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Understanding the define.xml File and Converting It to a Relational Database

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ABSTRACT

When submitting clinical study data in electronic format to the FDA, not only information from trials has to be submitted, but also information to help understand the data. Part of this information is a data definition file, which is the metadata describing the format and content of the submitted data sets. When submitting data in the CDISC SDTM format it is required to submit the data definition file in the Case Report Tabulation Data Definition Specification (define.xml) format as prepared by the CDISC define.xml team.

This paper illustrates how the define.xml can be transformed into relational SAS® data sets by using SAS XML Mapper technology. Once the content of the define.xml is available in SAS data sets it can be presented as a PDF file with the use of SAS ODS (Output Delivery System).

The relational SAS data sets can also be used to validate the metadata contained in the define.xml file against the SAS transport files and the different types of SDTM metadata:

- metadata for domain datasets
- metadata for domain content (including value level metadata)
- metadata for controlled terminology

INTRODUCTION

The FDA issued the Final Guidance on Electronic Submissions using the eCTD specifications in April 2006. The latest revision of this guidance was published in June 2008 [1]

Technical specifications associated with this guidance are provided as stand-alone documents. Among these are Study Data Specifications [2] that provide further guidance for submitting animal and human study data in electronic format when providing electronic submissions to the FDA. Study data includes information from trials submitted to the agency for evaluation and information to understand the data (data definition). The study data includes both raw and derived data.

As of January 1, 2008, sponsors submitting data electronically to the FDA are required to follow the new eCTD guidance. The previous guidance, originally issued in 1999, has been withdrawn as of the same date.

The new guidance differs from the 1999 guidance in one significant aspect: The application table of contents is no longer submitted as a PDF file, but is submitted as XML (eXtensible Markup Language). This means that the electronic submissions will now be XML based.

The current version of the Study Data Specifications contains specifications for the Data Tabulation data sets of human drug product clinical studies and provides a reference to the Study Data Tabulation Model (SDTM) [3][4][5][6] developed by the Submission Data Standard (SDS) working group of the Clinical Data Interchange Standard Consortium (CDISC).

Further, the Study Data Specifications document gives a reference to the Case Report Tabulation Data Definition Specification (CRT-DDS or define.xml) developed by the CDISC define.xml Team [7].

DATA DEFINITION TABLES: define.xml

Released for implementation in February 2005, the Case Report Tabulation Data Definition Specification (CRT-DDS or define.xml) Version 1.0 [7] specifies the standard for providing Case Report Tabulations Data Definitions in an XML format for submission to regulatory authorities (e.g., FDA). The XML schema used to define the expected structure for these XML files is based on an extension to the CDISC Operational Data Model (ODM). The current version of the CRT-DDS (version 1.0) is based on version 1.2.1 of the CDISC ODM [8], which is both semantically and syntactically identical to Version 1.2.0 of the CDISC ODM.

The Data Definition Document provides a list of the data sets included in the submission along with a detailed description of the contents of each data set. To increase the level of automation and improve the efficiency of the Regulatory Review process, the define.xml file can be used to provide the Data Definition Document in a machine-readable format.

In July 2007 The CDISC Submission Data Standards (SDS) Metadata Team released a draft version of the Metadata Submission Guidelines, Appendix to the Study Data Tabulation Model Implementation Guide 3.1.1 for review [9]. This release included a sample electronic submission that contains examples of CRF annotations, metadata associated with the submission domains, SDTM domains, and an example of a define.xml file.

WHY CONVERT THE DEFINE.XML INTO RELATIONAL SAS DATA SETS?

In this section we will present business cases that justify the effort of converting the metadata that is contained in a define.xml file into relational SAS data sets.

PRINTING THE DEFINE.XML

In January 2008 CDISC published a report that summarizes the work, experiences and findings of the first CDISC SDTM / ADaM Pilot Project [10]. The objective of the pilot project was to test how well the submission of CDISC-adherent data sets and associated metadata met the needs and the expectations of both medical and statistical FDA reviewers.

This pilot report mentions the following issue:

> *"A major issue identified by the regulatory review team was the difficulty in printing the Define file. The style sheet used in the pilot submission package was developed with the primary target of web browser rendering, which is not readily suited to printing. Reviewers who attempted to print the Define file found that the file did not fit on portrait pages, that page breaks were not clean, and that printing only a portion of the file was difficult. Opening the document in another application (e.g., Microsoft Word) provided a work-around, but was not an option that was user friendly or efficient."*
>
> …
>
> *As stated previously, style sheets used for viewing of the Define file do not facilitate printing the file in such a way as to produce a reasonably formatted document. Solutions to allow both easy viewing and printing of Define files have not been identified. This problem could be viewed as an implementation issue that sponsors will need to handle, after discussing the issue with their FDA reviewers. For example, a sponsor might choose to provide two versions of the style sheet – XML for viewing and PDF for printing. Ideally, a reminder of the issue would be included somewhere in the CRT-DDS guidance (e.g., a note that consideration be given to how the sponsor will respond to a request from reviewers for a print-friendly version of the style sheet). It should be noted that the regulatory review team for the pilot project emphasized that the ability to print the document would be essential for the future use of XML files.* [10]

Once the metadata that is contained in the define.xml is converted to relational SAS data sets, we can use the extensive reporting capabilities of SAS to present the define.xml metadata in a variety of output formats like PDF, RTF or Excel. The PDF representation of the define.xml will allow us to print the metadata contained in the define.xml.

ASSESSING THE QUALITY OF THE DEFINE.XML

When submitting clinical study data in electronic (SDTM) format to the FDA it is obvious that the metadata that is contained in the define.xml file, that comes along with this data, should accurately describe the data. The process used to create the define.xml file may not guarantee this. For this reason, it is important to validate the define.xml file against the data independently from the process that created the define.xml file. Once the metadata that is contained in the define.xml is converted to relational SAS data sets, we can use SAS to perform various checks to validate the define.xml against the clinical study data.

XML 101

In this section we present a short introduction to XML.

BASIC SYNTAX

The Extensible Markup Language (XML) [11] is a general-purpose markup language. It is classified as an extensible language because it allows users to define their own elements. Its primary purpose is to facilitate the sharing of structured data across different information systems. XML is a language that is hierarchical, text-based and describes data in terms of markup tags. A good introductory guide to XML can be found in the reference section [12].

Every XML document starts with the **XML declaration**. This is a small collection of details that prepares an XML processor for working with the document.

syntax	XML declaration	example
<?xml *param1 param2 …* ?>		<?xml version="1.0" encoding="ISO-8859-1" ?>

Elements are the basic building blocks of XML, dividing a document into a hierarchy of regions. Some elements are containers, holding text or (child) elements. Others are empty and serve as place markers. Every XML file should have exactly 1 root element that contains all other elements.

syntax	Container Element	example
< **name** *attribute1 attribute2 …* > *content* </ **name** >		<def:leaf ID="**Location.DM**" xlink:href="**dm.xpt**"> <def:title>**dm.xpt**</def:title> </def:leaf>

An **empty element** is similar, but contains no content or end tag.

syntax	Empty Element	example

< **name** *attribute1 attribute2 …* />		<ItemRef ItemOID="**STUDYID**" OrderNumber="**1**"
		Mandatory="**Yes**" Role="**IDENTIFIER**"
		RoleCodeListOID="**RoleCodeList**" />

In the element starting tag there can be information about the element in the form of an **attribute**. Attributes define properties of elements. They associate a name with a value, which is a string of character data enclosed in quotes. There is no limit to how many attributes an element can have, as long as no two attributes have the same name.

syntax	Attributes	example

name = " *value* "		ItemOID="**STUDYID**" OrderNumber="**1**"
		Mandatory="**Yes**" Role="**IDENTIFIER**"
		RoleCodeListOID="**RoleCodeList**"

Namespaces are a mechanism by which element and attribute names can be assigned to groups. They are most often used when combining different vocabularies in the same document. If each vocabulary is given a namespace then the ambiguity between identically named elements or attributes can be resolved.

syntax	Namespaces	example
xmlns: *name* = " *URI* "		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**"

Comments in an XML document are not interpreted by the XML processor:

syntax **Comments** example

```
<!-- comment text -->
```

```
<!--  File: define.xml                                   -->
<!--  Date: 02/02/2005                                   -->
<!--  Author: Clinical Data Interchange Standards        -->
<!--          Consortium (CDISC) define.xml team         -->
```

A **CDATA** (character data) section tells the XML parser that this section of the document contains no markup and should be treated as regular text. CDATA sections can be useful for large regions of text that contain a lot of ‘forbidden’ XML characters. They should be used with care though, since it may be hard to use any elements or attributes inside the marked region.

syntax **CDATA** example

```
<![CDATA unparsed character data
]]>
```

```
<TranslatedText xml:lang="en"><![CDATA[ Classifies
    subjects based on Hy's Law - 2 variations - For each
    variation, subject is classified as normal or abnormal at
    baseline and as normal or abnormal based on most
    extreme value during treatment, Safety population
]]></TranslatedText>
```

Processing instructions are meant to provide information to a specific XML processor, but may not be relevant to others. It is a container for data that is targeted toward a specific XML processor. The processing instruction looks like the XML declaration, but is targeted at a specific XML processor. The XML declaration can be viewed as a processing instruction for all XML processors.

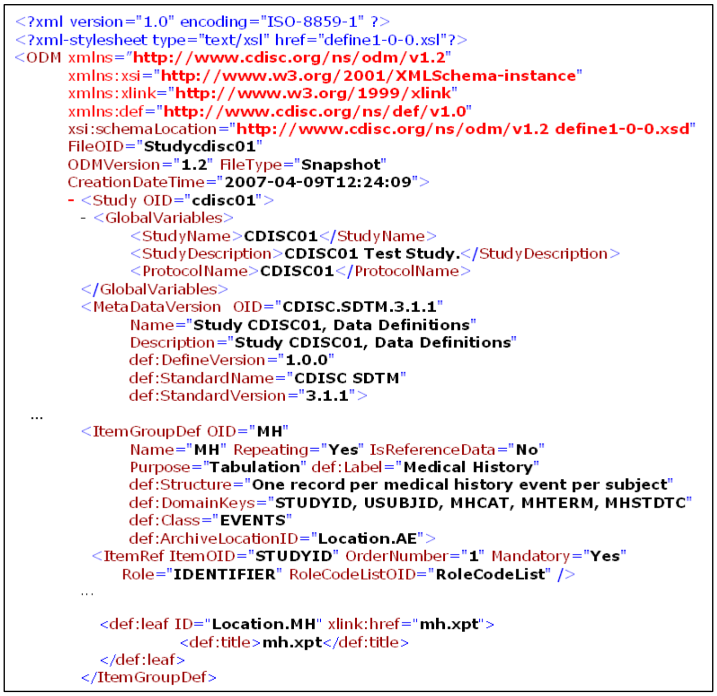
syntax **Processing Instructions** example

```
<? target data ?>
```

```
<?xml-stylesheet type="text/xsl" href="define1-0-0.xsl" ?>
```

Now that we have explained the most important building blocks of XML, we can look at a more complete example in Figure 1.

Figure 1: *Excerpt of an XML file (define.xml)*



```
<?xml version="1.0" encoding="ISO-8859-1" ?>
<?xml-stylesheet type="text/xsl" href="define1-0-0.xsl"?>
<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 define1-0-0.xsd"
     FileOID="Studycdisc01"
     ODMVersion="1.2" FileType="Snapshot"
     CreationDateTime="2007-04-09T12:24:09">
   - <Study OID="cdisc01">
     - <GlobalVariables>
          <StudyName>CDISC01</StudyName>
          <StudyDescription>CDISC01 Test Study.</StudyDescription>
          <ProtocolName>CDISC01</ProtocolName>
       </GlobalVariables>
       <MetaDataVersion  OID="CDISC.SDTM.3.1.1"
          Name="Study CDISC01, Data Definitions"
          Description="Study CDISC01, Data Definitions"
          def:DefineVersion="1.0.0"
          def:StandardName="CDISC SDTM"
          def:StandardVersion="3.1.1">
 ...
       <ItemGroupDef OID="MH"
          Name="MH" Repeating="Yes" IsReferenceData="No"
          Purpose="Tabulation" def:Label="Medical History"
          def:Structure="One record per medical history event per subject"
          def:DomainKeys="STUDYID, USUBJID, MHCAT, MHTERM, MHSTDTC"
          def:Class="EVENTS"
          def:ArchiveLocationID="Location.AE">
        <ItemRef ItemOID="STUDYID" OrderNumber="1" Mandatory="Yes"
          Role="IDENTIFIER" RoleCodeListOID="RoleCodeList" />
       ...

         <def:leaf ID="Location.MH" xlink:href="mh.xpt">
                <def:title>mh.xpt</def:title>
         </def:leaf>
       </ItemGroupDef>
```

The first line is the XML declaration.

The second line contains a processing instruction to include the XSL style sheet to display the XML file in a human readable form in a browser.

<ODM> is the root element.

<Study>, <GlobalVariables>, <MetaDataVersion>, <StudyName>, <ItemGroupDef>, etc are elements.

<Study> is a child element of the <ODM> element.

FileOid, ODMVersion, etc are attributes of the <ODM> element.

The 4 lines starting with “xmlns:” are namespace declarations.
This excerpt contains no comments or CDATA sections.

WELL-FORMED AND VALIDATED

An XML file is said to be *well-formed* if it conforms to the rules of XML syntax. At a very basic level this means:

- A single element, called the root element, contains all other elements in the document (in the define.xml the root element is <ODM>)
- Elements should be properly opened and closed
- Elements do not overlap, e.g. are properly nested
- Attributes are properly quoted
- The document does not contain illegal characters.
  For example, the "<" character has special meaning because it opens a tag. So, if this character is part of the content, it should be should substituted as "&lt;"

A conforming XML parser is not allowed to process an XML document that is not well-formed.

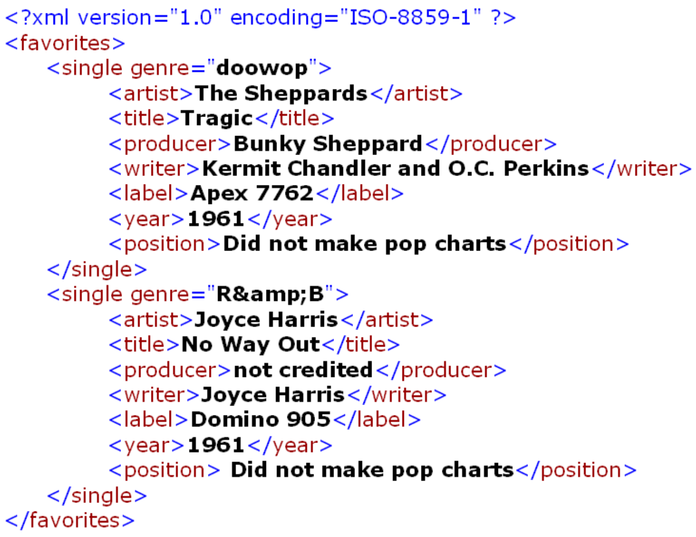
An **XML schema** is a description of a type of XML document, typically expressed in terms of constraints on the structure and content of documents of that type. This description goes above and beyond the basic syntax constraints imposed by well-formedness of an XML document [13].

The schema defines the allowed elements and attributes, order of the elements, overall structure, etc...

A schema might also describe that the content of a certain element is only valid if it conforms to the ISO 8601 date and time specification. An XML document is *valid*, if it conforms to a specific XML schema.

The following example illustrates the difference between ***well-formed*** and ***validated***. The XML document in Figure 2 is a well-formed XML document, but is obviously not valid with respect to the schema that defines a valid define.xml file.

Figure 2: *A well-formed XML document, but not a valid define.xml document*



```
<?xml version="1.0" encoding="ISO-8859-1" ?>
<favorites>
    <single genre="doowop">
        <artist>The Sheppards</artist>
        <title>Tragic</title>
        <producer>Bunky Sheppard</producer>
        <writer>Kermit Chandler and O.C. Perkins</writer>
        <label>Apex 7762</label>
        <year>1961</year>
        <position>Did not make pop charts</position>
    </single>
    <single genre="R&amp;B">
        <artist>Joyce Harris</artist>
        <title>No Way Out</title>
        <producer>not credited</producer>
        <writer>Joyce Harris</writer>
        <label>Domino 905</label>
        <year>1961</year>
        <position> Did not make pop charts</position>
    </single>
</favorites>
```

XPATH AND XSL

In order to be able to understand the XML structure of a define.xml file, we need to briefly discuss a few more XML related standards and concepts.

To be able to extract information from an XML document the **XPath** standard gives XML developers a tool for navigating the structure of an XML document. We can simply demonstrate this by 2 examples from Figure 2.

- The XPath location path **`/favorites/single/artist`** returns all artist elements: "The Sheppards" and "Joyce Harris".

- The XPath location path `/favorites/single/@genre` returns the “doowop” and “R&amp;B” attributes.

The **XPath** standard is part of the **XSL** family of standards.

XSL is the Extensible Style sheet Language [14], one of the most complicated – and most useful – parts of XML. While XML itself is intended to define the structure of a document, it does not contain any information on how it is to be displayed. In order to do this we need a language, XSL, to describe the format of a document, ready for use in a display application (computer screen, cell phone screen, paper,).

XSL is actually a family of transformation languages which allows one to describe how files encoded in the XML standard are to be formatted or transformed.

The following three languages can be distinguished:

- XSL Transformations (XSLT): an XML language for transforming XML documents.
- XSL Formatting Objects (XSL-FO): an XML language for specifying the visual formatting of an XML document
- The XML Path Language (XPath): a non-XML language used by XSLT, and also available for use in non-XSLT contexts, for addressing the parts of an XML document.

THE STRUCTURE OF THE DEFINE.XML

The previous section explained the building blocks of XML. This section will specifically describe the structure of a define.xml file that conforms to the Case Report Tabulation Data Definition Specification (CRT-DDS or define.xml) version 1.0 as developed by the CDISC define.xml Team [7].

SCHEMA STRUCTURE

The CRT-DDS (define.xml) standard is based on the CDISC operational model (ODM). The ODM is defined by an XML schema that allows extension [8]. This extension mechanism has been implemented by expressing the ODM schema using two files:

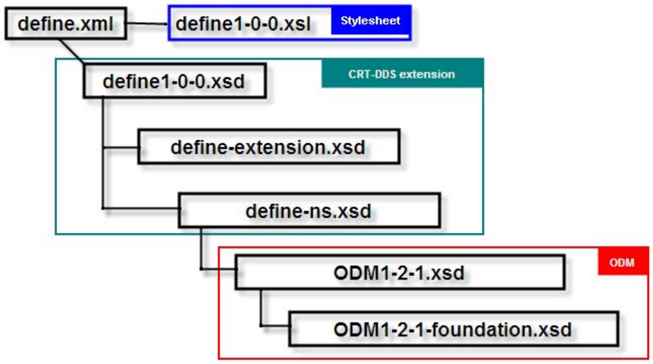
- a *foundation* XML Schema file (ODM1-2-1-foundation.xsd), which defines the elements, attributes and structure of the base ODM schema.
- an *application* XML Schema file (ODM1-2-1.xsd.) which imports the foundation XML Schema and other schema definitions needed by ODM, such as the core W3C XML schema (xml.xsd) and the XML schema that defines the W3C XML Signature standard (xmldsig-core-schema.xsd).

To create the define.xml extension three files have been provided:

- A *namespace* XML schema (define-ns.xsd) that defines the extension namespace and any new elements and attributes.
- An *extension* XML Schema file (define-extension.xsd) defines the location of the extensions within the ODM.
- An *application extension* XML Schema file (define1-0-0.xsd) that will import the extension XML Schema file and, in turn, any files imported in the ODM root schema.

In November 2009 CDISC published a XML Schema Validation for Define.xml white paper [15]. This white paper, created by the CDISC XML Technology team, provides guidance on validating define.xml documents against the define.xml XML schemas and proposes practices and tools to improve define.xml schema validation.

Figure 3: *The define.xml (CRT-DDS) and the associated style sheet and schemas*



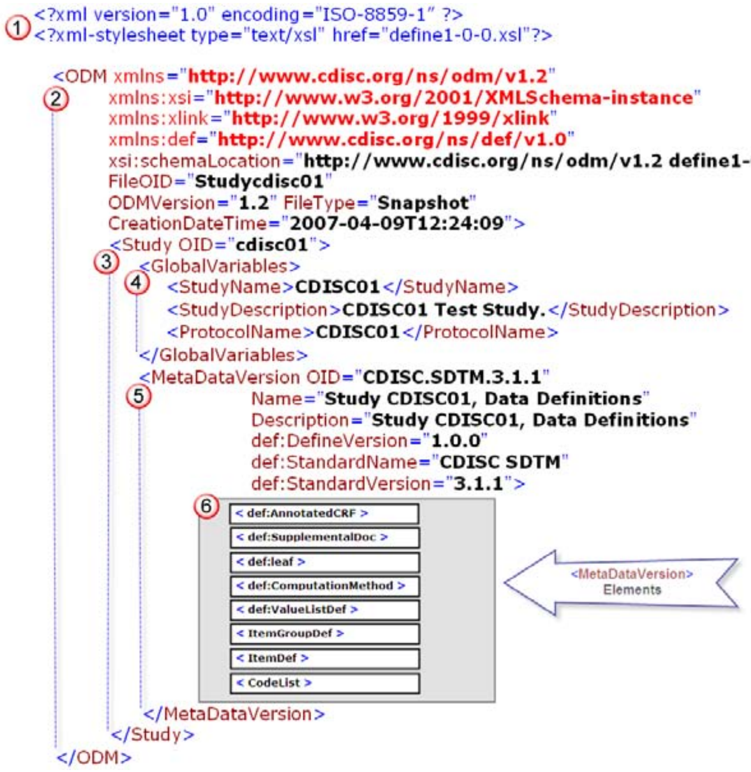
DEFINE.XML BUILDING BLOCKS

In this paragraph we will show the building blocks of the define.xml. As mentioned before, the CRT-DDS standard (define.xml) is an extension of ODM. The ODM model defines many elements and attributes that are optional.

We will only mention required elements and attributes, or elements and attributes that were found in the example define.xml file.

Figure 4 shows a high-level overview of a define.xml file.

Figure 4: *The building blocks of the define.xml (CRT-DDS)*



```
<?xml version="1.0" encoding="ISO-8859-1" ?>
<?xml-stylesheet type="text/xsl" href="define1-0-0.xsl"?>

<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 define1-0-0.xsd"
     FileOID="Studycdisc01"
     ODMVersion="1.2" FileType="Snapshot"
     CreationDateTime="2007-04-09T12:24:09">
     <Study OID="cdisc01">
       <GlobalVariables>
         <StudyName>CDISC01</StudyName>
         <StudyDescription>CDISC01 Test Study.</StudyDescription>
         <ProtocolName>CDISC01</ProtocolName>
       </GlobalVariables>
       <MetaDataVersion OID="CDISC.SDTM.3.1.1"
                 Name="Study CDISC01, Data Definitions"
                 Description="Study CDISC01, Data Definitions"
                 def:DefineVersion="1.0.0"
                 def:StandardName="CDISC SDTM"
                 def:StandardVersion="3.1.1">
            < def:AnnotatedCRF >
            < def:SupplementalDoc >
            < def:leaf >
            < def:ComputationMethod >
            < def:ValueListDef >
            < ItemGroupDef >
            < ItemDef >
            < CodeList >
       </MetaDataVersion>
     </Study>
</ODM>
```

We will now describe the different parts of the define.xml file.

① The **header section** of the define.xml is important for the XML processor.

The first line identifies the file as an XML document and specifies the XML version (“1.0”) and the encoding of the document (“ISO-8859-1”). The second line includes a reference to the style sheet (“define1-0-0.xsl”) that can be used by an XSL processor to render the document. In this case the style sheet can be used by the XSL processor in a web browser to render the XML file as HTML for display. As mentioned before, the HTML that gets created by the browser depends on the particular browser application.

② Following the header section is the **ODM** root element. All other elements in the define.xml file will be contained within the ODM element. The ODM element contains attributes that define the namespaces and the location of the schema that specifies the XML document.

Other required ODM attributes are displayed in Table 1.

Table 1: *ODM required attributes*

Attribute	Description
FileType	Type of transmission. For define.xml the only valid value is “Snapshot”. This means that the document contains only the current state of the data and metadata it describes, and no transactional history.
FileOID	A unique identifier for this file. FileOIDs should be universally unique if at all possible.
CreationDateTime	Date and Time when the define.xml file was last modified (ISO 8601 datetime).
ODMVersion	The version of the ODM standard used. According to the ODM schema, this is an optional attribute. However, a missing ODMVersion should be interpreted as "1.1". Documents based on ODM 1.2 should have ODMVersion="1.2".

③ **Study** is the first element contained in the ODM root element. The Study element collects static structural information about an individual study. It has one attribute “OID”, which is the unique identifier of the Study.

The Study element has two child-elements in the define.xml:

- GlobalVariables - General summary information about the Study.
- MetaDataVersion - Domain and variable definitions within the submission.

④ **GlobalVariables** is a required child element of the **Study** element and contains three required child elements:

- StudyName - Short external name for the study.
- StudyDescription - Free-text description of the study.
- ProtocolName - The sponsor’s internal name for the protocol.

⑤ The **MetaDataVersion** is a child element of the **Study** element and contains the domain and variable definitions included within a submission. Table 2 lists the MetaDataVersion attributes that are part of the define.xml file. The attributes with a prefix of “def:” are extensions to the ODM schema.

Table 2: *MetaDataVersion required attributes*

Attribute	Description
OID	The unique identifier of the MetaDataVersion
Name	Name of the MetaDataVersion
Description	Further description of the data definition document
def:DefineVersion	The schema version used for the define.xml
def:StandardName	Short name of the MetaDataVersion (e.g. CDISC SDTM)
def:StandardVersion	The version of an external standard to which the data conforms (e.g. 3.1.1)

⑥ Table 3 lists the MetaDataVersion child elements. The ItemGroupDef and ItemDef elements are required.

Table 3: *MetaDataVersion child elements*

Element	Description
def:AnnotatedCRF	This element can be used to reference an Annotated Case Report Form (CRF), a PDF file that maps the data collection fields used to collect subject data to the corresponding variables or discrete variable values contained within the data sets
def:SupplementalDoc	This element can be used to reference a PDF file with supplemental data definition information. A reason for this document can be the need for further explanations or descriptions of variables contained within the data sets.
def:leaf	This element has to be present if either the def:AnnotatedCRF and/or the def:SupplementalDoc are provided. The def:leaf element will then contain the actual location of the PDF file relative to the define.xml
def:ComputationMethod	This element is available for every unique computational algorithm that is referenced by variable metadata or variable value-level metadata. It contains the method name and the computation rule in a kind of pseudo code.
def:ValueListDef	This element provides additional value-level metadata for certain variables that are part of a normalized data structure. For example, the Vital Signs domain has a measurement parameter (VSTESTCD) that stores the name of a measurement (height, weight, systolic blood pressure, …). A corresponding value list will then describe each unique value of the measurement (“HEIGHT”, “WEIGHT”, “SYSBP”, …)
ItemGroupDef	For every data set in the submission there is an ItemGroupDef element describing data set metadata (label, structure, keys, variables, location of transport file, …)
ItemDef	For every variable referenced in either def:ValueListDef or ItemGroupDef there will be an ItemDef element. This element will describe properties like name, label, length, computation method, range or code list restrictions, and several other properties.
CodeList	The CodeList element defines a discrete set of permitted values for an item. The definition can be an explicit list of values or a reference to an externally defined code list.

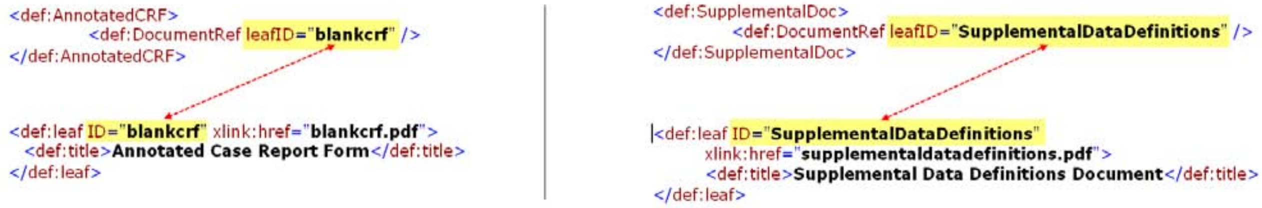
METADATAVERSION ELEMENT DETAILS

In this paragraph we will dive deeper into the sub-elements of the **MetaDataVersion** element. We will see how the different elements relate to each other.

def:AnnotatedCRF, def:SupplementalDoc and def:leaf

As mentioned before, these elements can be used to reference PDF files. Figure 5 shows the relation between these elements. The **def:DocumentRef/@leafID** must match the corresponding **def:leaf/@ID**.

Figure 5: *Referencing external PDF files*



```
<def:AnnotatedCRF>
        <def:DocumentRef leafID="blankcrf" />
</def:AnnotatedCRF>

<def:leaf ID="blankcrf" xlink:href="blankcrf.pdf">
  <def:title>Annotated Case Report Form</def:title>
</def:leaf>
```

```
<def:SupplementalDoc>
        <def:DocumentRef leafID="SupplementalDataDefinitions" />
</def:SupplementalDoc>

<def:leaf ID="SupplementalDataDefinitions"
        xlink:href="supplementaldatadefinitions.pdf">
        <def:title>Supplemental Data Definitions Document</def:title>
</def:leaf>
```

ItemGroupDef

For every data set in the submission there will be an ItemGroupDef element with domain-level metadata. Table 4 lists the ItemGroupDef attributes.

Table 4: *ItemGroupDef attributes*

Attribute	Status	Description
OID	Required	The unique identifier of the domain.
Name	Required	The file name of the data set or data domain name (e.g., “DM” for Demographics)
Repeating	Required	“Yes” for domains with more than one record per subject whereas, “No” for domains with 1 record per subject.
IsReferenceData	Optional	“Yes” for domains that contain reference data only, no subject-level data. “No” indicates subject-level data. Absence of this attribute indicates subject-level data.
SASDatasetName[1]	Optional	Name of SAS data set.
Purpose	Optional	Purpose for the data set (e.g., “Tabulation”, “Analysis”).
def:Label	Required	Brief description of the data domain.
def:Structure	Optional	Data domain structure (e.g. “One record per subject per visit”).
def:DomainKeys	Optional	Comma-separated text string that contains the data set variables that uniquely identify a data record.
def:Class	Optional	General class of the domain as defined in the SDTM model (e.g., “Events”, “Interventions”, “Findings”, “Special Purpose”, “Trial Design”, ...)
def:ArchiveLocationID	Required	Reference to the def:leaf element that contains a link to the location of the data set.

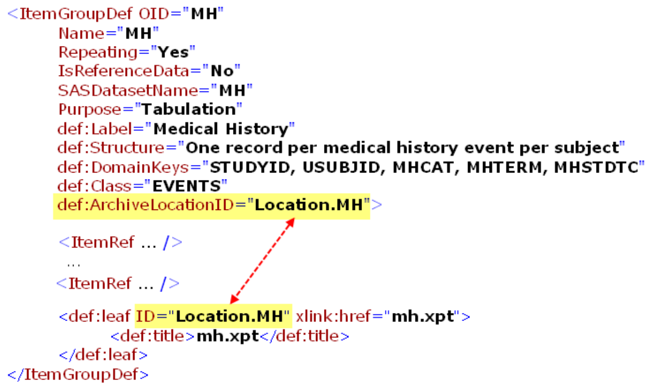
ItemGroupDef elements have:

- One ItemRef child element per variable in the data set
- Exactly one def:leaf element that contains the XLink information that is referenced by the def:ArchiveLocationID attribute.

The relation between the **ItemGroupDef/@def:ArchiveLocationID** and the **def:leaf/@ID** is illustrated in Figure 6.

[1] SASDatasetName is an optional attribute that is part of the ODM foundation. This means that it is a valid attribute in the define.xml. This attribute is not mentioned in the define.xml specification.

Figure 6: *Referencing external data sets*



```
<ItemGroupDef OID="MH"
        Name="MH"
        Repeating="Yes"
        IsReferenceData="No"
        SASDatasetName="MH"
        Purpose="Tabulation"
        def:Label="Medical History"
        def:Structure="One record per medical history event per subject"
        def:DomainKeys="STUDYID, USUBJID, MHCAT, MHTERM, MHSTDTC"
        def:Class="EVENTS"
        def:ArchiveLocationID="Location.MH">

        <ItemRef ... />
          ...
        <ItemRef ... />

        <def:leaf ID="Location.MH" xlink:href="mh.xpt">
                <def:title>mh.xpt</def:title>
        </def:leaf>
</ItemGroupDef>
```

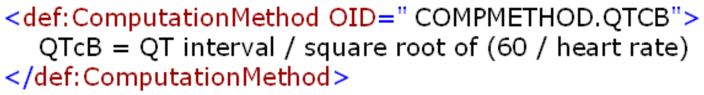
ItemRef and ItemDef

For every variable in a data set in the submission there will be an ItemRef and an ItemDef element with variable-level metadata. Table 5 lists the ItemRef attributes. Table 6 lists ItemDef attributes. ItemDef elements can have an optional associated CodeListRef or def:ValueListRef child element.

def:ComputationMethod

The def:ComputationMethod element has one attribute (OID) and contains the details about computational algorithms used to derive or impute variable values.

Figure 7: *Example of a ComputationMethod*



```
<def:ComputationMethod OID=" COMPMETHOD.QTCB">
    QTcB = QT interval / square root of (60 / heart rate)
</def:ComputationMethod>
```

Table 5: *ItemRef attributes*

Attribute	Status	Description
ItemOID	Required	The unique identifier of the variable.
OrderNumber	Optional	Provide an ordering on the ItemRefs (within the containing ItemGroupDef) for use whenever a list of ItemRefs is presented to a user.
Mandatory	Required	Indicates that the clinical data for an instance of the containing item group would be incomplete without an instance of this type of item. Variables that have an SDTM "Core" attribute given as "Required" should have Mandatory="Yes" in the define.xml. SDTM variables that have a "Core" attribute as "Expected" or "Permissible" should have Mandatory="No" in the define.xml.
Role	Optional	Variable classification (e.g., "Identifier", "Topic", ."Timing Variable", ...). Values are interpreted as codes from CodeList as specified by @RoleCodeListOID
RoleCodeListOID	Optional	The identifier of the corresponding Role Code List, which defines the full set roles from which the Role attribute values are to be taken.

Table 6: *ItemDef attributes*

Attribute	Status	Description
OID	Required	The unique identifier of the variable.
Name	Required	Variable name.
DataType	Required	Type of the data (e.g., text, integer, float, ...)
Length	Conditional	The variable length.
SignificantDigits	Conditional	The number of decimal digits.
SASFieldName[2]	Optional	
Origin	Optional	Indicator of the origin of the variable (e.g., CRF page number, derived, or a reference to other variable(s).
Comment	Required	Further information regarding variable definition, usage, etc.
Def:Label	Required	Variable label.
Def:DisplayFormat	Optional	Display format for numeric variables (e.g., 8.2)
Def:ComputationMethodOID	Optional	Unique identifier of the corresponding computation method.

CodeList and def:ValueListDef

Many variables in a submission have a discrete list of valid values or controlled terms associated with them. The CodeList element defines the controlled terminology. For variables whose values are restricted to a list of values, the corresponding ItemDef element has to include a CodeListRef element that references a CodeList element. The CodeListOID attribute of the CodeListRef element should match the OID attribute of the CodeList element.

The def:ValueListDef element provides additional value-level metadata for certain variables that are part of a normalized data structure. For example, the Vital Signs domain has a measurement parameter (VSTESTCD) that stores the name of a measurement (height, weight, systolic blood pressure, …). A corresponding value list will then describe each unique value of the measurement ("HEIGHT", "WEIGHT", "SYSBP", …). For these variables, the corresponding ItemDef element has to include a def:ValueListRef element that references a def:ValueListDef element. The **def:ValueListOID** attribute of the **def:ValueListRef** element should match the **OID** attribute of the **def:ValueListDef** element.

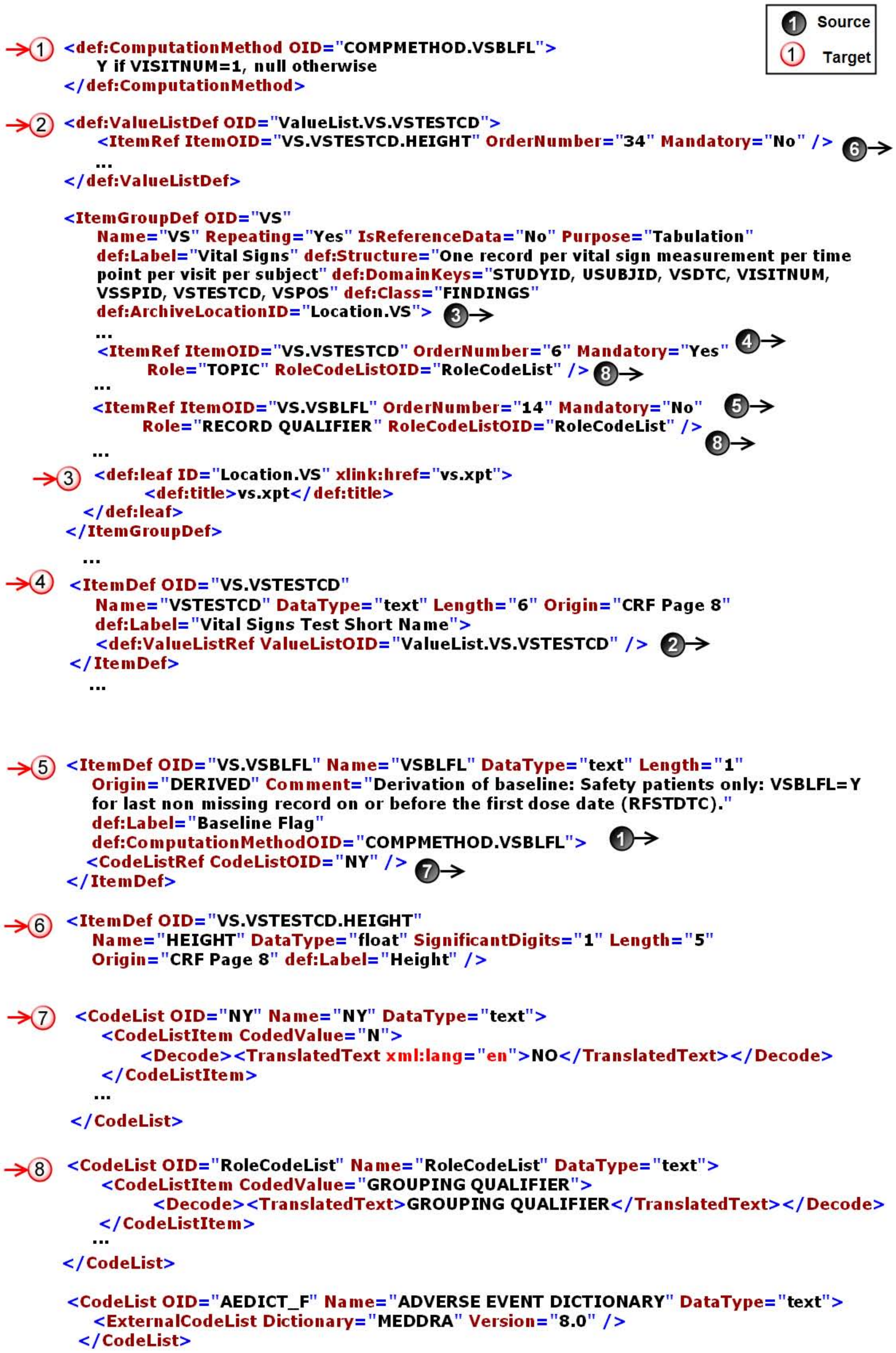
Figure 8 illustrates several concepts that are related to ItemRef, ItemDef, def:ComputationMethod, CodeList and def:ValueListDef elements.

[2] SASFieldName is optional an attribute that is part of the ODM foundation. This means that it is a valid attribute in the define.xml. This attribute is not mentioned in the define.xml specification.

The black numbers on the right side represent the source of a relation and a red numbers on the left side represent the target of a relation. In every relation there has to be a correspondence between the identifier of the source and the target.

For example: In relation 4: source identifier = **ItemRef/@ItemOID**, target identifier = **ItemDef/@OID** and the both have the value “VS.VSTESTCD”;

Figure 8: Relations within a define.xml



```
<def:ComputationMethod OID="COMPMETHOD.VSBLFL">
     Y if VISITNUM=1, null otherwise
</def:ComputationMethod>

<def:ValueListDef OID="ValueList.VS.VSTESTCD">
     <ItemRef ItemOID="VS.VSTESTCD.HEIGHT" OrderNumber="34" Mandatory="No" />
     ...
</def:ValueListDef>

<ItemGroupDef OID="VS"
     Name="VS" Repeating="Yes" IsReferenceData="No" Purpose="Tabulation"
     def:Label="Vital Signs" def:Structure="One record per vital sign measurement per time
     point per visit per subject" def:DomainKeys="STUDYID, USUBJID, VSDTC, VISITNUM,
     VSSPID, VSTESTCD, VSPOS" def:Class="FINDINGS"
     def:ArchiveLocationID="Location.VS">
     ...
     <ItemRef ItemOID="VS.VSTESTCD" OrderNumber="6" Mandatory="Yes"
            Role="TOPIC" RoleCodeListOID="RoleCodeList" />
     ...
    <ItemRef ItemOID="VS.VSBLFL" OrderNumber="14" Mandatory="No"
           Role="RECORD QUALIFIER" RoleCodeListOID="RoleCodeList" />
    ...
    <def:leaf ID="Location.VS" xlink:href="vs.xpt">
           <def:title>vs.xpt</def:title>
    </def:leaf>
</ItemGroupDef>
   ...
 <ItemDef OID="VS.VSTESTCD"
    Name="VSTESTCD" DataType="text" Length="6" Origin="CRF Page 8"
    def:Label="Vital Signs Test Short Name">
    <def:ValueListRef ValueListOID="ValueList.VS.VSTESTCD" />
 </ItemDef>
   ...

<ItemDef OID="VS.VSBLFL" Name="VSBLFL" DataType="text" Length="1"
    Origin="DERIVED" Comment="Derivation of baseline: Safety patients only: VSBLFL=Y
    for last non missing record on or before the first dose date (RFSTDTC)."
    def:Label="Baseline Flag"
    def:ComputationMethodOID="COMPMETHOD.VSBLFL">
   <CodeListRef CodeListOID="NY" />
</ItemDef>

<ItemDef OID="VS.VSTESTCD.HEIGHT"
    Name="HEIGHT" DataType="float" SignificantDigits="1" Length="5"
    Origin="CRF Page 8" def:Label="Height" />

 <CodeList OID="NY" Name="NY" DataType="text">
    <CodeListItem CodedValue="N">
         <Decode><TranslatedText xml:lang="en">NO</TranslatedText></Decode>
    </CodeListItem>
    ...
 </CodeList>

<CodeList OID="RoleCodeList" Name="RoleCodeList" DataType="text">
    <CodeListItem CodedValue="GROUPING QUALIFIER">
          <Decode><TranslatedText>GROUPING QUALIFIER</TranslatedText></Decode>
    </CodeListItem>
   ...
</CodeList>

<CodeList OID="AEDICT_F" Name="ADVERSE EVENT DICTIONARY" DataType="text">
   <ExternalCodeList Dictionary="MEDDRA" Version="8.0" />
 </CodeList>
```

DESIGNING A RELATIONAL DATA STRUCTURE FOR THE DEFINE.XML

In the previous paragraphs we have seen the structure of the define.xml file. Also, we have seen the relations between the different parts of the define.xml file. Since the define.xml file does not have a 2-dimensional data structure, it is not a trivial task to translate the define.xml to number of 2-dimensional SAS data set with rows and columns. We will need to create a relational data model from the define.xml.

According to the rules of ODM the OID (object identifier) for a MetaDataVersion, ItemGroupDef, ItemDef or CodeList element must be unique within a single study. Together with the Study OID, these object identifiers will serve as keys in the relational data model.

We can map the define.xml to the following data sets (all data sets also contain the MetaDataVersion OID, or SAS variables MetaDataVersion_OID):

- **MetaDataVersion** which contains one record:
  - ODM attributes (xsi:schemaLocation, FileOID, ODMVersion, FileType, CreationDateTime)
  - Study OID attribute
  - Text of GlobalVariables child elements: StudyName, StudyDescription and ProtocolName
  - MetaDataVersion attributes: OID, Name, Description, def:DefineVersion, def:StandardName and def:StandardVersion
- **AnnotatedCRF** which contains:
  - For every def:AnnotatedCRF element and every def:DocumentRef child element the leafID attribute
- **SupplementalDoc** which contains:
  - For every def:SupplementalDoc element and every def:DocumentRef child element the leafID attribute
- **Leaf** which contains:
  - For every def:AnnotatedCRF element the leafID attribute and the corresponding def:leaf@xlink:href and def:leaf/title
  - For every def:SupplementalDoc element the leafID attribute and the corresponding def:leaf@xlink:href and def:leaf/title
- **ItemGroupDef** which contains for every ItemGroupDef:
  - the ItemGroupDef attributes: OID, Name, Repeating, IsReferenceData, SASDatasetName, Purpose, def:Label, def:Structure, def:DomainKeys, def:Class, def:ArchiveLocationID
  - from ItemGroupDef/def:leaf the ID attribute, xlink:href attribute and the contents of the def:title child element (this is possible since every ItemGroupDef has exactly one def:leaf child element)
- **ItemGroupDef_ItemRef** which contains for every ItemRef element in an ItemGroupDef element:
  - The OID attribute of the parent ItemGroupDef element
  - ItemRef attributes: ItemOID, OrderNumber, Mandatory, Role and RoleCodeListOID
- **ItemDef** which contains for every ItemDef element:
  - ItemDef attributes: OID, Name, DataType, Length, SignificantDigits, SASFieldName, Origin, Comment, Def:Label, Def:DisplayFormat and Def:ComputationMethodOID
  - If applicable, the OID of the associated codelist: CodeListRef/@CodeListOID
  - If applicable, the OID of the associated valuelist: def:ValueListRef/@ValueListOID
- **ComputationMethod** which contains for every def:ComputationMethod element:
  - The OID attribute and the text content of the element.

  The OID for a def:ComputationMethod element must be unique within a single study.
- **CodeList** which contains for every CodeList element:
  - Attributes OID, Name, DataType and SASFormatName

- **CodeList_CodeListItem** which contains for every CodeListItem element:
  - OID Attribute of the parent CodeList element
  - CodeListItem attributes (CodedValue and Rank)
  - Content of CodeListItem/TranslatedText element and the CodeListItem/TranslatedText/@xml:lang attribute
- **ExternalCodeList** which contains for every ExternalCodeList element:
  - OID Attribute of the parent CodeList element
  - ExternalCodeList attributes (Dictionary and Version)
- **ValueList** which contains for every def:ValueListDef element:
  - The OID attributes

  The OID for a def:ValueListDef element must be unique within a single study.
- **ValueListItem** which contains for every def:ValueListDef/ItemRef:
  - OID Attribute of the parent def:ValueListDef element
  - ItemRef attributes: ItemOID, OrderNumber and Mandatory

The appendix shows an (incomplete) data model for the define.xml.

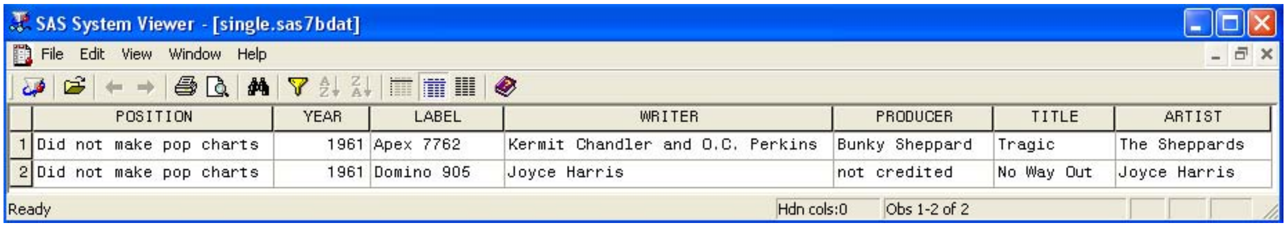
READING XML FILES WITH SAS

We can read an XML file and turn it into a SAS data set by using the XML engine on a libname statement. However, this is only possible if the XML file represents a 'rectangular' structure.

The XML file as we saw earlier in Figure 2 looks like a 'rectangular' structure, so we can read it easily with SAS:

```
LIBNAME favs xml "favorites.xml";
DATA single;
 SET favs.single;
RUN;
```

The resulting SAS data set looks like this:



	POSITION	YEAR	LABEL	WRITER	PRODUCER	TITLE	ARTIST
1	Did not make pop charts	1961	Apex 7762	Kermit Chandler and O.C. Perkins	Bunky Sheppard	Tragic	The Sheppards
2	Did not make pop charts	1961	Domino 905	Joyce Harris	not credited	No Way Out	Joyce Harris

We can already see an issue here, because the attribute /favorites/single/@genre (with values 'doowop' and 'r&b') has not been included in the SAS data set.

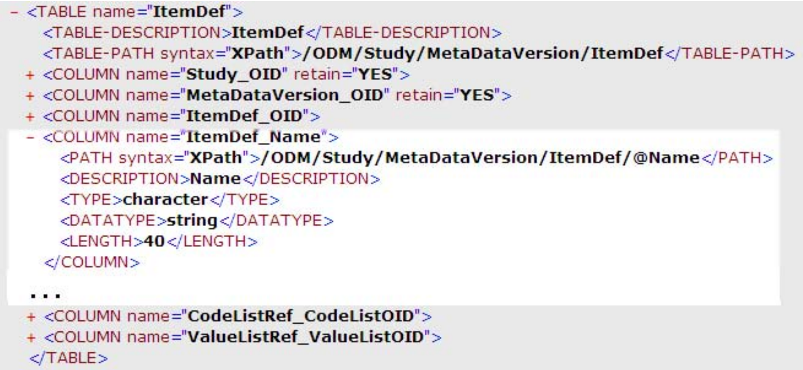
USING THE SAS XML MAPPER

To be able to read more complicated XML files like the define.xml file with SAS and create SAS data sets we need to create an XMLMAP. The XMLMap tells the SAS XML engine how to map the content in the hierarchical define.xml file to rows and columns in the rectangular SAS tables. An XMLMAP file is an XML file itself. Once we have an XMLMAP we can easily create SAS data sets with the following code:

```
FILENAME define  "c:\Projects\CDISC\Define.xml\define.xml";
FILENAME sxlemap "c:\Projects\CDISC\Define.xml\DefineXML.map";
LIBNAME  define XML XMLMAP=sxlemap access=READONLY;
PROC COPY IN=define OUT=outlib;
RUN;
```

Figure 9 shows part of an XMLMAP. It specifies that the data set **ItemDef** has a character variable named **ItemDef_Name** (length 40), whose content is defined by the XPath specification **/ODM/Study/MetaDataVersion/ItemDef/@Name**.

Figure 9: *XMLMAP example*[3]



```
- <TABLE name="ItemDef">
    <TABLE-DESCRIPTION>ItemDef</TABLE-DESCRIPTION>
    <TABLE-PATH syntax="XPath">/ODM/Study/MetaDataVersion/ItemDef</TABLE-PATH>
  + <COLUMN name="Study_OID" retain="YES">
  + <COLUMN name="MetaDataVersion_OID" retain="YES">
  + <COLUMN name="ItemDef_OID">
  - <COLUMN name="ItemDef_Name">
      <PATH syntax="XPath">/ODM/Study/MetaDataVersion/ItemDef/@Name</PATH>
      <DESCRIPTION>Name</DESCRIPTION>
      <TYPE>character</TYPE>
      <DATATYPE>string</DATATYPE>
      <LENGTH>40</LENGTH>
    </COLUMN>
   ...
  + <COLUMN name="CodeListRef_CodeListOID">
  + <COLUMN name="ValueListRef_ValueListOID">
  </TABLE>
```

THE SAS XML MAPPER

An XMLMAP can be created with the SAS XML Mapper, which is a Java-based graphical application that helps in creating and modifying XMLMaps [16]. Either the specific XML file (define.xml) or the schema that defines the rules of the XML file can be used as input for the XML Mapper. The advantage of using the schema is that it contains definitions of optional XML elements and attributes that may not be a part of the specific define.xml file. This will allow for the creation of a more generic XMLMAP. Figure 10 shows the SAS XML Mapper interface with the define.xml loaded in the left panel.

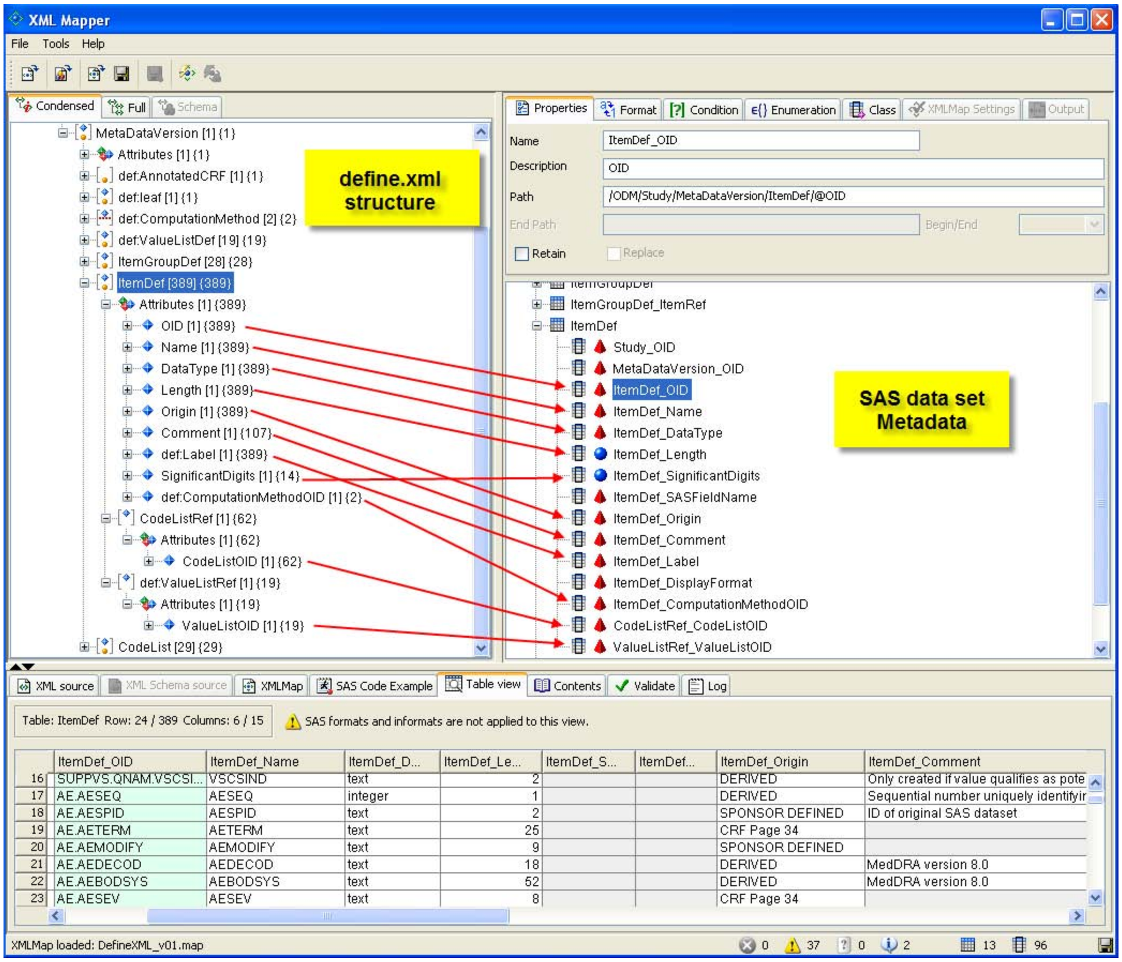
The latest version of the SAS XML Mapper is version 92.110 09w09 and was released in February 2009 [17].

A new feature of 9.2 is that you can now export an XML document from a SAS data set using the XMLMap that was created to import the XML document. SAS XML Mapper enables you to update the XMLMap to XMLMap syntax version 1.9, which provides elements for exporting.

Further, the AutoMap feature using XML automatically generates XMLMap syntax for the displayed XML document. SAS XML Mapper analyzes the XML document's tree structure. SAS XML Mapper generates an XMLMap TABLE element to contain a data set definition for each level in the XML document, except for leaf nodes, which contain columns. For each level, SAS XML Mapper generates an XMLMap COLUMN element to contain a variable definition for each nested element or attribute. For each level, SAS XML Mapper gives you the option to generate surrogate keys. Surrogate keys are system-generated counter variables that identify each observation in resulting SAS data sets. The surrogate keys preserve the XML structure so that the resulting SAS data sets can be rejoined.

[3] This particular XMLMap gave a warning in the XML Mapper application: "*Column (MetaDataVersion_OID) in table (ItemDef) has an XPath outside the scope of the table path. The contents of this column may not correspond to other row values and/or may be missing entirely.*" In this particular case using this XMLMap would not lead to unexpected results. However, to avoid that inexperienced SAS XML Mapper users start creating tables by dragging elements and attributes in the same SAS target table, regardless of the origin of the data in the XML source file, SAS decided to create help users with a warning when they go outside of the table boundary. This warning should be considered as a "safety net".

Figure 10: *SAS XML Mapper interface*



Name ItemDef_OID
Description OID
Path /ODM/Study/MetaDataVersion/ItemDef/@OID
End Path Begin/End
☐ Retain ☐ Replace

Table: ItemDef Row: 24 / 389 Columns: 6 / 15

SAS formats and informats are not applied to this view.

	ItemDef_OID	ItemDef_Name	ItemDef_D...	ItemDef_Le...	ItemDef_S...	ItemDef...	ItemDef_Origin	ItemDef_Comment
16	SUPPVS.QNAM.VSCSI...	VSCSIND	text	2			DERIVED	Only created if value qualifies as pote
17	AE.AESEQ	AESEQ	integer	1			DERIVED	Sequential number uniquely identifyir
18	AE.AESPID	AESPID	text	2			SPONSOR DEFINED	ID of original SAS dataset
19	AE.AETERM	AETERM	text	25			CRF Page 34	
20	AE.AEMODIFY	AEMODIFY	text	9			SPONSOR DEFINED	
21	AE.AEDECOD	AEDECOD	text	18			DERIVED	MedDRA version 8.0
22	AE.AEBODSYS	AEBODSYS	text	52			DERIVED	MedDRA version 8.0
23	AE.AESEV	AESEV	text	8			CRF Page 34	

XMLMap loaded: DefineXML_v01.map 0 37 0 2 13 96

VALIDATING THE DEFINE.XML

Earlier we talked about two different ways to verify whether XML files are coded correctly:

Well-formed The XML code must be syntactically correct.

Valid If the XML file has an associated XML Schema, the elements must appear in the defined structure and the content of the individual elements must conform to the declared data types specified in the schema.

There are numerous tools available that can check well-formedness and validate an XML file against an XML schema. As mentioned earlier in this paper, the CDISC XML Technologies Team has published a XML Schema Validation for Define.xml white paper, that provides guidance on validating define.xml documents against the define.xml XML schemas and proposes practices and tools to improve define.xml schema validation [15].

To further ensure the quality of the define.xml, more validation needs to be performed:

- Validate against the rules as specified in the Case Report Tabulation Data Definition Specification (define.xml) version 1.0 [7]. An example of this is the rule that the **ItemOID** attribute in an **ItemRef** element must match the **OID** attribute of a corresponding **ItemDef** element.
- Check the consistency between the define.xml content and the SAS transport files. For example, an **ItemGroupDef** element must contain an **ItemRef** element for each variable included in the corresponding SAS transport file.

- Check the consistency between the define.xml and the SDTM metadata. An example of this is the “Mandatory” attribute of the **ItemRef** element, which needs to be consistent with the SDTM Core attribute (Required, Expected, Permissible).

Once we have the define.xml converted into relational SAS data sets, it will be easy to perform these validation checks.

Some code examples:

To check for duplicate **ItemDef** elements:

```
PROC SQL;
  SELECT ItemDef_OID, ItemDef_Name, ItemDef_Label
  FROM ItemDef
  GROUP BY ItemDef_OID
  HAVING COUNT(*) > 1
  ORDER BY ItemDef_OID;
QUIT;
```

To check for duplicate **ItemRef** elements within an **ItemGroupDef** element:

```
PROC SQL;
  SELECT ItemGroupDef_OID, ItemRef_ItemOID, ItemRef_OrderNumber
  FROM ItemgroupDef_itemref
  GROUP BY ItemGroupDef_OID, ItemRef_ItemOID
  HAVING COUNT(*) > 1
  ORDER BY ItemGroupDef_OID, ItemRef_ItemOID;
QUIT;
```

To check for **ItemRef** elements within an **ItemDefGroup** without an **ItemDef** element:

```
PROC SQL;
    SELECT ItemRef_ItemOID
    FROM ItemgroupDef_itemref
  EXCEPT
    SELECT ItemDef_OID
    FROM ItemDef
QUIT;
```

CONCLUSION

SAS/Base together with the SAS XML Mapper enable the conversion of the define.xml into relational SAS data sets.

This enables the creation of a PDF rendition of the define.xml file and the use of SAS to perform various checks to validate the define.xml against the clinical study data. The methodology described in this paper is applicable to the current version of the define.xml file, but also to future extensions.

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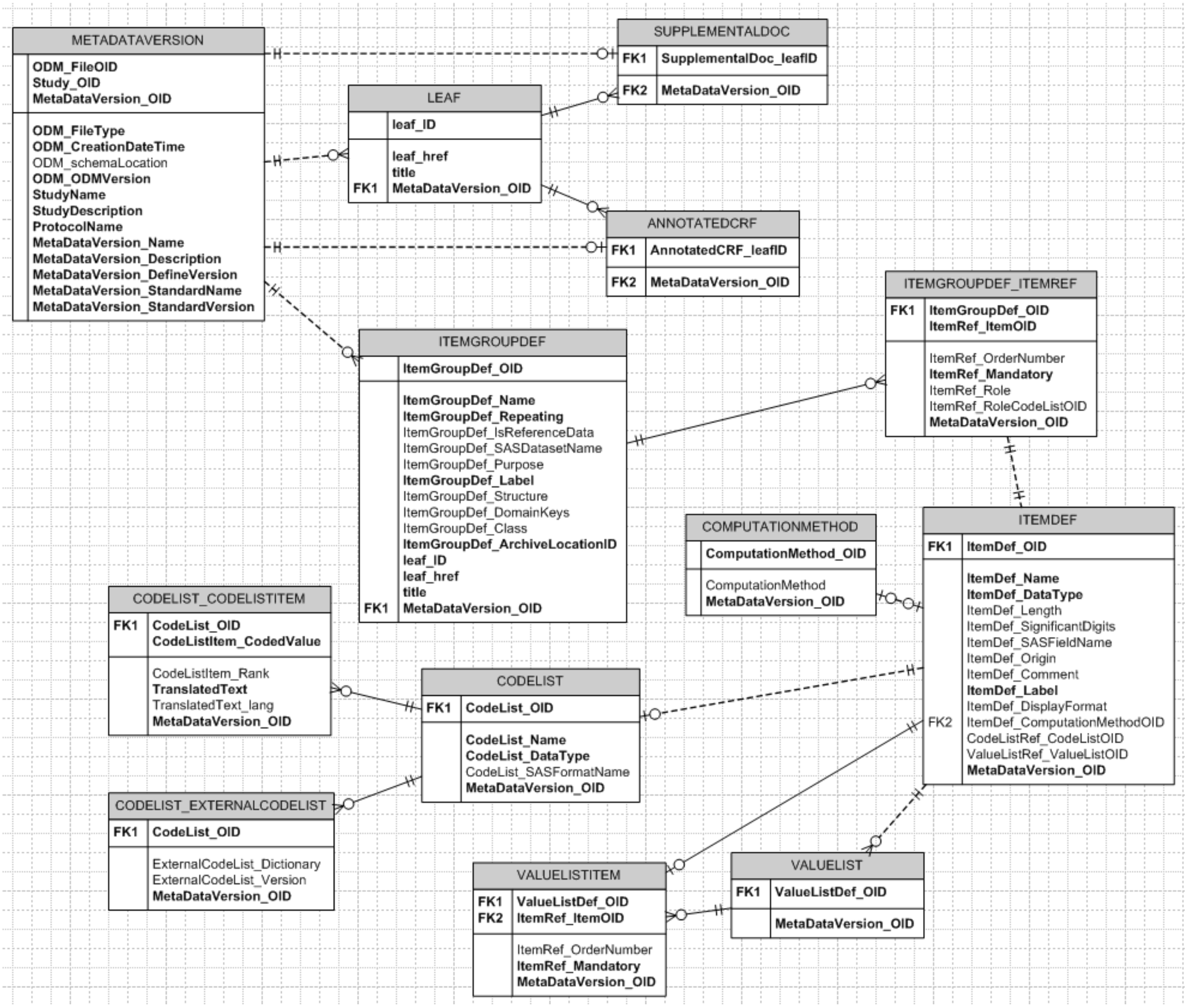
This paper can be found at http://www.lexjansen.com together with links to more than 10,000 other papers that were presented at SAS usergroups.

APPENDIX

(incomplete) data model for Define.xml


METADATAVERSION
ODM_FileOID
Study_OID
MetaDataVersion_OID
ODM_FileType
ODM_CreationDateTime
ODM_schemaLocation
ODM_ODMVersion
StudyName
StudyDescription
ProtocolName
MetaDataVersion_Name
MetaDataVersion_Description
MetaDataVersion_DefineVersion
MetaDataVersion_StandardName
MetaDataVersion_StandardVersion
SUPPLEMENTALDOC
FK1 SupplementalDoc_leafID
FK2 MetaDataVersion_OID
LEAF
leaf_ID
leaf_href
title
FK1 MetaDataVersion_OID
ANNOTATEDCRF
FK1 AnnotatedCRF_leafID
FK2 MetaDataVersion_OID
ITEMGROUPDEF_ITEMREF
FK1 ItemGroupDef_OID
ItemRef_ItemOID
ItemRef_OrderNumber
ItemRef_Mandatory
ItemRef_Role
ItemRef_RoleCodeListOID
MetaDataVersion_OID
ITEMGROUPDEF
ItemGroupDef_OID
ItemGroupDef_Name
ItemGroupDef_Repeating
ItemGroupDef_IsReferenceData
ItemGroupDef_SASDatasetName
ItemGroupDef_Purpose
ItemGroupDef_Label
ItemGroupDef_Structure
ItemGroupDef_DomainKeys
ItemGroupDef_Class
ItemGroupDef_ArchiveLocationID
leaf_ID
leaf_href
title
FK1 MetaDataVersion_OID
COMPUTATIONMETHOD
ComputationMethod_OID
ComputationMethod
MetaDataVersion_OID
ITEMDEF
FK1 ItemDef_OID
ItemDef_Name
ItemDef_DataType
ItemDef_Length
ItemDef_SignificantDigits
ItemDef_SASFieldName
ItemDef_Origin
ItemDef_Comment
ItemDef_Label
ItemDef_DisplayFormat
FK2 ItemDef_ComputationMethodOID
CodeListRef_CodeListOID
ValueListRef_ValueListOID
MetaDataVersion_OID
CODELIST_CODELISTITEM
FK1 CodeList_OID
CodeListItem_CodedValue
CodeListItem_Rank
TranslatedText
TranslatedText_lang
MetaDataVersion_OID
CODELIST
FK1 CodeList_OID
CodeList_Name
CodeList_DataType
CodeList_SASFormatName
MetaDataVersion_OID
CODELIST_EXTERNALCODELIST
FK1 CodeList_OID
ExternalCodeList_Dictionary
ExternalCodeList_Version
MetaDataVersion_OID
VALUELISTITEM
FK1 ValueListDef_OID
FK2 ItemRef_ItemOID
ItemRef_OrderNumber
ItemRef_Mandatory
MetaDataVersion_OID
VALUELIST
FK1 ValueListDef_OID
MetaDataVersion_OID