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A SAS based solution for define.xml

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ABSTRACT

When submitting data to the FDA, a data definition file, describing the structure and contents of the data, is a mandatory deliverable. For data submitted in the CDISC SDTM format the define.xml as published by the CDISC define.xml team is the preferred type of a data definition file.

Compared to define.pdf, the previous data definition file format, define.xml is more suitable for providing the different types of metadata required to adequately describe data in the SDTM format. An additional benefit of define.xml is its machine-readability.

After Accovion successfully implemented an automated process for define.pdf in SAS, building a SAS based automation process for define.xml was the logical consequence.

This paper illustrates the process chosen by Accovion to compile all the necessary metadata and build a define.xml as described in the CDISC Case Report Tabulation Data Definition Specification (define.xml) V1.0 Standard [1]. And as this standard will evolve over the next couple of years, it will briefly touch on the expected enhancements for define.xml.

INTRODUCTION

A data definition file, formally called Case Report Tabulation Data Definitions (CRT DD), is necessary to facilitate the review of the study data submitted to a regulatory authority. Well-defined, standardized metadata minimizes the time needed to familiarize with the data, which can speed up the overall review process.

The Case Report Tabulation Data Definition Specification (define.xml) V1.0 Standard as prepared by the CDISC define.xml team in 2005 has been referenced in the FDA's eCTD Study Data Specifications [6] as the preferred data definition file when data are submitted in the SDTM format.

The most important benefit of define.xml compared to define.pdf, the previous data definition file format, is that an XML file is both human- and machine-readable. Whereas the human-readability helps the reviewer to understand and work with the data, machine-readable metadata can be exploited when transferring data between different systems. They also provide the basis for automation of transposing the data submitted into different structures.

Even the generation of define.xml can be automated, taken into account that a lot of the metadata required for define.xml are already inherent in the datasets themselves.

The SAS based automation solution for define.xml presented in this paper refers to the Case Report Tabulation Data Definition Specification (define.xml) V1.0 Standard and the sample define.xml as prepared by the CDISC define.xml team in 2005. End of July 2007, the CDISC Submission Data Standards (SDS) Metadata team has released a draft version of the Metadata Submission Guidelines [2], Appendix to the Study Data Tabulation Model Implementation Guide 3.1.1 [3], for review. A sample electronic submission with a new sample define.xml is included with this Appendix. These new documents provide some further guidance on how to describe the metadata of the data submitted. The navigation through define.xml has improved via additional hyperlinks and bookmarks. Therefore, relevant differences between the new (2007) and the old (2005) define.xml sample will be highlighted throughout this paper, where necessary.

XML BASICS

In order to build define.xml with SAS, a basic understanding of the XML technology is required. In essence there are three different file types that work together to achieve the human and machine readable characteristic of the XML technology:

- Schema (extension: .XSD)
  Definition and declaration of elements and their attributes (prerequisite for machine-readability)
- XML file (extension: .XML)
  Description of data and metadata in machine-readable format using the elements defined in the schema
- Style sheet (extension: .XSL)
  Definition of the layout in a browser tool for the human readable representation of the XML file

Example:
When opening a define.xml file with a text editor, it looks like this:

```
<?xml version="1.0" encoding="ISO-8859-1"?>
<?xml-stylesheet type="text/xsl" href="define1-0-0.xsl"?>
<ODM
  ...
<ItemGroupDef OID="DM"
  Name="DM"
  Repeating="No"
  IsReferenceData="No"
  Purpose="Tabulation"
  def:Label="Demographics"
  def:Structure="One record per subject"
  def:DomainKeys="STUDYID USUBJID"
  def:Class="Special Purpose"
  def:ArchiveLocationID="Location.DM">
  ...
```

The style sheet reference “define1-0-0.xsl” in the second line (style sheet used in the 2005 define.xml sample) leads to the following representation of define.xml in the Internet Explorer:

Datasets for Study <XY>

Dataset	Description	Structure	Purpose	Keys	Location
…					
DM	Demographics	Special Purpose - One record per subject	Tabulation	STUDYID, USUBJID	crt/datasets/<XY>/DM.xpt
…					

(Underlined texts indicate hyperlinks)

The style sheet defines how the define.xml elements (e.g., ItemGroupDef) and their attributes (e.g., Name=) are displayed in a browser tool. The elements and their attributes themselves are declared in the schema file(s) and referenced both in the XML file and the XSL file. Some attributes are relevant for the machine-readability mainly (e.g., Repeating=). If these attributes are not described in the style sheet, they are omitted from the human readable representation of define.xml.
When a layout change is desired, only the style sheet and not the XML file itself has to be modified. Applying the style sheet included in the 2007 define.xml sample to this specific piece of information, the layout looks slightly different, and a bookmark panel (not displayed below) is also included in the new browser representation:

Datasets for Study <XY>

Dataset	Description	Class	Structure	Purpose	Keys	Location
…						
DM	Demographics	SPECIAL PURPOSE	One record per subject	Tabulation	STUDYID, USUBJID	Dm.xpt
...						

The define.xml schema, an extension to the CDISC ODM (Operational Data Model) [4], and the style sheet define1-0-0.xsl (either the 2005 or the 2007 version) can be used for the define.xml generation as prepared by the CDISC teams. Only the contents of the define.xml file has to be adapted to the respective data.

DEFINE.XML SECTIONS (ELEMENTS)

The define.xml as displayed via the style sheet define1-0-0.xsl provided by the CDISC define.xml team in 2005 has the following sections:

- Data Metadata (TOC)
- Variable Metadata
- Variable Value Level Metadata
- Computational Algorithms
- Controlled Terminology/Code Lists

Additionally the following external and internal hyperlinks are included:

- External links to the first page of the annotated CRF
- External links to a supplemental data definitions document
- External links to the respective SAS Version 5 transport files
- Internal links to the top of the define.xml document (=TOC)
- Several internal links between different define.xml sections

Their purpose and their contents are described in the following subsections.

Comparing this layout with the layout obtained via the style sheet used in the 2007 define.xml sample, especially the hyperlinking capability has been greatly extended to better suit a reviewer's needs. Comments on notable improvements when using the new style sheet will be included in the following subsections under "Notable Changes".

DATA METADATA (TOC)

The Data Metadata Section serves as a table of contents (TOC). It describes each dataset in a standardized fashion.

Excerpt of selected datasets:

Datasets for Study <XY>					
Dataset	**Description**	**Structure**	**Purpose**	**Keys**	**Location**
DM	Demographics	Special Purpose - One record per subject	Tabulation	STUDYID, USUBJID	crt/datasets/<XY>/DM.xpt
LB	Laboratory Tests	Findings - One record per lab test per time point per visit per subject	Tabulation	STUDYID, USUBJID, LBTESTCD, VISITNUM, LBTPTNUM	crt/datasets/<XY>/LB.xpt
SUPPDM	Supplemental Qualifiers for DM	Related - One record per variable value per subject	Tabulation	STUDYID, RDOMAIN, USUBJID, QNAM	crt/datasets/<XY>/SUPPDM.xpt
…					

When clicking on the location link the SAS V5 transport file of the respective dataset opens up in the associated program, e.g., SAS System Viewer. The description link leads to the Variable Metadata of the selected dataset.

Notable changes

Except for splitting the contents displayed in the column Structure into the two columns Class and Structure, no further changes have been performed on the TOC section.

However, the Draft Metadata Submission Guidelines recommend a specific order for the display of the datasets. The datasets should be listed alphabetically within their domain class. Sponsor-defined domains should appear after all of the CDISC domains in the respective class. The domain class order is: Trial Design, Special Purpose, Interventions, Events, Findings, Relationships (including Supplemental Qualifiers).

VARIABLE METADATA

All variables included in a certain dataset are described per dataset in the Variable Metadata Section.

Excerpt of selected variables:

Laboratory Tests Dataset (LB)						
Variable	**Label**	**Type**	**Controlled Terms or Format**	**Origin**	**Role**	**Comment**
USUBJID	Unique Subject Identifier	text		Sponsor Defined	Identifier	Concatenation of Study, Site and Subject Identifiers separated by '-'
LBTESTCD	LAB Test or Examination Short Name	text		CRF	Topic	CRF pages 5, 10, 15, 20
LBTEST	LAB Test or Examination Name	text		CRF	Synonym Qualifier	CRF pages 5, 10, 15, 20
LBORRES	Result or Finding in Original Units	text		CRF	Result Qualifier	CRF pages 5, 10, 15, 20
LBORRESU	Original Units	text	LBORU	CRF	Variable Qualifier	CRF pages 5, 10, 15, 20
LBSTRESN	Numeric Result/Finding in Standard Units	float		Derived	Result Qualifier	LBSTRESN = numeric representation of LBORRES converted to standard unit
LBSTRESU	Standard Units	text	LBSTU	Sponsor Defined	Variable Qualifier	Sponsor defined standard unit for analysis
LBBLFL	Baseline Flag	text	YF	Derived	Record Qualifier	See Computational Method: COMPMETHOD.LBBLFL
LBDTC	Date/Time of Specimen Collection	datetime		CRF	Timing	CRF pages 5, 10, 15, 20

- The columns **Variable** and **Label** are self-explaining.
- The **Type** conforms to the data type definitions of the ODM schema. Valid values are: text, integer, float, datetime, date and time.
- For variables with a discrete list of values attached (e.g., No/Yes questions) a format name is provided in the **Controlled Terms or Format** column that links to the Controlled Terms/Code Lists Section. In the target section the possible values and their decodes are listed.
- The **Origin** of a variable may be Sponsor Defined, CRF or Derived.
- The **Role** values correspond to the metadata definition of the SDTM.
- The **Comment** column contains CRF page references for variable originated from the CRF, a short explanation of Sponsor Defined variables or, for derived variables, the derivation rule or a computational method reference. This reference links to the computational algorithms section for complex derivations or derivations used more than once.

In normalized datasets of vertical format, e.g., findings datasets built with test short name, test name and test result variables, the variable 'Test Short Name' links to the Variable Value Level Metadata Section.

Notable changes

In the 2007 define.xml sample the same information is displayed like this:

Excerpt of selected variables:

Laboratory Tests Dataset (LB)						**lb.xpt** (1.)
Variable	**Label**	**Type**	**Controlled Terms or Format**	**Origin**	**Role**	**Comment**
USUBJID	Unique Subject Identifier	text		Sponsor Defined	IDENTIFIER	Concatenation of Study, Site and Subject Identifiers separated by '-'
LBTESTCD	LAB Test or Examination Short Name	text		CRF Pages 5, 10, 15, 20	TOPIC (2.)	
…						
LBORRES	Result or Finding in Original Units	text		CRF Pages 5, 10, 15, 20 (3.)	RESULT QUALIFIER	
…						
LBSTRESN	Numeric Result/Finding in Standard Units	float		Derived	RESULT QUALIFIER	LBSTRESN = numeric representation of LBORRES converted to standard unit
…						
LBBLFL	Baseline Flag	text	YF	Derived	RECORD QUALIFIER	See Computational Method: COMPMETHOD.LBBLFL
LBDTC	Date/Time of Specimen Collection	text		CRF Pages 5, 10, 15, 20	TIMING	
…						
Supplemental Qualifier Dataset (ValueList.SUPPLB.QNAM) (4.)						

The style sheet improvements include:

1. Link to respective SAS transport file
2. Link to the Role Codelist details in the Controlled Terminology / Codelists section
3. Links to specific Annotated CRF pages
4. Link to the Variable Value Level Metadata of QNAM if a supplemental qualifier dataset exist for the respective domain.

In order to make use of the specific CRF page link functionality, the list of respective CRF pages have to appear in the Origin column following the keywords “CRF Page” or “CRF Pages”, respectively. The page numbers listed have to be identical with the physical page numbers in the Annotated CRF PDF document.

It is also noteworthy that the Draft Metadata Submission Guidelines clearly state, that the type description of date or datetime variables should be “text” as long as data are submitted in the SAS V5 transport format.

Additionally, the new keyword EDT (Electronic Data Transfer) is introduced as code of origin, if data have not been collected on the CRF but have been received electronically.

VARIABLE VALUE LEVEL METADATA

The Variable Value Level Metadata describes each unique value of a certain test short name similarly to the variables described in the Variable Metadata. For review and analysis a distinction between each of the single tests is required. The list of short names allows for a quick selection. Attributes like origin, data type and format may differ between the single tests available in a dataset, and the data type and format information of the respective test result is especially useful for transposing the vertical datasets to horizontal datasets, i.e. variables per test, if required.

Excerpt of selected variable values:

Source Variable	Value	Label	Type	Controlled Terms or Format	Origin	Role	Comment
LBTESTCD	ALB	Albumin	float		CRF		CRF pages 5, 15
LBTESTCD	OPIATES	Opiates	text	POSNEGF	CRF		CRF pages 10, 20
QNAM	ITT	Intent to Treat Population Flag	text	YNF	Derived		See Computational Method: COMPMETHOD.ITT
QNAM	PPROT	Per Protocol Set Flag	text	YNF	Derived		See Computational Method: COMPMETHOD.PPROT

Notable changes

In the 2007 define.xml sample, there are separate bookmarked sections per variable explained in the Variable Value Level Metadata. This is particularly helpful to link the information for supplemental qualifier datasets back to their parent dataset (e.g., section title: Value Level Metadata (ValueList.SUPPDM.QNAM)). For the ease of navigation, a link to the Variable Metadata of the parent dataset is included in these cases (e.g., link via table footnote "Dataset (DM)").

As mentioned above, the CRF page references are best to be placed into the Origin column in order to use the CRF page link functionality.

For Variable Value Level Metadata there is another option to express the Origin of a variable value, i.e., specifying the name of the result variable in the parent dataset. The variable displayed is the variable which holds the value that would become the new variable value when transposing the vertical SDTM dataset to a horizontal structure. Applying this option to the excerpt above, the Origin of the variable value ALB becomes LBSTRESN whereas LBSTRESC is the Origin for OPIATES. This option focuses on the machine-readability. However, for the review of the metadata at the regulatory authority the CRF page references or the derivation descriptions seem preferable.

COMPUTATIONAL ALGORITHMS

All computational methods referred to by either the variable metadata or the variable value level metadata are shown in the Computational Algorithms Section. It includes the computational method name and the derivation rule described in a kind of pseudo code.

Excerpt of selected computational algorithms:

Computational Algorithms Section	
Reference Name	**Computation Method**
COMPMETHOD.LBBLFL	Derive mean of pre-treatment measurements. Create new record with result and flag LBBLFL='Y'.
...	

Notable changes

None

CONTROLLED TERMINOLOGY / CODE LISTS SECTION

All format names referred to by either the variable metadata or the variable value level metadata, their values and their decodes are displayed in the Controlled Terminology/Code Lists Section. As the code values correspond to the values stored in the datasets, they may be equal to the decode values, e.g., result codes of NEGATIVE or POSITIVE.

Excerpt of selected code lists:

Controlled Terminology (Code Lists) Section	
Code Value	**Code Text**
POSNEGF, Reference Name (POSNEGF)	
NEGATIVE	NEGATIVE
POSITIVE	POSITIVE
YF, Reference Name (YF)	
Y	YES
YNF, Reference Name (YNF)	
N	NO
Y	YES

Notable changes

Each referenced code list is bookmarked separately.

The 2007 define.xml sample additionally includes a subsection for external code list references like medical dictionaries.

Example:

Controlled Terminology (External Dictionaries)	
ADVERSE EVENT DICTIONARY, Reference Name (AEDICT)	
External Dictionary	**Dictionary Version**
MEDDRA	8.0
DRUG DICTIONARY, Reference Name (CMDICT)	
External Dictionary	**Dictionary Version**
WHODRUG	200204

HYPERLINKS

A standard footer is included at the end of each of the single metadata tables/sections of the 2005 define.xml sample, that links to the annotated CRF, the supplemental data definitions document and the top of define.xml (TOC).

Footer example:

Annotated Case Report Form (blankcrf.pdf)
Supplemental Data Definitions Document (supplementaldatadefinitions.pdf)
Go to the top of the define.xml
Date of document generation (2007-08-06T16:59:49)

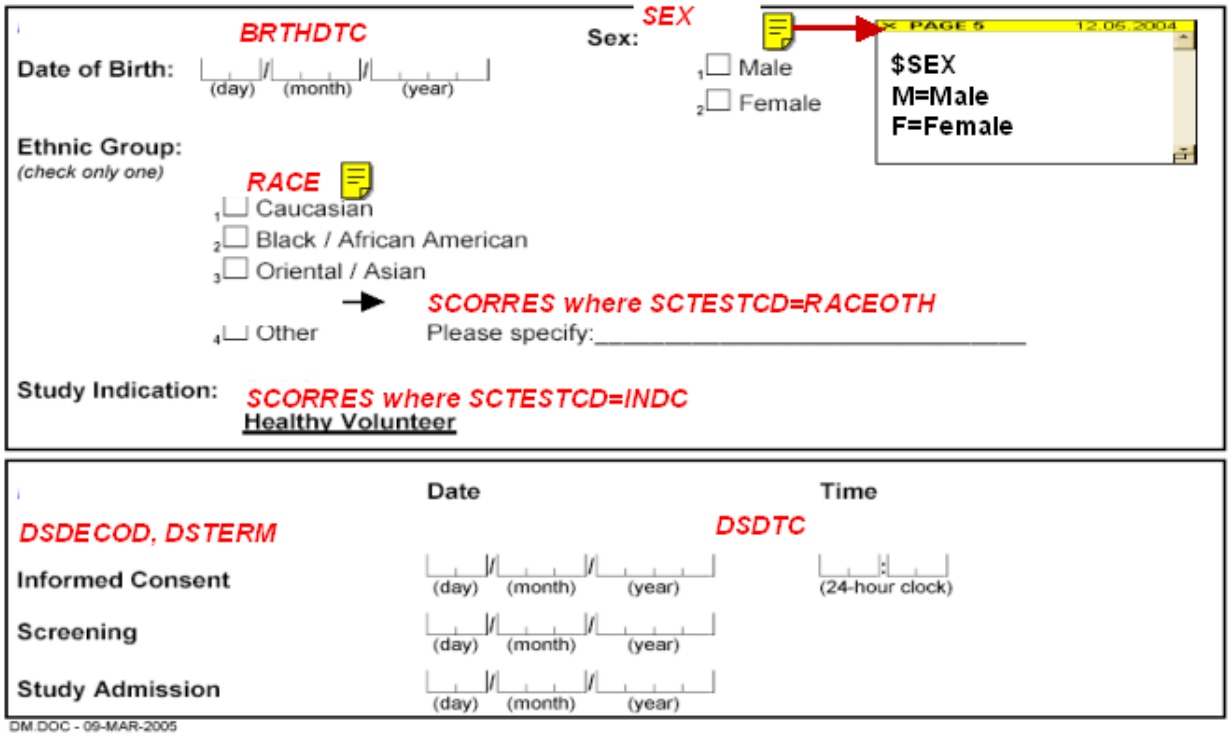
Notable changes

Since the stylesheet used in the 2007 define.xml sample includes bookmarks for the annotated CRF and the supplemental data definitions document, if available, the footer in this version is reduced to the link to the Top of define.xml and to the Date of document generation.

ANNOTATED CRF

According to the FDA's eCTD Study Data Specifications the annotated CRF has to be named 'blankcrf ' and has to be provided in PDF format. All variables captured on the CRF (i.e. with Origin CRF) should appear in the annotated CRF. Annotations for the test short names as described in the variable value level metadata are also helpful. Information on controlled terminology, if attached to a variable, can also be included.

Excerpt of an annotated CRF:



Notable changes

The Draft Metadata Submission Guidelines include detailed recommendations on Annotating CRFs. A blankcrf.pdf file is part in the sample electronic submission, too.

Two especially noteworthy recommendations are to

- Annotate repeat CRF pages with references to the first appearance of the page only, e.g., "see Page 5"
- Annotate data fields not included in the case report tabulation datasets, e.g., monitoring questions like "Check if no AE occurred" with "[NOT SUBMITTED]".

SUPPLEMENTAL DATA DEFINITIONS DOCUMENT

The supplemental data definitions document is another PDF document. It includes any additional information, that is deemed necessary to facilitate the review of the submitted data, and that do not fit into the metadata structures described above, e.g., general assumptions or flow charts to illustrate derivation dependencies.

Notable changes

A supplemental data definition document is not included in the latest submission sample provided by CDISC, but the functionality to include such a document is still available.

DEFINE.XML GENERATION PROCESS

After a look at what is required for define.xml, it becomes apparent that a lot of the metadata to be described is already included in the datasets. Thus, rather than creating duplicate information manually, which might be necessary when using other tools, an automated solution for the generation of define.xml based on SAS seems preferable, especially when taking into account the good experiences with the SAS based define.pdf generation.

EXPERIENCES WITH DEFINE.PDF AUTOMATION

Data definition files for the documentation of submitted datasets have already been requested by the FDA before the CDISC initiative. In the 1999 FDA's guidance document, Providing Regulatory Submissions in Electronic Format [7], define.pdf was described.

Since a lot of information required for define.pdf is inherent in the SAS data themselves, an automated process for the generation of define.pdf using SAS was developed at Accovion as presented at PHARMASUG in 2003 [8].

The main ideas of this process are:

- Use all the metadata already available in SAS
- Provide the additional information required (basically the contents of the comment column describing each variable) in an Excel spreadsheet
- Combine metadata and additional information in SAS
- Create RTF code for the define document in SAS
- Convert define.rtf into define.pdf with Adobe Acrobat Distiller

Comparing the contents of define.xml with the contents of define.pdf as described by the FDA in 1999, more additional information, not already included in the SAS dictionary tables, is required for define.xml. Whereas for define.pdf, only the contents of the comments column has to be provided from an external source, more than one look-up file for additional information is required for define.xml.

Nevertheless, a similar approach for creating define.xml is feasible. This time XML code instead of RTF has to be written in SAS. The details on the required XML code can be picked up from the CDISC Case Report Tabulation Data Specification (define.xml), V1.0. The sample define.xml prepared by the CDISC define.xml team also proved to be extremely helpful when familiarizing with the task of define.xml code generation.

METADATA ALREADY AVAILABLE IN SAS

As mentioned before, a lot of information required to describe the data submitted is inherent in the data themselves. The following information, required for the different define.xml sections/elements, can either be extracted from the SAS dictionary tables, the contents of certain variables of a dataset, or a format catalog.

DEFINE.XML SECTION	TARGET COLUMN/ELEMENT ATTRIBUTE IN DEFINE.XML	SOURCE
Data Metadata	• Dataset • Description • Location (= standard path + dataset name)	DICTIONARY.COLUMNS/ SASHELP.VCOLUMN
Variable Metadata	• Variable • Label • Type (derivation required) • Controlled Terms or Format Element attributes not displayed but required for machine-readability: • Length • Significant Digits • Display Format	DICTIONARY.COLUMNS/ SASHELP.VCOLUMN

DEFINE.XML SECTION	TARGET COLUMN/ELEMENT ATTRIBUTE IN DEFINE.XML	SOURCE
Variable Value Level Metadata	• Source Variable • Value • Label	• Value = Value of source variable in source dataset (e.g., --TESTCD) • Label = Value of corresponding test name variable in source dataset (e.g., --TEST)
Controlled Terminology/Code Lists	• Reference Name • Code Value • Code Text Element attributes not displayed but required for machine-readability: • Data Type	SAS format library

EXCEL FILES FOR SUPPLEMENTARY INFORMATION

In order to build the full define.xml, external look-up tables for the information that is not inherent in the SAS data are required. Excel is one possibility to capture the supplementary information because the contents of those files can be easily transferred to SAS.

Several Excel files or worksheets are necessary to provide the extra information required, basically at least one file per define.xml section, i.e., Data Metadata (List of Datasets), Variable Metadata, Variable Value Level Metadata and Computational Algorithms. Only the Controlled Terminology/Code Lists Section can be created without additional look-up files.

Data Metadata (List of Datasets)

The Excel file structure chosen to capture the information for the Data Metadata looks very much like the Data Metadata Section of define.xml in a browser tool. It has the following columns:

- Dataset (dataset name)
- Description (dataset label)
- CDISC Domain Class (e.g., Findings, Interventions, Events, Special Purpose)
- Structure (e.g., One record per lab test per time point per visit per subject)
- Purpose ('Tabulation' for all SDTM datasets)
- Keys (e.g., STUDYID, USUBJID, LBTESTCD, VISITNUM, LBTPTNUM for dataset LB)

A list of datasets is often generated at the design and specification phase of a programming project. If this list is already prepared in the format mentioned above, redundancies and inconsistencies can be avoided.

Variable Metadata

When looking for an Excel file structure for the Variable Metadata, the SDTM Domain Models as set up in the CDISC SDTM Implementation Guide, Version 3.1.1, are the ideal starting point. This structure is also worth considering when creating specifications for SDTM datasets. To link the SDTM Domain Model to a specific study, just one additional column is required that contains the contents of comment column for define.xml.

Excerpt of selected variables from Excel file for Variable Metadata:

Seq. For Order	Observation Class	Domain Prefix	Variable Name (minus domain prefix)	Variable	Label	Type	Controlled Terms or Format	Origin	Role	COLUMN ADDED FOR DEFINE.XML COMMENT COLUMN	CDISC Notes (for domains) Description (for General Classes)	Core	References
3	Findings	LB	USUBJID	USUBJID	Unique Subject Identifier	Char		Sponsor Defined	Identifier	**Concatenation of Study, Site and Subject Identifiers separated by '.'**	Unique subject identifier within the submission.	Req	SDTM 2.2.4
8	Findings	LB	TESTCD	LBTESTCD	LAB Test or Examination Short Name	Char		CRF	Topic	**CRF pages 5, 10, 15, 20**	Short name of the measurement, test, or examination described in LBTEST. It can be used as a column name when converting a dataset from a vertical to a horizontal format. The value in LBTESTCD cannot be longer than 8 characters, nor can it start with a number (e.g.'1TEST'). LBTESTCD cannot contain characters other than letters, numbers, or underscores. Examples: ALT, LDH.	Req	
9	Findings	LB	TEST	LBTEST	LAB Test or Examination Name	Char		CRF	Synonym Qualifier	**CRF pages 5, 10, 15, 20**	Verbatim name of the test or examination used to obtain the measurement or finding. Note any test normally performed by a clinical laboratory is considered a lab test. The value in LBTEST cannot be longer than 40 characters. Examples: Alanine Aminotransferase, Lactate Dehydrogenase.	Req	
12	Findings	LB	ORRES	LBORRES	Result or Finding in Original Units	Char		CRF	Result Qualifier	**CRF pages 5, 10, 15, 20**	Result of the measurement or finding as originally received or collected.	Exp	SDTMIG 4.1.5.1
13	Findings	LB	ORRESU	LBORRESU	Original Units	Char	*	CRF	Variable Qualifier	**CRF pages 5, 10, 15, 20**	Original units in which the data were collected. The unit for LBORRES. Example: g/L.	Exp	SDTMIG 4.1.3.2
18	Findings	LB	STRESN	LBSTRESN	Numeric Result/Finding in Standard Units	Num		Derived	Result Qualifier	**LBSTRESN = numeric representation of LBORRES converted to standard unit**	Used for continuous or numeric results or findings in standard format; copied in numeric format from LBSTRESC. LBSTRESN should store all numeric test results or findings.	Exp	SDTMIG 4.1.5.1
19	Findings	LB	STRESU	LBSTRESU	Standard Units	Char	*	Sponsor Defined	Variable Qualifier	**Sponsor defined standard unit for analysis**	Standardized unit used for LBSTRESC or LBSTRESN.	Exp	
30	Findings	LB	BLFL	LBBLFL	Baseline Flag	Char	**Y or Null	Derived	Record Qualifier	**COMPMETHOD.LBBLFL**	Indicator used to identify a baseline value.	Exp	SDTMIG 4.1.3.7
33	Findings	LB	TOX	LBTOX	Toxicity	Char	*	Derived	Variable Qualifier	**Not needed**	Description of toxicity quantified by LBTOXGR. Sponsor should specify which scale and version is used in sponsor comments. Example: NCI CTCAE short name	Perm	
38	Findings	LB	DTC	LBDTC	Date/Time of Specimen Collection	Char	ISO 8601	CRF	Timing	**CRF pages 5, 10, 15, 20**		Exp	SDTMIG 4.1.4.1

Except for the addition of the study specific comment column, the following edits might be necessary:

- Controlled Terms and Formats:
  The '*' indicates that there is a controlled terminology for a variable, which will be explained via format codes and decodes in the Controlled Terminology/Code Lists Section. For test short name and test name variables that are further explained by the variable value level metadata this column should be blank.
- Origin:
  The contents of this column in the CDISC SDTM Domain Model might include choices, e.g., "CRF or Derived". The unique study specific origin is required for define.xml.
- Study specific comment = 'Not needed':
  Not all variables included in the SDTM Domain Models might be required for a study. Permissible variables can be omitted. Rather than deleting these rows from the dataset specification files, one might agree on a certain keyword, e.g., "Not needed", in the new study specific comment column.

If the structure and contents of the SDTM Domain Models are retained as much as possible, the data that are redundant to the metadata taken from the datasets themselves, e.g., Label, Type and whether a variable is formatted can be used for SDTM conformance checks of the data to be described by define.xml.

The extra information for the variable metadata can be organized in either one big file or separate files per domain/dataset. Separate files are preferable when the look-up file preparation is divided between several programmers.

Variable Value Level Metadata

The Excel look-up file for the variable value level metadata can either be created manually or in SAS using the SDTM datasets contents and the data of the study specific comment column of the variable metadata/dataset specification files. We decided on the automated generation of a draft in SAS as this ensures consistency with the data submitted without any extra checks required. Nevertheless, this Excel file requires manual adaptation, as type, length, significant digits, display format, origin, role and comment might differ between the unique values of a source variable, e.g., numeric lab test results vs. character lab test results.

Variable value level metadata is required for the trial summary dataset, each findings and each supplemental qualifiers dataset.

The columns of the variable value level metadata Excel file, their source and contents, and whether editing might be required after the initial draft has been created, can be depicted from the following table.

Column	**Source/Contents**	**Editing required?**
Source Dataset	Name of source dataset (applicable for findings and supplemental qualifier datasets)	No
Source Variable	Variable --TESTCD for findings datasets, variable QNAM for supplemental qualifiers datasets	No
Value	Each unique value of TSPARMCD, --TESTCD or QNAM, respectively	No
Label	Corresponding value of TSPARM, --TEST or QLABEL	No
Type	Defaulted to text	No
Length*)	Defaulted to: 200	Yes
Significant Digits*)	Defaulted to: blank	Yes
Display Format*)	Defaulted to: blank	Yes
Controlled Terms or Format	Defaulted to: blank	Yes
Origin	Origin of --ORRES or QVAL according to variable metadata/dataset specification files	Yes
Comment	Comment for --ORRES or QVAL according to variable metadata/dataset specification files	Yes

**) Not displayed via style sheet define1-0-0.xsl but required according to schema to ensure machine-readability.*

Computational Algorithms

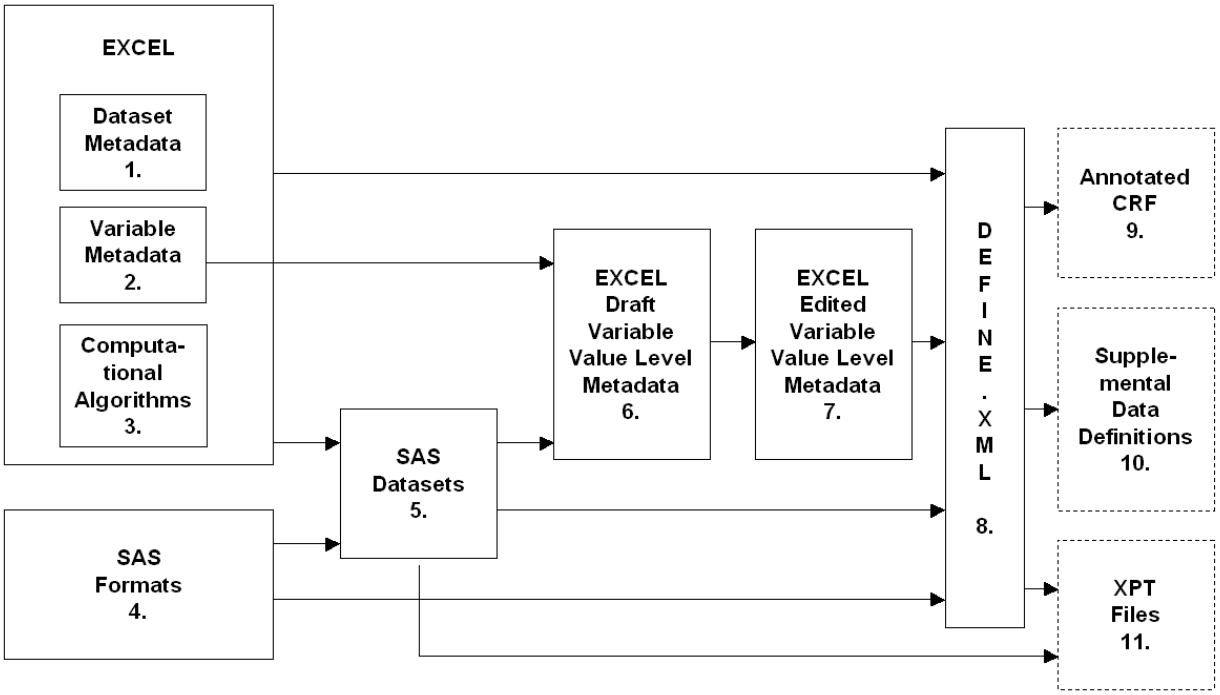
The Excel file structure chosen to capture the information for the Computational Algorithms conforms to the browser representation of the Computational Algorithms Section in define.xml. It has to following columns:

- Reference Name:
  Name specified in the comment column of the variable metadata or the variable value level metadata
- Computation Method:
  Complex derivation rule expressed in pseudo code

A computation method reference rather than the derivation description itself is put into the comment columns of either the variable metadata or the variable value level metadata when the size of the derivation description compromises the tabular structure.

PROCESS FLOW

The define.xml implementation process chosen at Accovion, using SAS internal metadata and metadata compiled externally, can be summarized as follows.



1. Create Excel file Dataset Metadata (List of Datasets)
2. Create Excel files Variable Metadata/Dataset Specifications per dataset
3. Create Excel file Computational Algorithms
4. Create permanent formats required for the variables/variable values with a discrete list of values attached (e.g., proc format library=library; value $SEXF "M"="Male" "F"="Female";)
5. Create datasets according to the specifications
   - Assign defined formats to variables with a discrete list of values
   - Assign numeric formats to variables of type float, e.g., 'format LBSTRESN 9.3;'
6. Create Preliminary Excel file Variable Value Level Metadata in SAS
7. Edit Excel file Variable Value Level Metadata as necessary
8. Create define.xml in SAS
   - Retrieve metadata available in SAS
   - Import Excel files with additional information
   - Combine and structure as required for the define.xml generation
   - Check metadata inherent in SAS for SDTM conformity
   - Create required XML code
9. Provide annotated CRF (blankcrf.pdf) for hyperlinking
10. Provide Supplemental Data Definitions Document in PDF format for hyperlinking
11. Provide datasets in SAS V5 transport format for hyperlinking

12. Place define.xml, referenced style sheet, blankcrf.pdf, supplementaldatadefinitions.pdf and the XPT files of the datasets in the same target directory

XML CODE GENERATION IN SAS

The XML code for define.xml is generated as described in the CDISC define.xml V1.0 standard and shown in the sample define.xml. The XML elements are written to define.xml in the following order.

- XML header including style sheet reference
- **ODM** open tag + schema references + ODM attributes incl. **FileOID**="<STUDY ID>"
- **Study** open tag with **OID**="<STUDY ID>"
- **GlobalVariables** defining study attributes
- **MetaDataVersion** open tag
- **def:AnnotatedCRF** for link to Annotated CRF
- **def:SupplementalDoc** for link to supplemental data definition file

- **def:ComputationMethod** per computational algorithm available
  (Attribute **OID** is set to reference name, e.g., “COMPMETHOD.LBBLFL”)
- **def:ValueListDef** per variable to be explained by variable value level metadata
  (Attribute **OID** is set to ‘ValueList’.<dataset name>.<variable name>, e.g., “ValueList.LB.LBTESTCD”)
  - **ItemRef** per variable value of variable listed in **def:ValueListDef**
    (Attribute **ItemOID** is set to <dataset name>.<variable name>.<variable value>, e.g., “LB.LBTESTCD.ALB”)
- **ItemGroupDef** per dataset for data metadata
  (Attribute **OID** is set to dataset name, e.g., “LB”)
  - **ItemRef** per variable included in the dataset
    (Attribute **ItemOID** is set to <dataset name>.<variable name>, e.g., “LB.LBTESTCD”)
- **ItemDef** per variable referenced in **ItemGroupDef**
  (Attribute **OID** is set to <dataset name>.<variable name>, e.g., “LB.LBTESTCD”, to link with **ItemRef** attribute **ItemOID** for dataset variables;
  attribute **def:ComputationMethodOID** is set to reference name of computational algorithm, if applicable, to link with **def:ComputationMethod** attribute **OID)**
  - **def:ValueListRef** for link to variable value level metadata, if applicable
    (Attribute **ValueListOID** is set to ‘ValueList’.<dataset name>.<variable name>, e.g., “ValueList.LB.LBTESTCD”)
  - **CodeListRef** for link to controlled teminology/code lists, if applicable
    (Attribute **CodeListOID** is set to format name, e.g., “YF”)
- **ItemDef** per variable value referenced in **def:ValueListDef**
  (Attribute **OID** is set to <dataset name>.<variable name>.<variable value>, e.g., “LB.LBTESTCD.ALB”, to link with **ItemRef** attribute **ItemOID** for variable values;
  attribute **def:ComputationMethodOID** and child element **CodeListRef** as for dataset variables **ItemDef**s, if applicable)
- **CodeList** per controlled terminology/code list name
  (Attribute OID is set to format name, e.g., “YF”, to link with the **CodeListOID** referenced in **ItemDef)**
  - **CodeListItem** per coded value of parent code list
- **MetaDataVersion** close tag
- **Study** close tag
- **ODM** close tag

Following the order of elements described above, define.xml can easily be created by several data steps, ‘putting’ the contents of the combined define.xml metadata datasets into XML code.

The dependencies/interactions between the single define.xml elements are illustrated in the following excerpt of define.xml as displayed in a text editor. These dependencies are facilitated in the define1-0-0.xsl style sheet to create the hyperlinks in define.xml when displayed in a browser tool.

```
...
<def:ComputationMethod OID="COMPMETHOD.LBBLFL">     ◄ Target of internal link 1
Derive mean of pre-treatment measurements. Create new record with result and flag
LBBLFL=&apos;Y&apos;
</def:ComputationMethod>
...
<def:ValueListDef OID="ValueList.LB.LBTESTCD">      ◄ Target of internal link 2
  <ItemRef ItemOID="LB.LBTESTCD.ALB"                ◄ Internal link 3
     OrderNumber="1"  Mandatory="No"/>
  ...
</def:ValueListDef>
...
<ItemGroupDef OID="LB"
  Name="LB" Repeating="Yes" IsReferenceData="No" Purpose="Tabulation"
  def:Label="Laboratory Tests"
  def:Structure="One record per lab test per time point per visit per subject"
  def:DomainKeys="STUDYID USUBJID LBTESTCD VISITNUM LBTPTNUM"
  def:Class="Findings"
  def:ArchiveLocationID="Location.LB">              ◄ Internal link 4
  ...
  <ItemRef ItemOID="LB.LBTESTCD"                    ◄ Internal link 5
    OrderNumber="5"  Mandatory="Yes"  Role="Topic"/>
```

```
  ...
  <ItemRef ItemOID="LB.LBBLFL"                          ◄ Internal link 6
    OrderNumber="22" Mandatory="No"   Role="Record Qualifier"/>
  ...
  <def:leaf ID="Location.LB" xlink:href="LB.xpt"> ◄ Target of internal link 4 + External link
    <def:title>crt/datasets/<study>/LB.xpt </def:title>
  </def:leaf>
</ItemGroupDef>
...
<ItemDef OID="LB.LBTESTCD"                              ◄ Target of internal link 5
  Name="LBTESTCD"  DataType="text"  Length="15"  Origin="CRF"
  Comment="CRF page 98"
  def:Label="LAB Test or Examination Short Name">
  <def:ValueListRef ValueListOID="ValueList.LB.LBTESTCD"/> ◄ Internal link 2
</ItemDef>
...
<ItemDef OID="LB.LBBLFL"                                ◄ Target of internal link 6
  Name="LBBLFL"  DataType="text"  Length="1"  Origin="Derived"
  def:Label="Baseline Flag"
  def:ComputationMethodOID="COMPMETHOD.LBBLFL">    ◄ Internal link 1
  <CodeListRef CodeListOID="YF"/>                  ◄ Internal link 7
</ItemDef>
...
<ItemDef OID="LB.LBTESTCD.ALB"                          ◄ Target of internal link 3
  Name="ALB"  DataType="float" Length="8" SignificantDigits="1"
  Origin="CRF" Comment="CRF pages 5, 15"
  def:Label="Albumin" def:DisplayFormat="5.1"/>
...
<CodeList OID="YF"                                      ◄ Target of internal link 7
 Name="YF" DataType="text">
  <CodeListItem CodedValue="Y">
    <Decode>
      <TranslatedText xml:lang="en">YES</TranslatedText>
    </Decode>
  </CodeListItem>
</CodeList>
...
```

- *Special characters like ampersand, apostrophe, quote, less than, greater than must be treated specially. They are replaced with '&', ''', '"', '<', '>', respectively, when creating define.xml in SAS to ensure XML conformity.*
- ***OID**s must be unique*

CONSISTENCY CHECKS

When using the CDISC SDTM Domain Models as look-up files for the additional information required for define.xml, their contents can also be used for a SDTM adherence check of the datasets.

The following SDTM adherence checks are possible:

- Availability of datasets and variables
- Order of variables in a dataset
- Dataset label and variable labels
- Variable data type
- Variables with controlled terminology (a SAS format should be attached)

Since the information required for define.xml comes from different sources, it is also important to include define.xml specific consistency checks to ensure conformance to the CRT DD Specification and provision of a well-formed XML file.

Those checks include:

- COMPMETHOD reference but no details provided and vice versa
- Format reference but format not available in format catalog and vice versa
- Variable value level metadata link but no variable value level metadata provided and vice versa

Consistency of data metadata with variable metadata is available through the SAS metadata themselves.

ADAPTATION TO THE NEW CDISC DEFINE.XML SAMPLE

The define.xml automation process described above was built according to the sample define.xml provided by the CDISC team in 2005. For new submissions, the adaptation to the new sample define.xml as included in the Draft Metadata Submission Guidelines Review Package should be considered.

When applying the formatting of the new style sheet to a define.xml file constructed according to the 2005 define.xml sample, the majority of the increased functionality (e.g., bookmarks, hyperlinks to SAS transport files from variable metadata, hyperlinks to supplemental qualifiers, if applicable) is already available, because the style sheet enhancements are only built on the information already inherent in the XML file and the SDTM naming conventions (e.g., supplemental qualifier dataset for DM is called SUPPDM).

In order to exploit the full functionality of the new style sheet, there are just some minor straightforward changes required to the SAS macro generating the define.xml code.

- Links to the referenced annotated CRF pages only work when the list of CRF page references is assigned to the Origin attribute of the ItemDef element. Thus, whenever the contents of the comment column from the variable metadata look-up file starts with “CRF Page” the information has to be assigned to the Origin attribute rather than the Comment attribute. However, this should only be done, if the page numbers printed on the CRF equal the physical page numbers of the blankcrf.pdf.
- For the links from the Role column values of the variable metadata to the Role Code List the attribute RoleCodeListOID has to be added to each ItemRef, which includes the attribute Role. A new permanent format has to be created for each possible Role value, which will be described in the Controlled Terminology/Code Lists section. The format name becomes the value referenced by RoleCodeListOID.
- In the CDISC define.xml sample of 2005, -DTC variables were shown as date or datetime variables. According to the Draft Metadata Submission Guidelines, the data type of these variables should be text. Thus, the SAS algorithms to derive the corresponding ODM data type of each variable for the Type attribute of the element ItemDef can even be simplified.
- The pilot define.xml implementation at Accovion did not include external dictionary references via the Controlled Terms or Format column. The respective coding dictionary and its version were only described in the Comment column of the dictionary coded variables, e.g., AEDECOD. To comply with the latest CDISC define.xml sample, the define.xml code generation could be extended to handle predefined external dictionary reference names, e.g., MEDDRA and WHODD as required.
- The Draft Metadata Submission Guidelines introduce a specific way to describe the metadata of multiple questionnaire CRFs included in one QS dataset. In order to describe the variable values per questionnaire CRF, a first level of variable value level metadata is created for the QSCAT variable, which contains the different questionnaire names. A second level of variable value level metadata is provided for the QSTESTCD variable per questionnaire, i.e., per unique value of QSCAT. The SAS algorithm has to be extended to describe these data appropriately in the XML code.
- Finally, when using the style sheet define1-0-0.xsl of the electronic submission sample from 2007, the files define.css, icon1.gif, icon2.gif, and icon3.gif, referenced by this style sheet have to be placed into the submission data folder.

EXPECTED DEFINE.XML ENHANCEMENTS

The define.xml according to the CDISC Case Report Tabulation Data Definition Specification (define.xml) V1.0 Standard was constructed to meet or exceed the minimum FDA requirements for a data definition file. End of June 2007 the Draft Metadata Submission Guidelines were released for review. This document provides detailed recommendations on how to describe the metadata of SDTM datasets efficiently for regulatory review. It clarifies a lot of the areas not yet unambiguously defined in the CDISC define.xml V1.0 standard. The new define.xml sample referenced in the Draft Metadata Submission Guidelines, includes most of the functionality missed in the first implementation sample of define.xml, e.g., links to single CRF pages. Nevertheless, some further enhancements might come up.

CORRECTION OF SOFTWARE ISSUES WITH LATEST DEFINE.XML SAMPLE

The internal and external hyperlinks implemented in the style sheet of the 2007 define.xml sample are quite extensive. However, depending on the Software versions used, not all links might work as expected. For correct linking to specific CRF pages Adobe Versions other than Adobe 7 should be used. With Adobe 7 the links will always lead to the first page of the blankcrf.pdf. In some cases the back arrows do not work when navigating within define.xml. This issue might be attributable to the Internet Explorer Version used.

ADAPTATION TO LATEST CDISC ODM STANDARD

The current CDISC define.xml standard is based on the CDISC ODM Version 1.2. The current CDISC ODM Version is Version 1.3. New versions of the define.xml standard will probably be based on the latest available CDISC ODM standard to make use of the new functionality available.

IMPROVED PRINTABILITY

The human readable browser representation of define.xml works well when reviewing the contents on the screen, but in order to print it properly, a workaround has to be used. The sample electronic submission referenced in the Draft Metadata Submission Guidelines includes a file define.xml_printable.pdf. The final version of the guidelines document might include further information on how this file was created and whether it should generally be included in an electronic submission.

EXTENSION FOR CDISC ADAM SPECIFIC METADATA

The CDISC define.xml V1.0 standard focuses on the documentation of Case Report Tabulation Datasets in SDTM format. For the statistical review of the study results, more analysis ready datasets constructed according to the Analysis Data Model (ADaM) [5] are also required. These datasets and at least the most important analysis results themselves also have to be documented via standard metadata concepts. The Metadata tables described in the CDISC Analysis Data Model, Version 2.0, are similar but not equal to the metadata sections of the current define.xml. The Analysis Metadata, for example, which describe the most important analysis results and link them to the respective datasets, can only be included in define.xml via a sponsor specific schema extension. However, a standard format is desirable. The CDISC define.xml team is currently working on an integration of the ADaM specific metadata as one of the results from the FDA-CDISC Pilot, a mock submission to the FDA to test the interoperability of the CDISC standards and to demonstrate that these standards meet the needs of the FDA reviewers.

EXECUTABLE COMPUTATIONAL ALGORITHMS

Currently, the Computational Algorithms Section of define.xml is just a human readable description of the computations or derivations performed. One of the CDISC visions is to also embed some executable code to allow for reproduction of the results submitted. However, this is probably the least likely standard enhancement to be seen in the near future.

CONCLUSIONS

The SAS based solution for the automated generation of define.xml presented in this paper is just one possibility to implement define.xml. People with more XML experience might chose XML tools rather than SAS to perform this task.

For people with a SAS programming background, on the other hand, XML code can easily be created in SAS following the well-documented CDISC define.xml standard and the recommendations provided in the Draft Metadata Submission Guidelines. The more challenging part of the define.xml implementation process is to compile the necessary additional, non-SAS inherent, information and to organize them in a format ready for input into SAS.

When deciding for a SAS based solution, there are several options to integrate the define.xml generation into the submission datasets preparation process. Structuring the design and specification documents as needed for the define.xml generation increases consistency and avoids redundancy.

Facilitating the CDISC SDTM domain model tables as input files, also allows for a SDTM adherence check of the data submitted.

When using a SAS based implementation process, no cross checks between the metadata described in define.xml and metadata inherent in the datasets submitted are necessary as there is built-in consistency with the data.

Finally, SAS PROC CDISC will probably offer an alternative solution for the define.xml generation in the future. So before starting a define.xml implementation, it might be worth checking on the PROC CDISC status. However, according to the latest development notes on PROC CDISC, SAS has deferred the work on define.xml until the CDISC define team progresses further in their discussion of a new version that supports data submission via XML.

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