nontraditional Digital Collection Sources

  Collection screens of nontraditional digital devices (e.g., ePROs) should be appended to the end of the traditional eCRF. This ensures consistency of data collection sources utilized in a single acrf.pdf.

  Further clarification on what nontraditional digital collection sources may have been included, may be provided within the cSDRG.

Annotated CRF

Appearance of Annotations

- Recommendations to maximize annotation appearance and readability:
  - Each domain represented on the CRF page should have its own annotation
    - Sponsors should ensure consistency in annotation placement based on their CRF design.
    - Annotate domain names rather than dataset (including split dataset) names (e.g., annotate "QS (Questionnaire)" for split QS datasets (QSPH and QSSL))
    - Supplemental qualifier domain names do not need to be annotated. Corresponding supplemental qualifier domain variable are annotated in equivalence to the parent domain.
  - Domain annotations in black text with bold formatting. Example in example SDTM submission package uses Arial font. Sponsors should always consult the respective regulatory agency guidance and / or requirements.

Annotated CRF

Appearance of Annotations

- Variable annotations in black text without bold formatting. Example in example SDTM submission package uses Arial font. Sponsors should always consult the respective regulatory agency guidance and / or requirements.
- Annotations in 12pt font size. Exceptions:
  - Sponsors can increase / reduce font size, if necessary.
  - Regulatory agency guidance / requirements
- Annotations for variables and dataset codes should be capitalized (e.g., AEACN01 in SUPPAE).
- Instructional text and comments should be sentence case, excluding variables and dataset codes, which should be capitalized.

Annotated CRF

Appearance of Annotations

- Use colors when annotating multiple domains on a single CRF page. Apply the following RGB Codes:

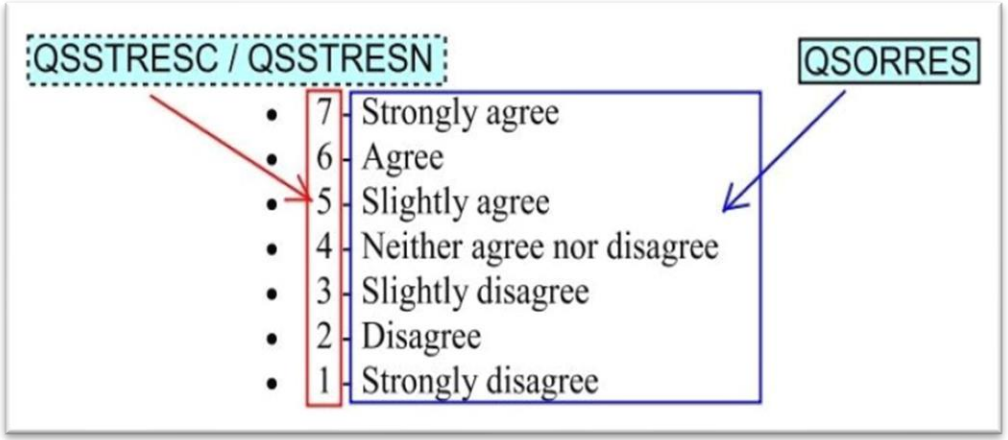
BLUE	DM (Demographics)	191, 255, 255
YELLOW	DS (Disposition)	255, 255, 150
GREEN	SC (Subject Characteristics)	150, 255, 150
ORANGE	VS (Vital Signs)	255, 190, 155

Sponsors who need more colors should use consistent colors and take color blindness into consideration

Annotated CRF

Appearance of Annotations

- Notes, which are no direct variable annotations, should have the color of the domain to which them pertain. Notes that pertain to multiple domains should have an appropriate background that signifies that they are not domain-specific. Sponsors can give such notes a dashed border to differentiate them from collected-variable annotations.
- Avoid covering up text on CRF page
- Supplemental references via boxes, arrows and lines can also be used for further clarification (but avoid when not necessary)



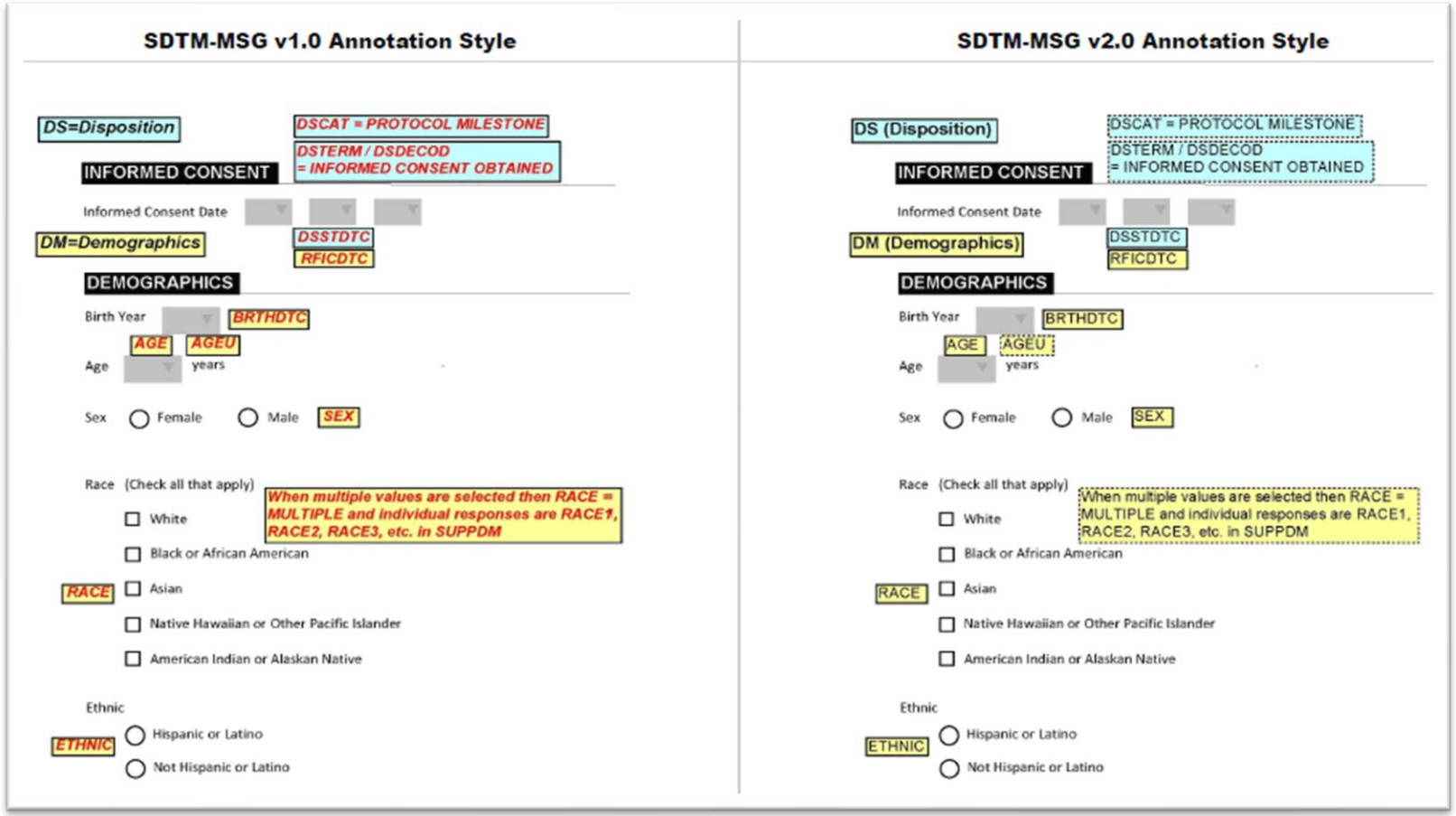
Annotated CRF

Appearance of Annotations

- Use forward slash "/" to separate variables when they are annotated within one annotation box.
- Collected data which will not be in the SDTM data should be annotated as "[NOT SUBMITTED]".
- Do not use quotes when referencing values (e.g., DSCAT = PROTOCOL MILESTONE instead of DSCAT = "PROTOCOL MILESTONE") – but there may be instances where using quotes provides clarity.
- When constructing a "when / then" annotation statement use the format
  <variable> when <variable> = <value>
  e.g., VSORRES / VSORRESU when VSTESTCD = TEMP

Annotated CRF

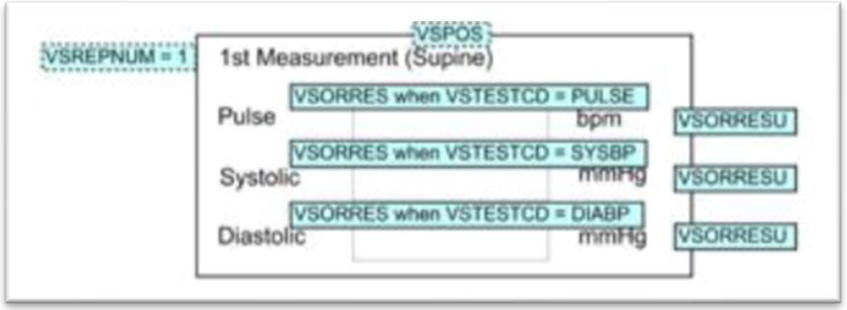
Appearance of Annotations

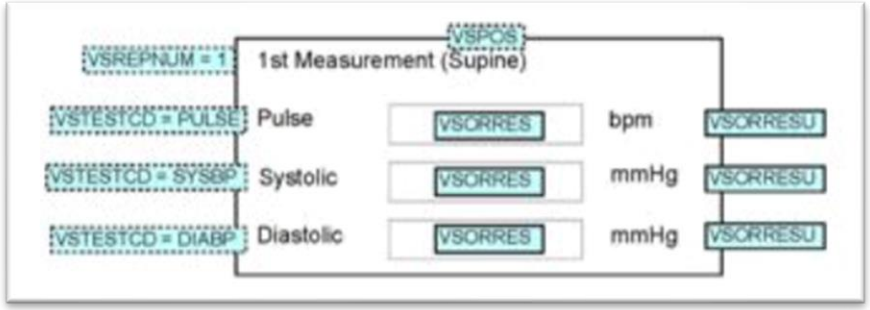


Annotated CRF

Annotating Specific Types of Data

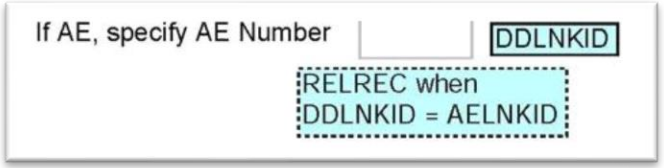
- Findings
  - Due to vertical structure of SDTM findings domain it may be necessary to provide the --TESTCD in the annotation.





- Supplemental Qualifiers

- RELREC
  - When a form indicates a relationship between collected data, the annotations should indicate the collection as well as the RELREC



Annotated CRF

Replacement of Deprecated Pages

- Best Practice

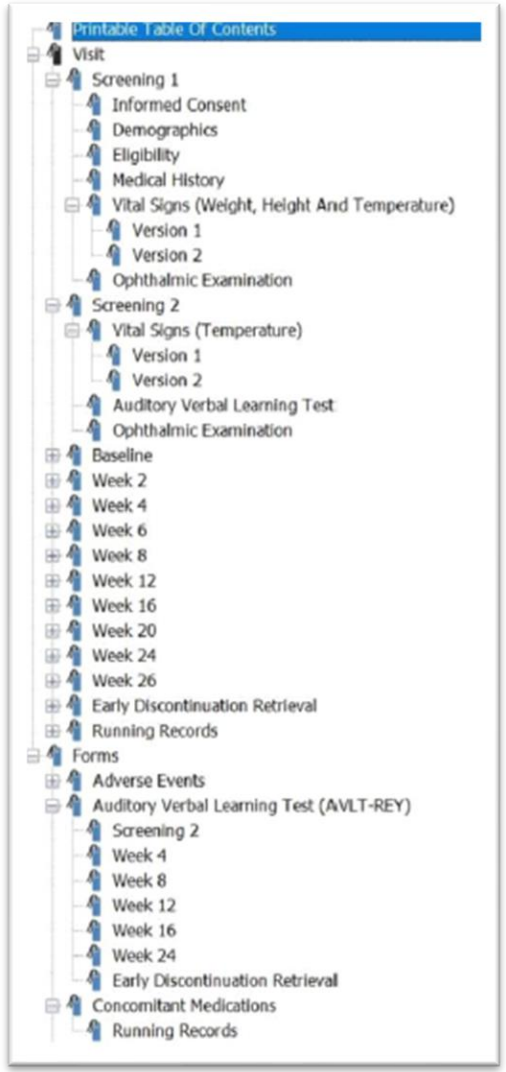
  For traceability purposes, sponsors may need to include a CRF page that was used to collect data but was later deprecated due to protocol changes or other reasons as part of the annotated CRF. There are multiple ways for sponsors to handle such a situation and they should choose how to best represent that in their annotated CRF. This should also be further explained in the cSDRG.

- Example included in example submission package.

Annotated CRF

Bookmarking CRFs/eCRFs

- Dual bookmarking
  - Bookmarks by chronology (ordered according to the study Schedule of Activities (SoA))
    - Pages that are independent of visits (e.g., Adverse Events) should be presented last, under a “Running Records” bookmark.
    - Within each chronological bookmark, topic bookmarks should appear in the order that they appear in the aCRF.
  - Bookmarks by CRF topics / forms (ordered alphabetically or according to appearance in CRF)
    - Within each topic bookmarks should be ordered chronologically according to the SoA.
    - “Domains” in MSG v1.0 has now changed to “Forms” as “Domains” implies SDTM domains.



Annotated CRF

Bookmarking CRFs/eCRFs

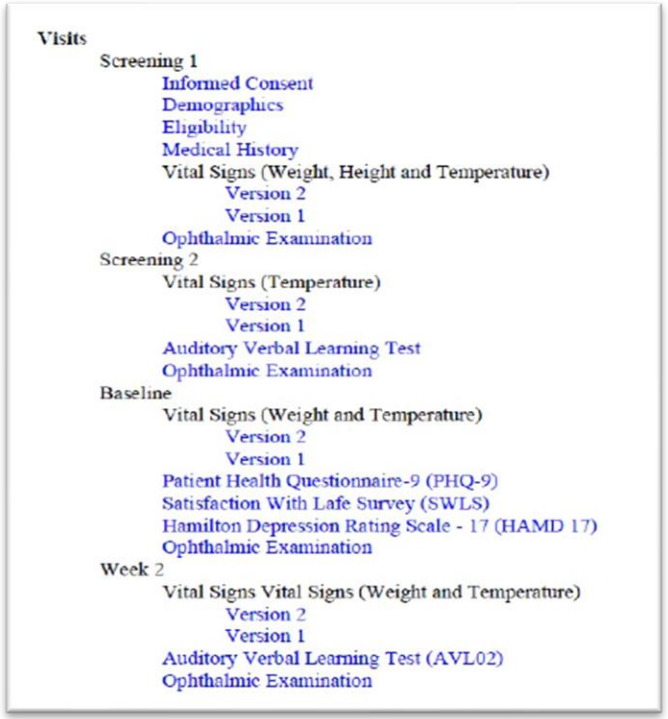
- General Note: Bookmarking Nontraditional Digital Collection Sources

  The SDTM-MSG v2.0 does not provide recommendations regarding bookmarking nontraditional digital collection sources (e.g., ePRO). In such cases, sponsors should follow their own respective standard operating procedures and/or guidelines.

Annotated CRF

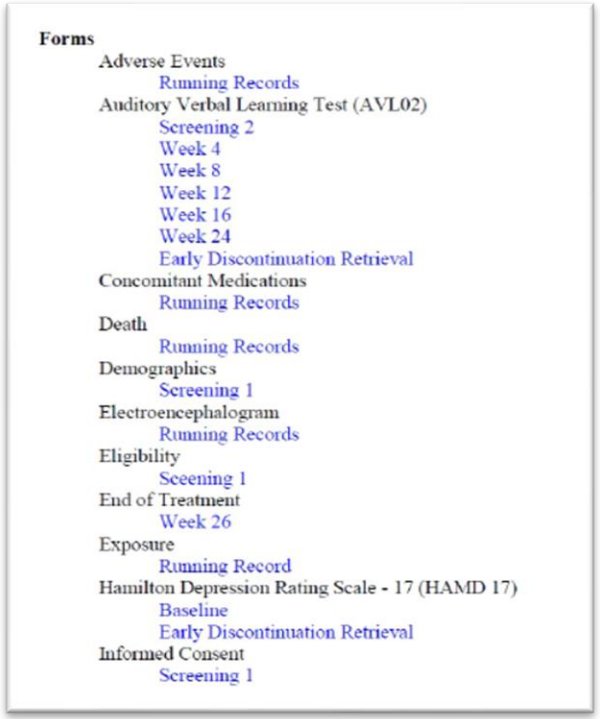
Table of Contents for the aCRF

- A printable TOC may be included at the beginning of the aCRF. The entries should be hyperlinked to the respective CRF page as done with the corresponding bookmarks.



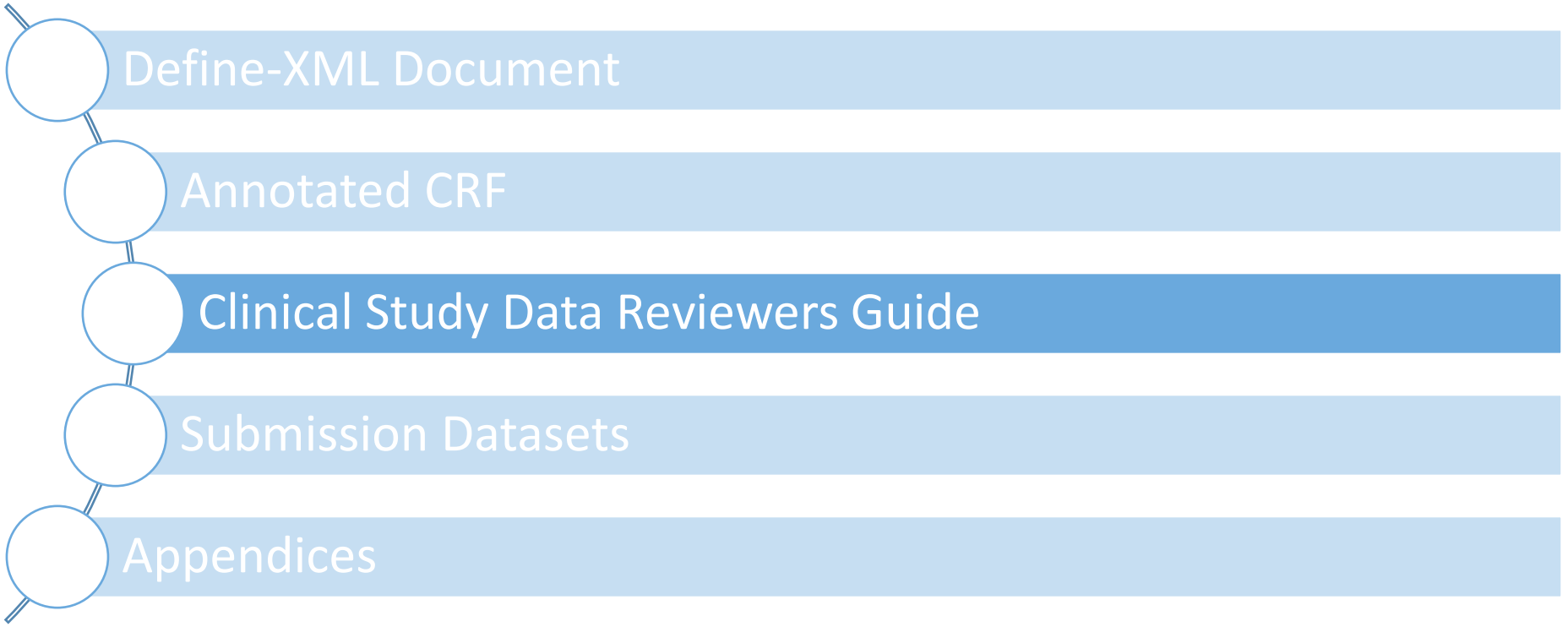
Visits

- Screening 1
  - Informed Consent
  - Demographics
  - Eligibility
  - Medical History
  - Vital Signs (Weight, Height and Temperature)
    - Version 2
    - Version 1
  - Ophthalmic Examination
- Screening 2
  - Vital Signs (Temperature)
    - Version 2
    - Version 1
  - Auditory Verbal Learning Test
  - Ophthalmic Examination
- Baseline
  - Vital Signs (Weight and Temperature)
    - Version 2
    - Version 1
  - Patient Health Questionnaire-9 (PHQ-9)
  - Satisfaction With Lafe Survey (SWLS)
  - Hamilton Depression Rating Scale - 17 (HAMD 17)
  - Ophthalmic Examination
- Week 2
  - Vital Signs Vital Signs (Weight and Temperature)
    - Version 2
    - Version 1
  - Auditory Verbal Learning Test (AVL02)
  - Ophthalmic Examination



Forms

- Adverse Events
  - Running Records
- Auditory Verbal Learning Test (AVL02)
  - Screening 2
  - Week 4
  - Week 8
  - Week 12
  - Week 16
  - Week 24
  - Early Discontinuation Retrieval
- Concomitant Medications
  - Running Records
- Death
  - Running Records
- Demographics
  - Screening 1
- Electroencephalogram
  - Running Records
- Eligibility
  - Sceening 1
- End of Treatment
  - Week 26
- Exposure
  - Running Record
- Hamilton Depression Rating Scale - 17 (HAMD 17)
  - Baseline
  - Early Discontinuation Retrieval
- Informed Consent
  - Screening 1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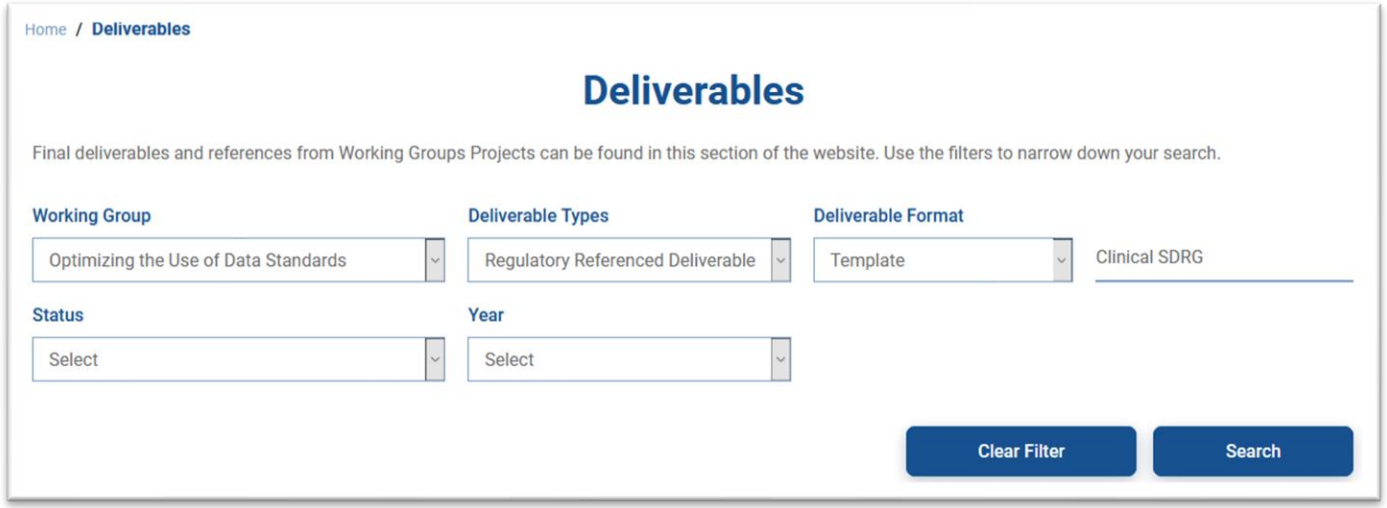
Clinical Study Data Reviewers Guide

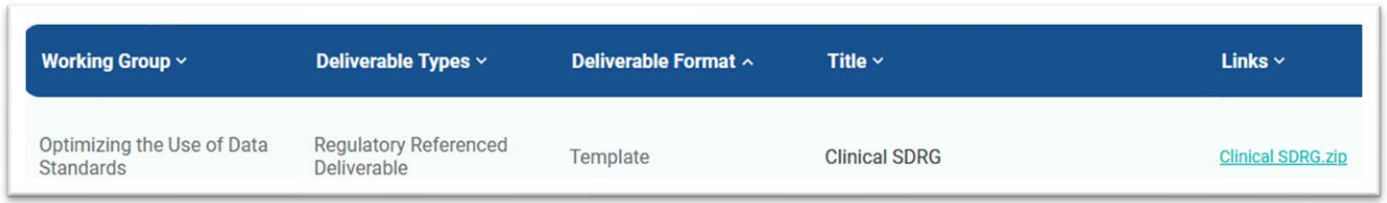
- The cSDRG provides additional information for reviewers about the submitted data which does not belong in the Define-XML document and / or aCRF.
- No specific format required by health authorities, refer to PHUSE template (see next slide).
- All details described within the PHUSE cSDRG
- At the time of SDTM-MSG v2.0 publication the cSDRG should be named
  - “csdrg.pdf” for FDA submissions
  - “study-data-reviewers-guide.pdf” for PMDA submissions

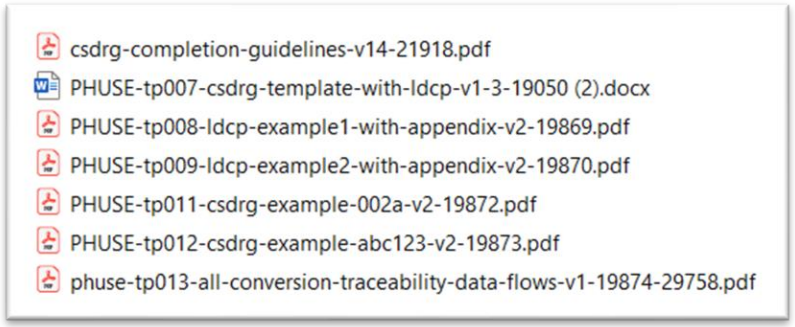
➢ **Check for the latest recommendations**

Clinical Study Data Reviewers Guide

- No specific format required by health authorities, refer to PHUSE template:
  - re-organization of PHUSE website, new link: https://phuse.global/

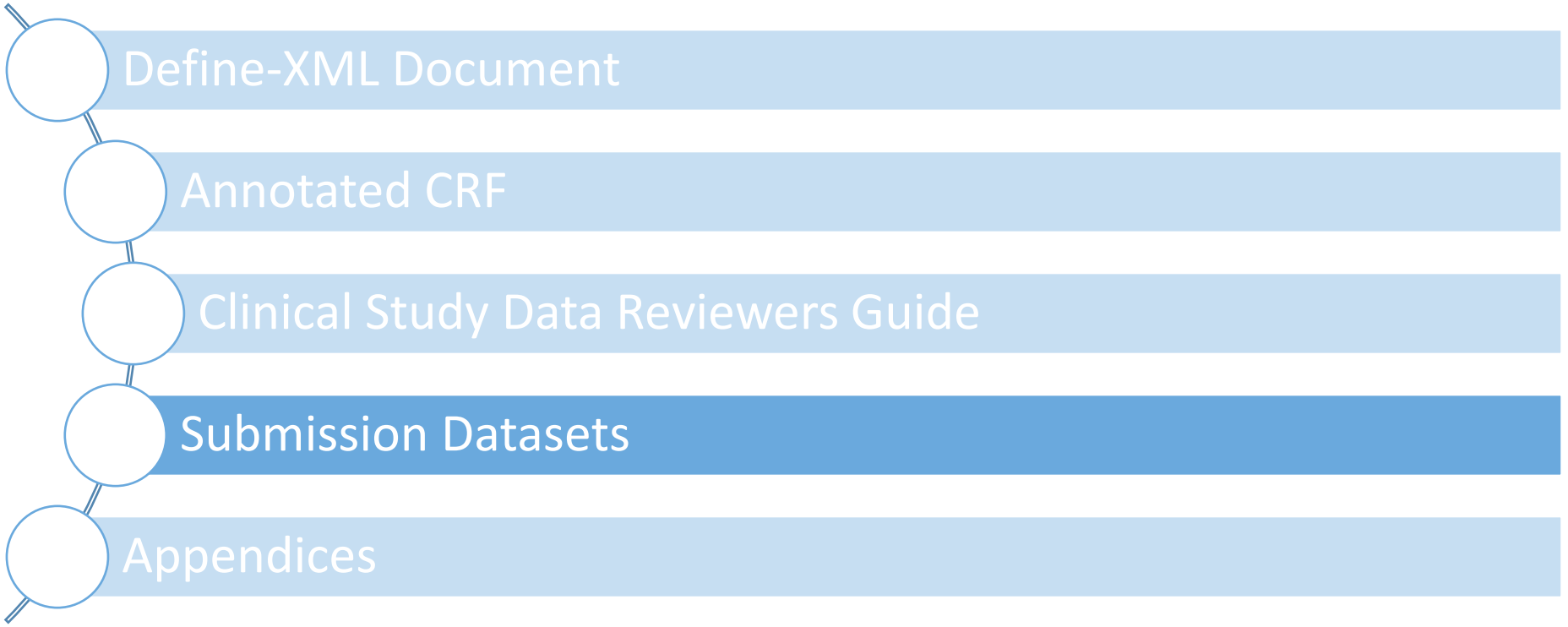






Clinical Study Data Reviewers Guide

- Continuous run of compliance checks and resolving as much issues as possible is expected. Remaining issues needs to be explained in cSDRG of final submission study data package.
  - Define-XML should be validated against the Define-XML conformance rules.
  - SDTM data should be validated with Define-XML against SDTM conformance rules.
  - Put extra effort into explaining compliance checks:
    - Avoid generic explanations, or explanations which simply repeat the wording of the compliance checks.
    - Provide details.
- Additional documents can be included as separate PDFs at a sponsor's discretion, e.g., complex scoring materials provided in support of a questionnaire, or oncology-related derivations (not included in example submission package)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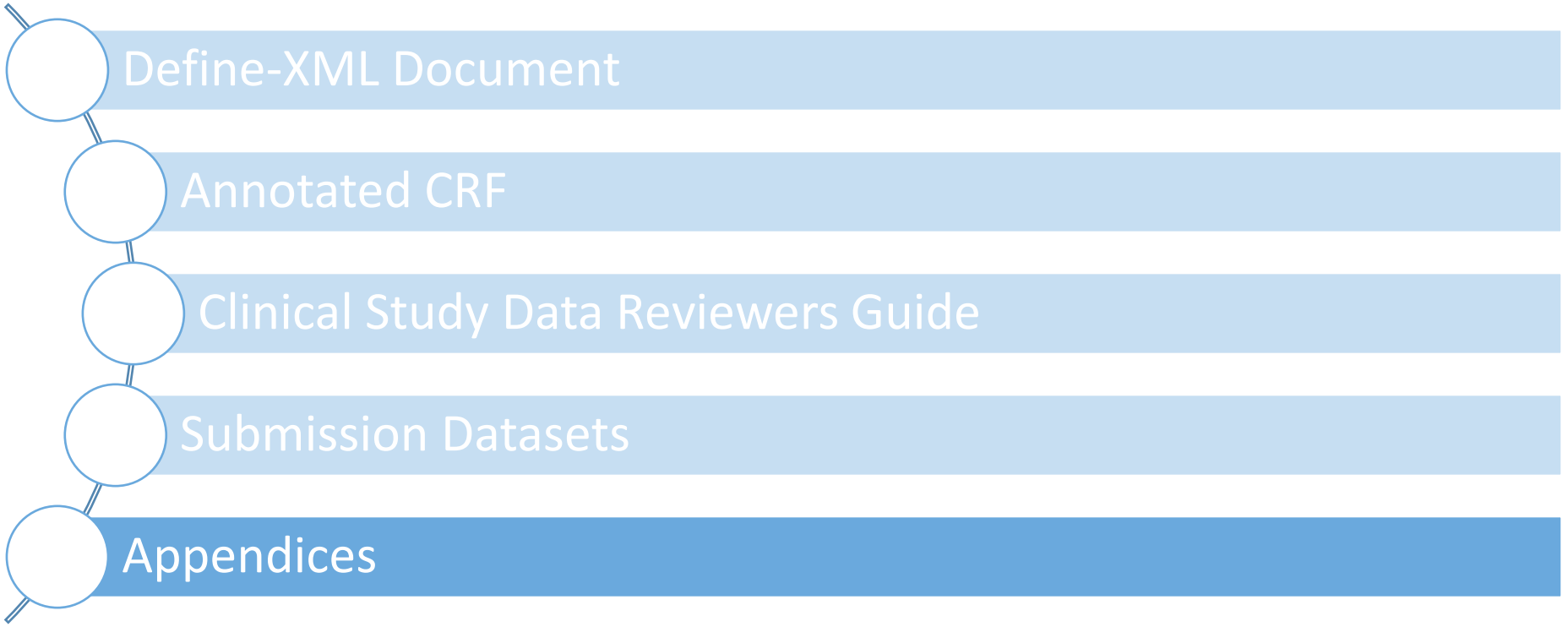
Submission Datasets

- Highlighting noteworthy aspects of domains in the example submission package.
- Description of an implementation choice made by the MSG team for:
  - Trial Inclusion/Exclusion Criteria (TI)
  - Trial Summary (TS)
  - Demographics (DM)
  - Exposure as Collected (EC) and Exposure (EX)
  - Adverse Events (AE)
  - Laboratory Test Results (LB)
  - Nervous System Findings (NV)
  - Questionnaires, Ratings, and Scales (QRS)
  - Vital Signs (VS)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Appendices

- A: CDISC SDS MSG Team
- B: Submission Package Software Issues
- C: MSG Package Disclaimers
  - Hamilton Depression Rating Scale (HDRS) (HAMD-17)
  - Patient Health Questionnaire – 9 (PHQ-9)
  - Dataset-XML
  - Annotation Differences: CDASH & MSG
- D: Representations and Warranties, Limitations of Liability, and Disclaimers

Questions?

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mainanalytics GmbH

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