

How to easily generate define.pdf from Define.XML - Submission Request

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ABSTRACT

Define.XML is already a well-known requirement for each US Submission in order to explain SDTM and ADaM data. If a Define.XML version 2.0 or later version along with the related style sheet is submitted an additional Define.PDF does not need to be provided, because the Define.XML is already in a printable format.

However in one of our submissions, we have received a request to prepare a fully functioning Define.PDF. This paper will explain how to easily generate a Define.PDF from one or multiple Define.XML files within very little amount of time. The solution presented will detail necessary modifications of the XSL stylesheet and demonstrate that no other software than Adobe Acrobat and Adobe Acrobat Create PDF Toolbar in Internet Explorer is needed.

INTRODUCTION

When submitting clinical data to the Food and Drug Administration (FDA), XPT files following the Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM), will be put into context by information describing the content and use of the data which ultimately should enable a reviewer to understand and work with the data. SDTM data is explained by a study data reviewer guide (SDRG) and its related Define.XML, while ADaM data is explained by an analysis data reviewer guide (ADRG) and its Define.XML. During the review the agency can request additional analyses along with more data if not already part of the submission package.

In one of our submissions, we have received during the review period several questions, and needed to provide along with the answers additional XPT files and also its related Define.XML. After all answer have been provided to the agency we have been asked to prepare ONE text searchable, "Master" Define.PDF file that describes all of the datasets with all the bookmarks and links to each dataset. For example, the AE define file will be contained in this one master Define.PDF. It should be specifically bookmarked in a way so that the reviewer can click on the bookmark (bookmarks usually appear on the left hand side in adobe acrobat) and go directly to the first page of the AE define file. After a follow up call with FDA, we received the information, that the reviewer needs a readable hard copy of the Define.PDF that is independent of the server. The reviewer indicated that it will not be acceptable to submit a pure "print" of your XML define.

CONVERTING Define.XML TO Define.PDF

Programming a Define.pdf from scratch with all the features that are incorporated into the Define.XML processing was not an option due to limited time. Also we wanted to take advantage of all Define.XML features. We invested some time in order to find a way how to easily generate a Define.PDF from Define.XML.

Following steps need to be done:

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1. MODIFICATION OF XSL STYLESHEET

We realized that the existing bookmarks in Define.XML cannot be nicely converted into a Define.PDF and decided to remove it from the Define.XML. This can be done by removing “div id” in the existing official XSL stylesheet file (i.e. 102 to line 361 must be removed).

```
102      <div id="menu">
103          <!-- Skip Navigation Link for Accessibility -->
104          <a name="top" class="invisible" href="#main">Skip Navigation Link</a>
105
106      <span class="standard">
107      </span>
108
109      <ul class="hmenu">
110
111          <!-- ***** -->
112          <!-- ***** Annotated CRF ***** -->
113          <!-- ***** -->
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115          <xsl:if test="$g_xndMetaDataVersion/def:AnnotatedCRF">
116          </xsl:if>
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352      </a>
353      </li>
354      </xsl:for-each>
355      </ul>
356      </li>
357      </xsl:if>
358      </xsl:if>
359
360      </ul>
361      </div>
362      <!-- end of menu -->
```

To optimize the appearance of margins in the resulting Define.PDF the “main position” in the Define.XML needs to be changed as marked below in red:

Change from

```
2123      #main{
2124      position:absolute;
2125      left:22%;
2126      top:0px;
2127      overflow:auto;
2128      color:#000000;
2129      background-color:#FFFFFF;
2130      }
```

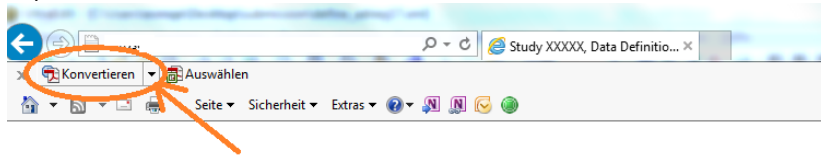
To

```
2123      #main{
2124      position:absolute;
2125      left:5%;
2126      top:0px;
2127      overflow:auto;
2128      color:#000000;
2129      background-color:#FFFFFF;
2130      }
```

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2. CONVERTING SINGLE Define.XML TO SINGLE Define.PDF

The Define.XML using the modified XSL Stylesheet has now the layout of Define.PDF. The single Define.XML files will be converted into single Define.PDF files using the Adobe Acrobat Create PDF Toolbar in Internet Explorer.



Analysis Datasets for Study XXXXX (xxxxxxxxxx)

Dataset	Description	Class
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Bookmarks will be created and need to be manually added and modified.

3. LINKS TO EXTERNAL FILES

All links to external files are transferred to full-paths and not relative-paths. So the links must be corrected.

Below how to edit the link using adobe acrobat:

Edit a link action

- 1 Select the Add or Edit link tool (Tools > Edit PDF > Link > Add or Edit).
- 2 Double-click the link rectangle.
- 3 In the Actions tab of the Link Properties dialog box, select the listed action you want to change, and click Edit.

(see <https://helpx.adobe.com/acrobat/using/links-attachments-pdfs.html>)

Example:

Efficacy.xpt linked to local computer

XX (xxxxxxxxxx)

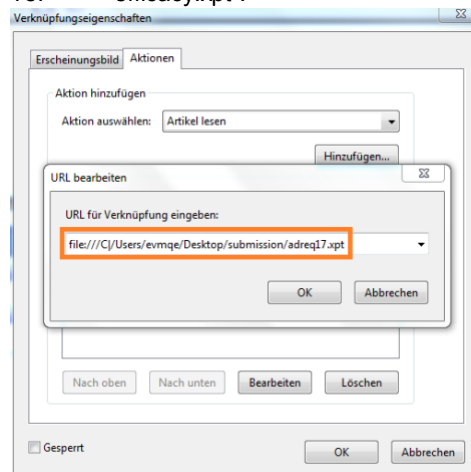
Structure	Purpose	Keys	Location	Documentation
One record per subject	Analysis	USUBJID	adreq17.xpt	

file:///C:/Users/evmqe/Desktop/submission/adreq17.xpt

The "hardcoded path" must be changed to relative path, so change the path

From: "file:///C:/Users/evmqe/Desktop/todo/Efficacy.xpt"

To: "efficacy.xpt".



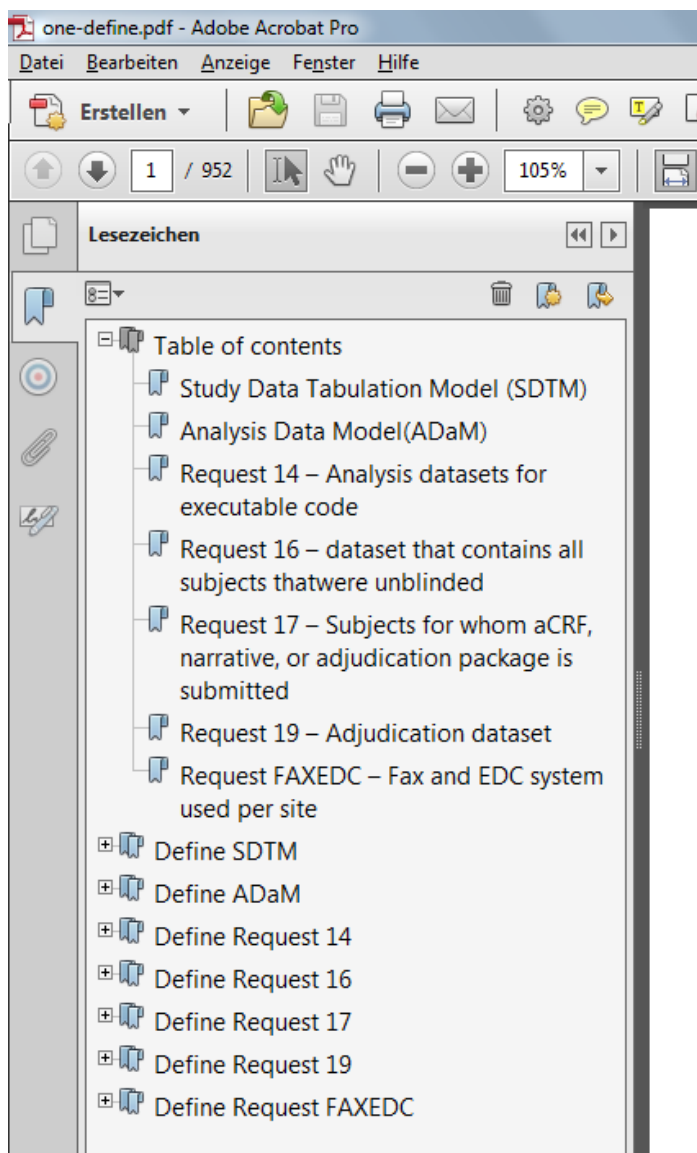
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Merging Single DEFINE.PDF's into Master DEFINE.pdf

The single Define.PDF files we have created so far, now only need to be converted into one "Master" Define.PDF. For this step we have been using Adobe Acrobat. (see: <https://helpx.adobe.com/acrobat/using/merging-files-single-pdf.html>)

The existing bookmarks and links of the single Define.PDF files will be automatically merged into the "master" Define.PDF.

The final layout of "master" Define.PDF is displayed in the following screenshot. It includes the desired features, i.e. relative links, bookmarks and is text searchable:



CONCLUSION

The agency has requested ONE text searchable, master define pdf file that includes ALL of the datasets. Generating define.pdf directly using metadata should be basically not difficult, but in some cases (besides the time critical requests), we might get the define.xml created by external vendors, so we don't have exact the same "configuration" to generate the define.pdf.

As the reviewer indicated that it will not be acceptable to submit a pure "print" of the define.xml's, so the easiest way to converting define.xml to define.pdf is doing the modification of XSL Stylesheet and converting using adobe acrobat.

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CONTACT INFORMATION (HEADER 1)

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