SDTM-ETL 3.1 User Manual and Tutorial

Author: Jozef Aerts, XML4Pharma

Last update: 2015-09-13

Creating and editing Trial Design datasets

When starting from an ODM file with metadata including SDM-XML (Study Design Model in XML), it is pretty straightforward to generate trial design datasets from the SDM-XML using the SDTM-ETL software (see separate manual).

However, not everyone is using SDM-XML yet, and most EDC systems do even not export SDM-XML. So, how can one generate the trial design datasets when the information is not, or only limited, in the ODM file with the study metadata?

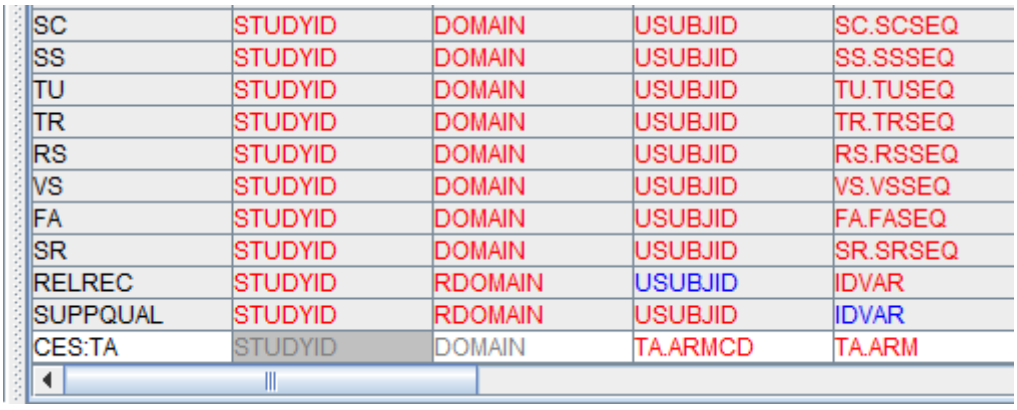
We have recognized this problem, and added a new module to the SDTM-ETL software: a "trial design dataset editor". This editor does not only allow to generate trial design datasets from scratch, but also allows to edit existing trial design in Dataset-XML format[1].

The editor can also be run in standalone method (so without using the SDTM-ETL software). This is explained later in this document.

In this tutorial, we will demonstrate the use of the "trial design dataset editor" using the TA (Trial Arms) as an example.

Starting the editor from within SDTM-ETL

After having loaded an SDTM template or existing define.xml with SDTM-ETL mappings, create a study-specific instance of the desired domain, in this case the TA domain. Do so by dragging the "TA" row from the template rows to the bottom of the table. This e.g. results in:



SC	STUDYID	DOMAIN	USUBJID	SC.SCSEQ
SS	STUDYID	DOMAIN	USUBJID	SS.SSSEQ
TU	STUDYID	DOMAIN	USUBJID	TU.TUSEQ
TR	STUDYID	DOMAIN	USUBJID	TR.TRSEQ
RS	STUDYID	DOMAIN	USUBJID	RS.RSSEQ
VS	STUDYID	DOMAIN	USUBJID	VS.VSSEQ
FA	STUDYID	DOMAIN	USUBJID	FA.FASEQ
SR	STUDYID	DOMAIN	USUBJID	SR.SRSEQ
RELREC	STUDYID	RDOMAIN	USUBJID	IDVAR
SUPPQUAL	STUDYID	RDOMAIN	USUBJID	IDVAR
CES:TA	STUDYID	DOMAIN	TA.ARMCD	TA.ARM

This ensures that the metadata for your TA dataset will be included in the define.xml file. You will also be able to use the trial design dataset editor without having dragged-and-dropped the TA row

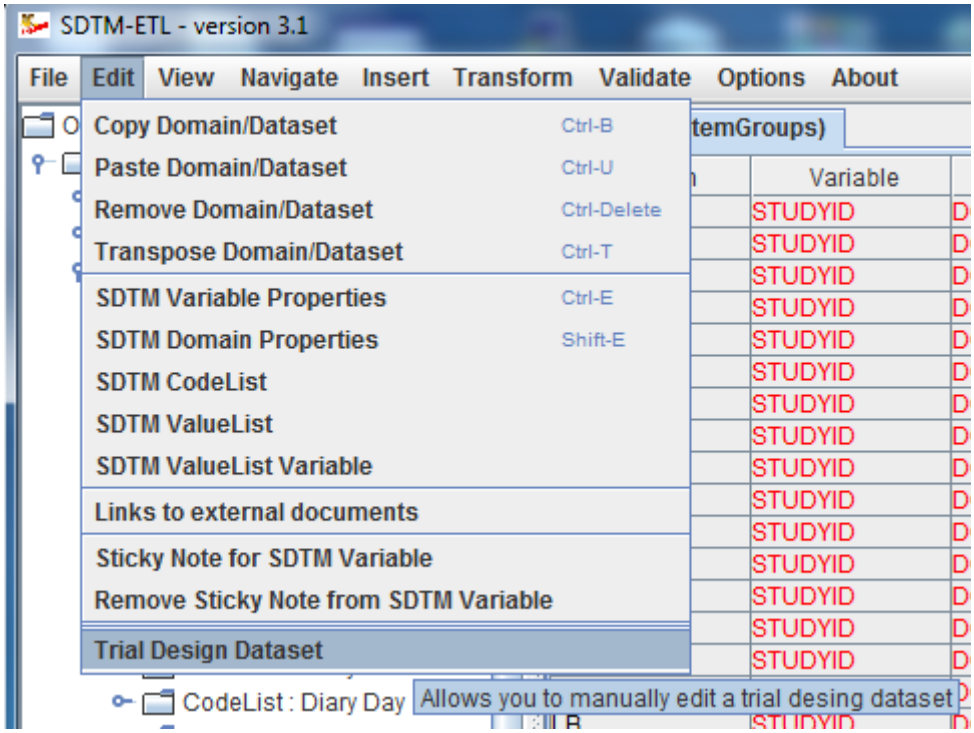
1 At this moment, using SAS Transport 5 format is not foreseen. One can however transform Dataset-XML files into SAS Transport 5 files using other tools. See http://wiki.cdisc.org/display/PUB/CDISC+Dataset-XML+Resources for a list of such tools.

(or one of the other "trial design" rows), but in that case, the metadata for that trial design dataset will not be in the define.xml. If you want to edit an existing trial design dataset, there is no need to drag-and-drop the TA row to the bottom and to create a study-specific instance (you might already have it).

It is important to realize that the generation of the trial design dataset is always driven by the metadata of a define.xml, be it the currently loaded define.xml (either using the TA template row, or using the study-specific instance), or an external define.xml file. So it is important that you have a good set of metadata for your trial design dataset, such as having set appropriate maximal lengths, and having assigned codelists for specific variables.

If you have created a study-specific instance of your trial design domain (such as CES:TA in our example), you might first want to work on the metadata for its variables, setting maximal lengths, adapt data types when necessary, and especially assign codelists (e.g. for the EPOCH variable). Changing metadata for SDTM/SEND variables is explained in the other manuals.

In order to start generating a new trial design dataset or editing an existing one, now use the menu "Edit - Trial Design Dataset":



This will start up a separate window, which is the starting window for this module.

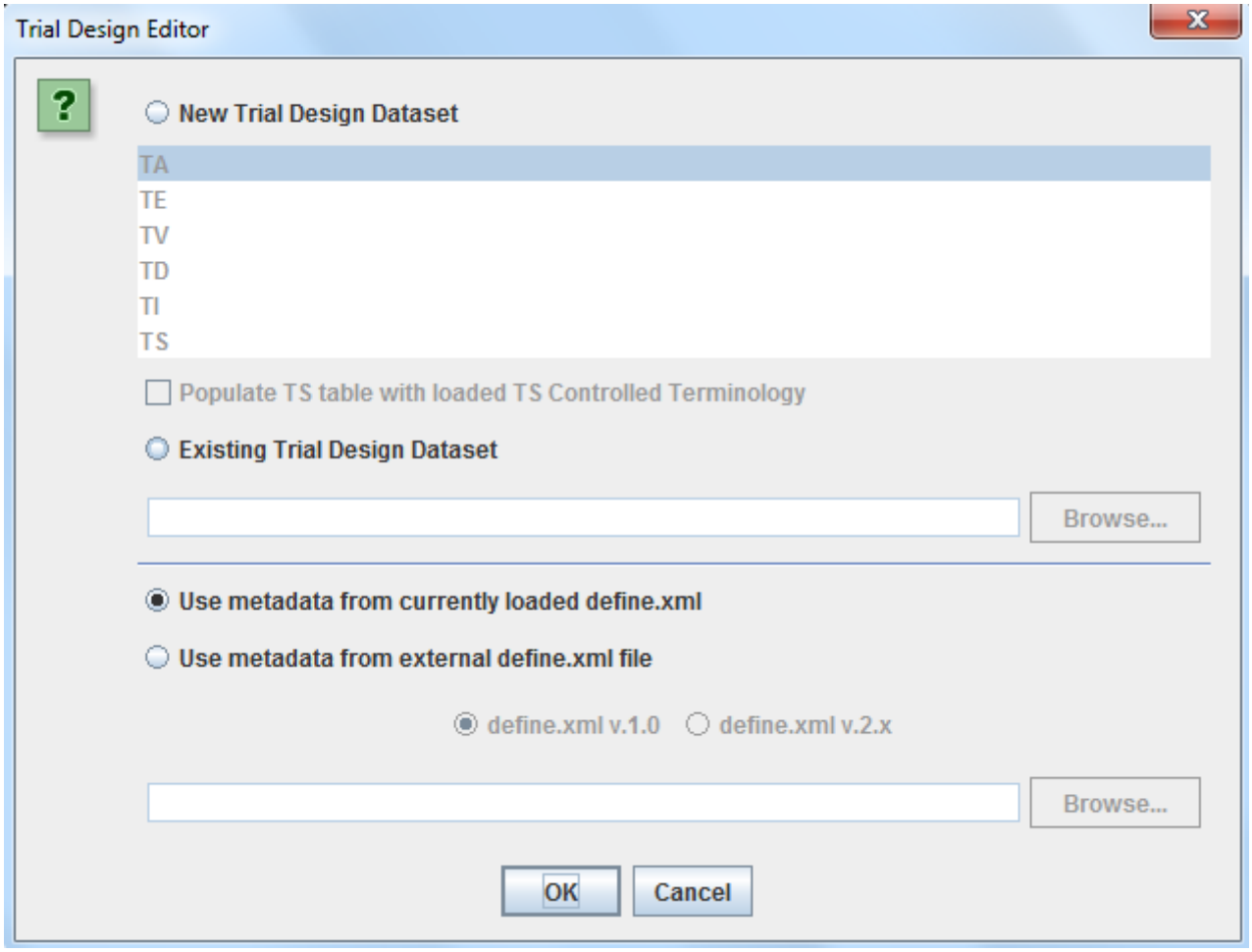
Starting the editor in standalone mode

There will be cases when you want to generate or edit a trial design dataset without starting SDTM-ETL. You can do so by double-click the icon for the file "TrialDesignEditor.bat". The start window will then appear.

Working with the trial design dataset editor

When the software has been started, either from within SDTM-ETL, or in standalone mode, the

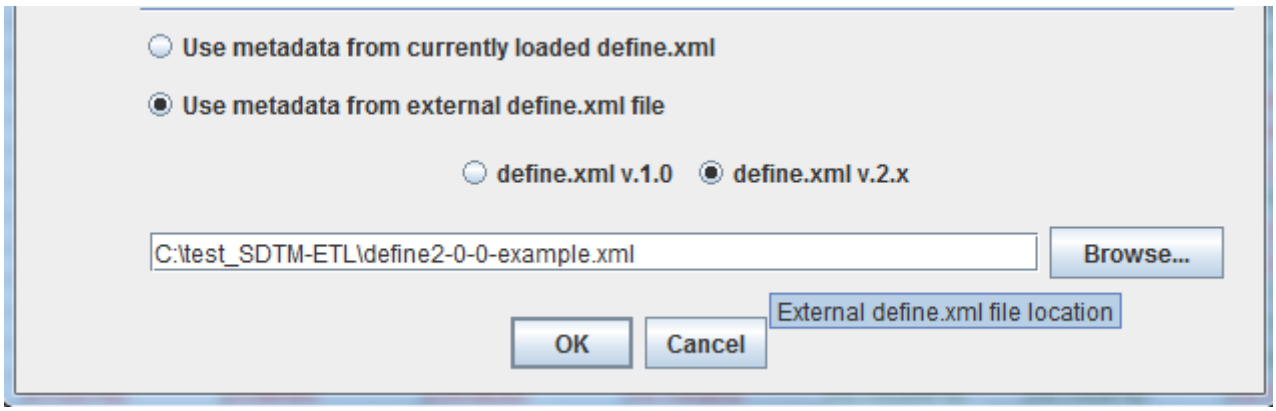
following start window is displayed:



In case the software was started from within SDTM-ETL, the radiobutton "Use metadata from currently loaded define.xml" is preselected. This means that the define.xml from the SDTM-ETL will be used (in its current state). One can however then also choose to choose another define.xml file containing the metadata for the trial design dataset(s).
In case the software was started in standalone, the radiobutton "Use metadata from external define.xml file" is preselected, and the radiobutton "Use metadata from currently loaded define.xml" is disabled. So in the latter case, it is always necessary to provide a define.xml file containing the trial design metadata.

In this tutorial we will continue with the option "Use metadata from external define.xml file".

First select the correct version of define.xml that you are working with. This is important as otherwise the file will not be parsed. In our case, we use a define.xml v.2.0 file. Select it using the "Browse" button on the right lower corner of the window. For example:

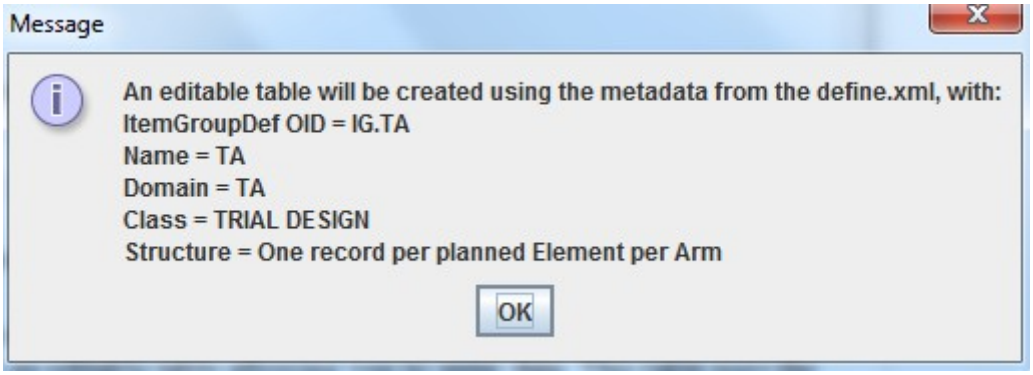


Now you need to decide whether you want to create a new trial design dataset (from scratch) or that you want to work on an already existing trial design dataset in Dataset-XML format.
We will first work with the case that one wants to start a completely new trial design dataset.
In order to do so, select the radiobutton "New Trial Design Dataset" and select a trial design domain from the list. For example:

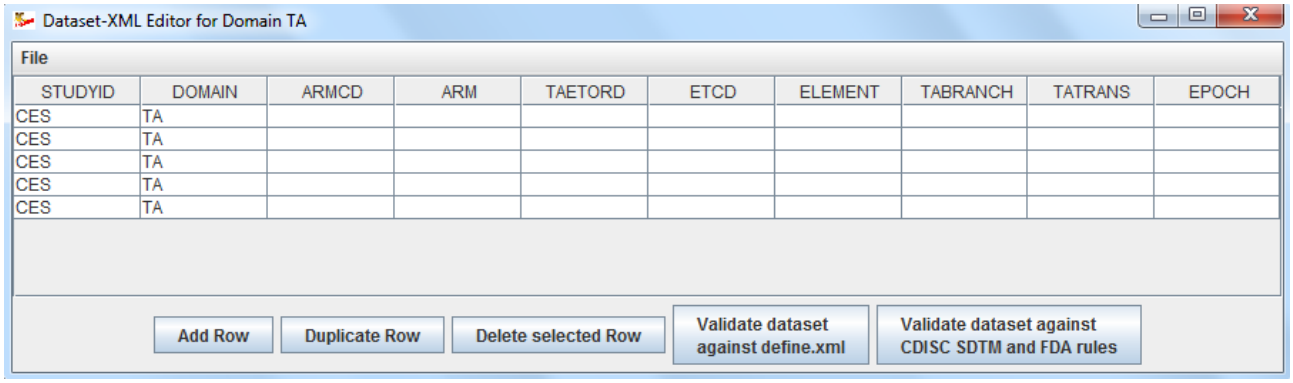
The tooltip on the selection shows the full name of the dataset.

The use of the checkbox "Populate TS table …" will be explained later. It is disabled for TA.
Now that a trial design domain and a define.xml containing the metadata has been selected, use the "OK" button to start generating an editable table allowing you to enter data. This table uses the metadata from the define.xml.

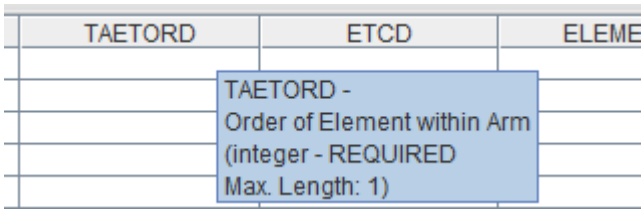
First a dialog is shown containing the most important information:



Click "OK" to continue. The editable table is displayed:



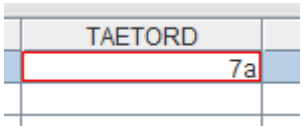
Hovering the mouse over a column header displays some of the most important metadata:



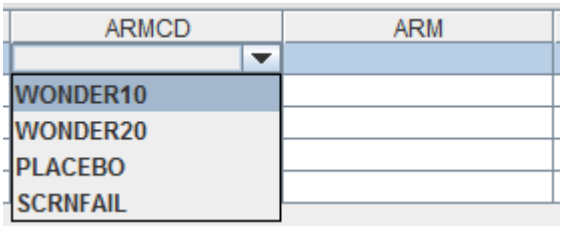
(in case you see things that you don't like, not a bad idea to quit and correct your define.xml …)

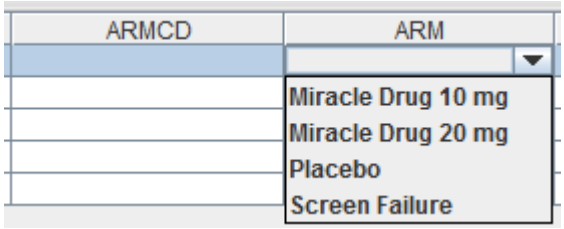
Near the bottom, some buttons are provided to add or delete rows, duplicate a row, start a simple validation against the define.xml, and start validation against CDISC SDTM and FDA SDTM validation rules:

The table editor is pretty "idiot proof". For example, if you try to enter text in a cell for which the datatype is "integer", the cell will be marked by a red border, and you will not be able to move to another cell before the error is corrected:



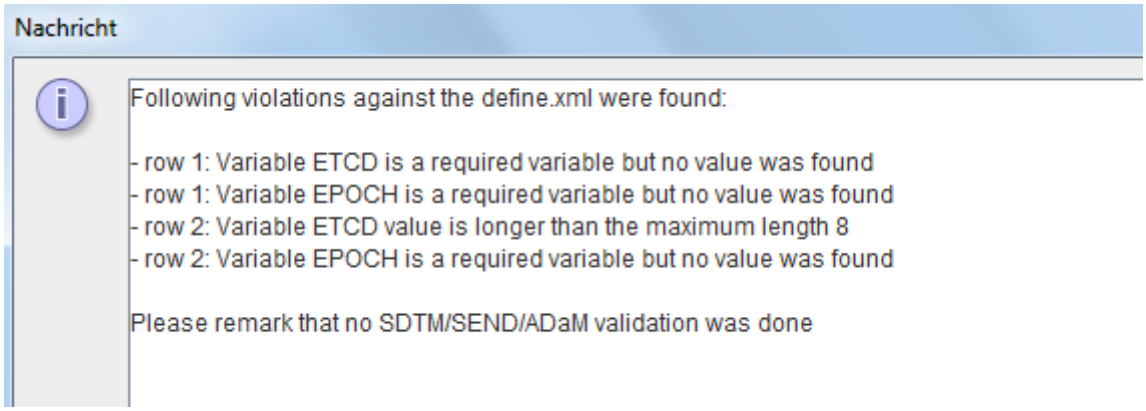
In case a codelist is given for a specific variable, you cannot enter any text, but you need to select a value from the combobox that is shown when trying to edit the cell. For example:





It is also always adviced to validate the table against the define.xml, using the button "Validate Dataset". A list is then show with information about violations in the table against the metadata in

the define.xml. For example:

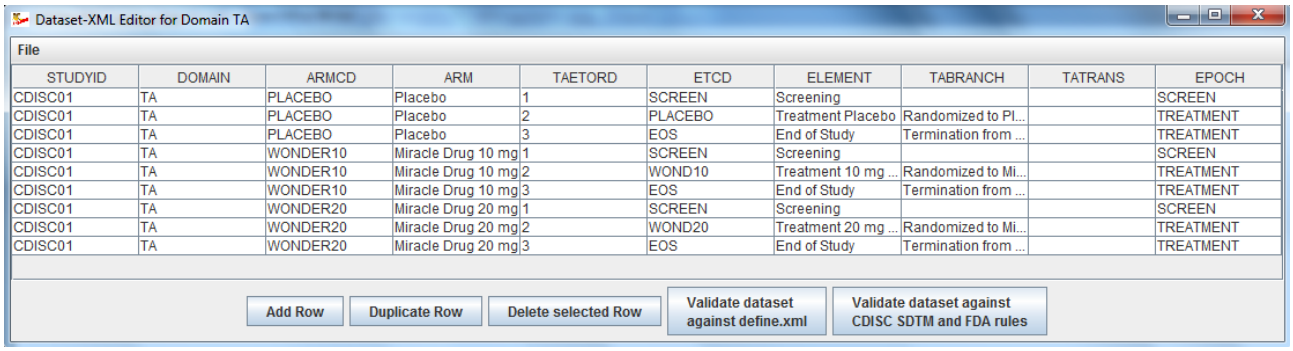


Also the cells that violate the definitions in the define.xml will then be colored red.

It is important to note that this is **NOT** an SDTM validation[2], only a validation against the define.xml. The SDTM validation will be explained later in the section "SDTM Validation".

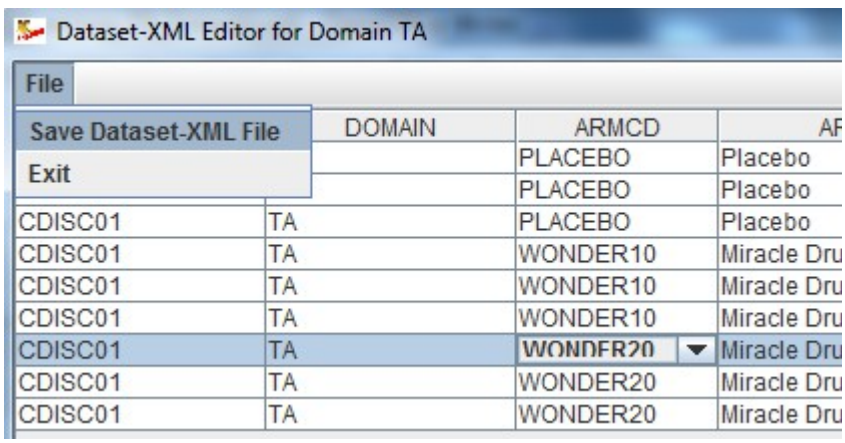
To add a new row, use the button "Add Row", to delete a selected row, use the button "Delete Row". One can also use the button "Duplicate Row", which can speed up filling up - but be aware that it is your own responsibility to ensure that each row is unique as described by the domain rules.

The following figure shows a picture of a complete table for TA (trial arms) that is compliant towards its define.xml:



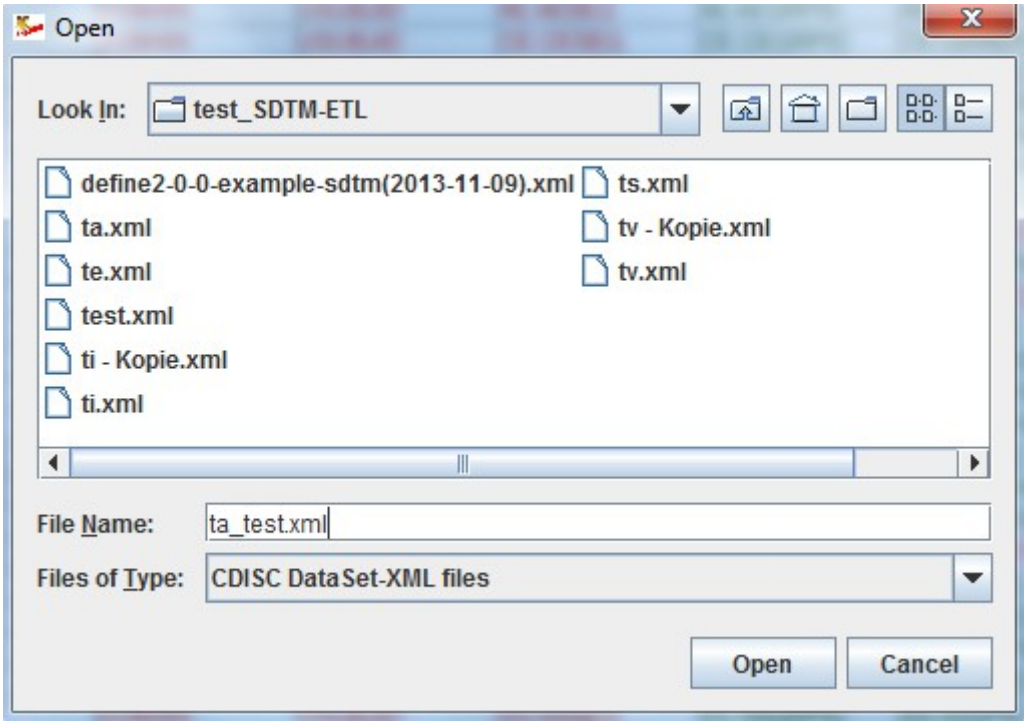
STUDYID	DOMAIN	ARMCD	ARM	TAETORD	ETCD	ELEMENT	TABRANCH	TATRANS	EPOCH
CDISC01	TA	PLACEBO	Placebo	1	SCREEN	Screening			SCREEN
CDISC01	TA	PLACEBO	Placebo	2	PLACEBO	Treatment Placebo	Randomized to Pl...		TREATMENT
CDISC01	TA	PLACEBO	Placebo	3	EOS	End of Study	Termination from ...		TREATMENT
CDISC01	TA	WONDER10	Miracle Drug 10 mg	1	SCREEN	Screening			SCREEN
CDISC01	TA	WONDER10	Miracle Drug 10 mg	2	WOND10	Treatment 10 mg ...	Randomized to Mi...		TREATMENT
CDISC01	TA	WONDER10	Miracle Drug 10 mg	3	EOS	End of Study	Termination from ...		TREATMENT
CDISC01	TA	WONDER20	Miracle Drug 20 mg	1	SCREEN	Screening			SCREEN
CDISC01	TA	WONDER20	Miracle Drug 20 mg	2	WOND20	Treatment 20 mg ...	Randomized to Mi...		TREATMENT
CDISC01	TA	WONDER20	Miracle Drug 20 mg	3	EOS	End of Study	Termination from ...		TREATMENT

Finally, you can save the table to file in Dataset-XML format, using the menu "File - Save Dataset-XML File":



2 Use other tools for SDTM validation, such as OpenCDISC.

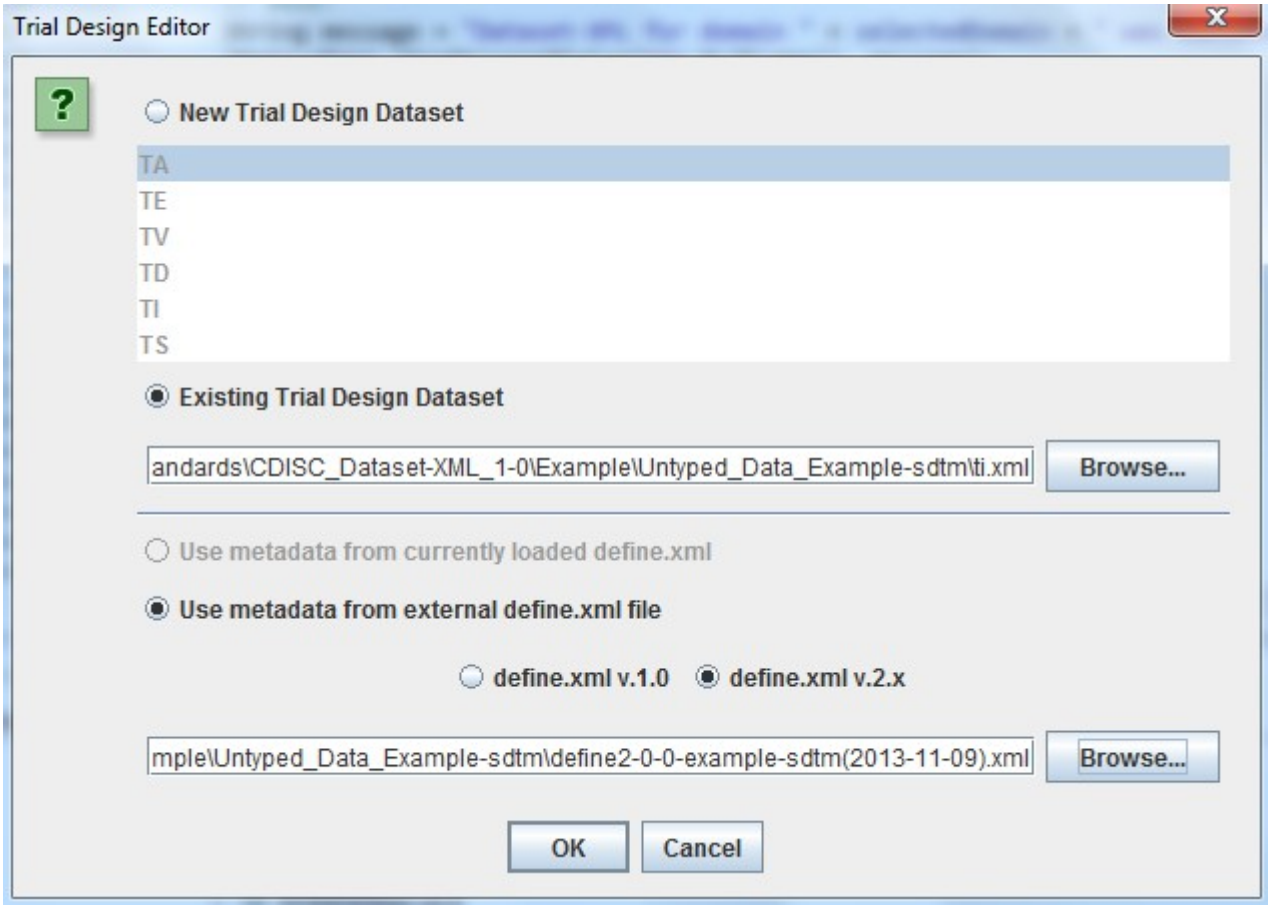
You will be prompted to provide a location to store the file. For example:



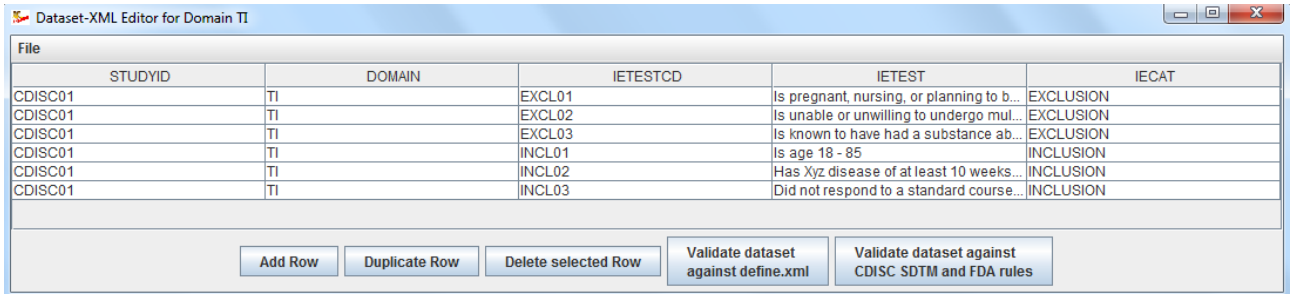
If the file already exists, the system than will ask for a confirmation to overwrite the file.

Editing an already existing trial design Dataset-XML file

To work on an existing trial design dataset in Dataset-XML format, use the radiobutton "Existing Trial Design Dataset", then use the "Browse" button to select a dataset.
Ensure that you also load a proper define.xml file. For example:



Clicking "OK" then loads the ti.xml file and the define.xml file containing the metadata for the TI dataset:

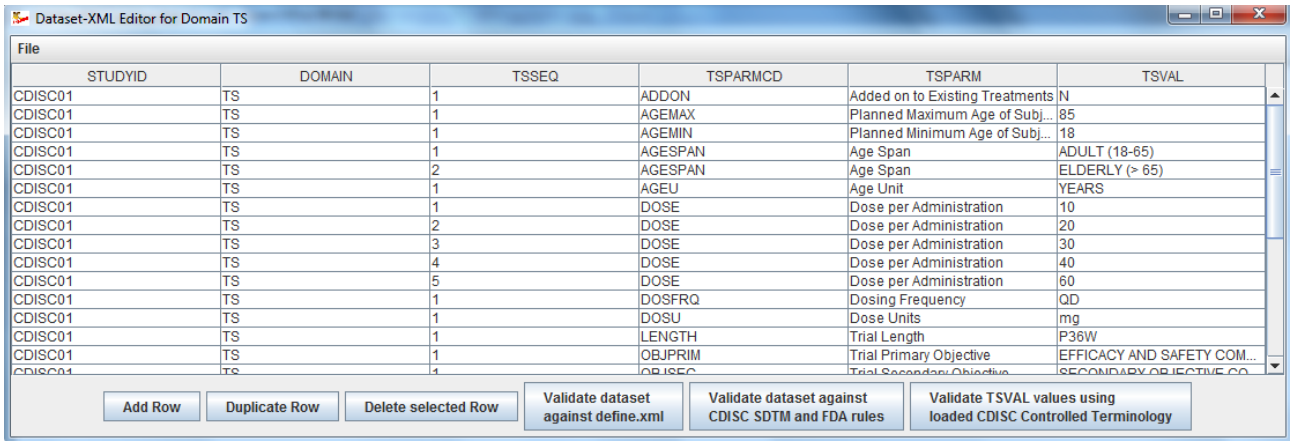


One can then start editing the information, add or remove rows, and validate the dataset against the define.xml that was selected or against the CDISC or FDA SDTM rules . Do not forget to use the menu "File - Save Dataset-XML File" to save the results to disc.

To exit, use the menu "File - Exit".

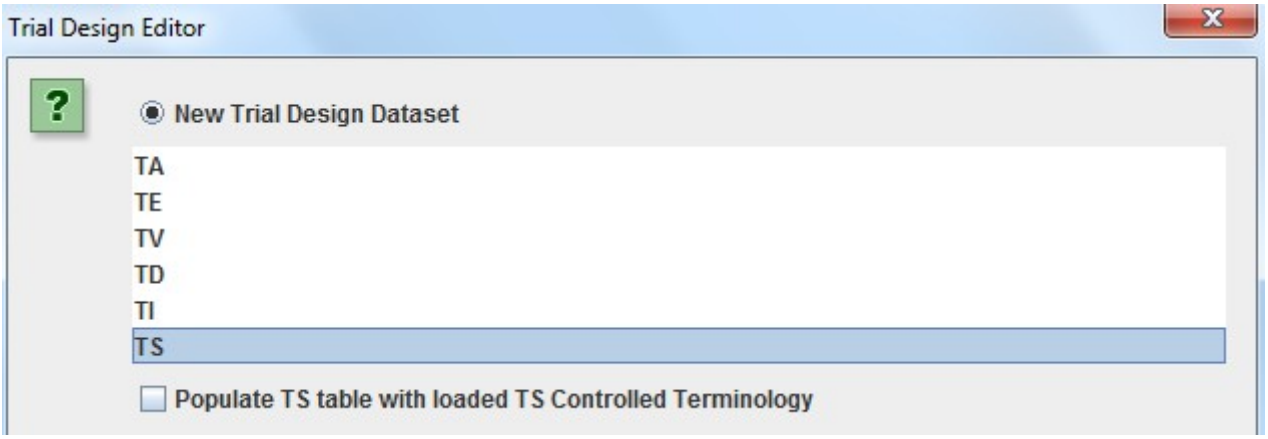
Working with the TS (Trial Summary) Dataset

The "Trial Summary" (TS) dataset is somewhat special as it essentially is a "Entity - Attribute - Value" table[3]. An example is shown below:



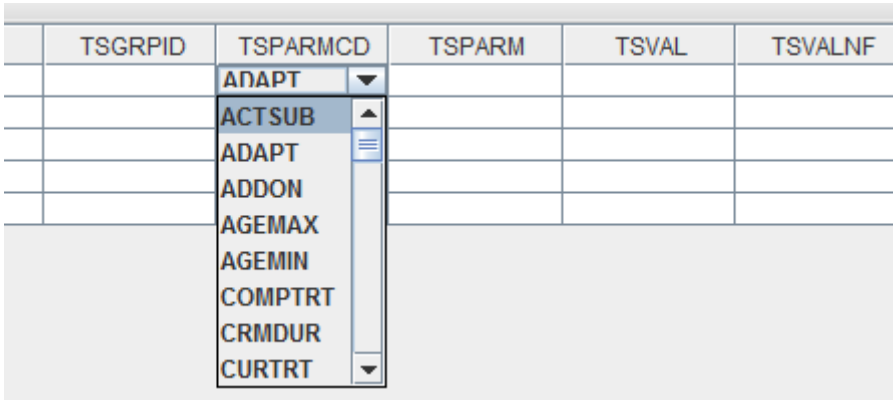
The "entity" is TSPARMCD ("trial summary parameter code") defining "what it is about". The "value" is TSVAL ("trial summary value"). All other columns contain "attributes".
TSPARMCD is coded, i.e. a list of allowed values for TSPARMC has been published by CDISC. The same applies to TSPARM ("trial summary parameter name"). Furthermore, some of the TSVAL values are coded, depending on the value for TSPARMCD. Also the expected data types can be different
For example, when TSPARMCD is AGEMAX, then a non-negative integer is expected. However, for TSPARMCD=TBLIND ("Blinding Type"), the only allowed values are: "SINGLE BLIND", "DOUBLE BLIND" and "OPEN LABEL".

Let us start a new TS dataset. To do so, use the menu "Edit - Trial Design Dataset" and select "New Trial Design Dataset", and then select "TS".



If the checkbox "Populate TS table with loaded TS Controlled Terminology" is not checked, an empty table will be generated, to which you will need to add TSPARMCD and TSPARM values yourself. As these are coded, this can easily be done using the dropdown. For example:

3 See e.g.: http://ycmi.med.yale.edu/nadkarni/Introduction%20to%20EAV%20systems.htm

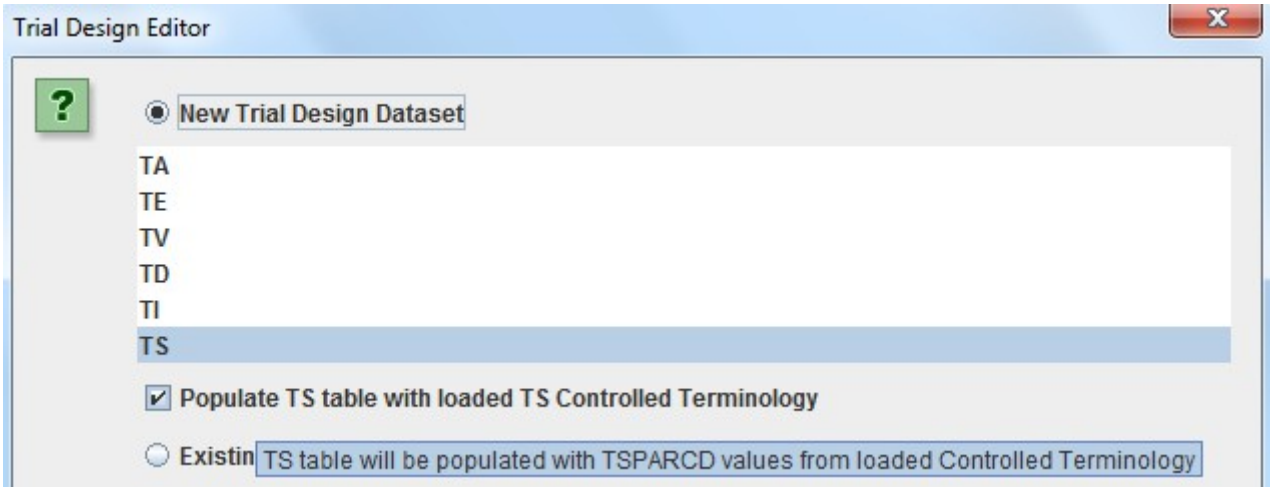


The same applies for TSPARM.

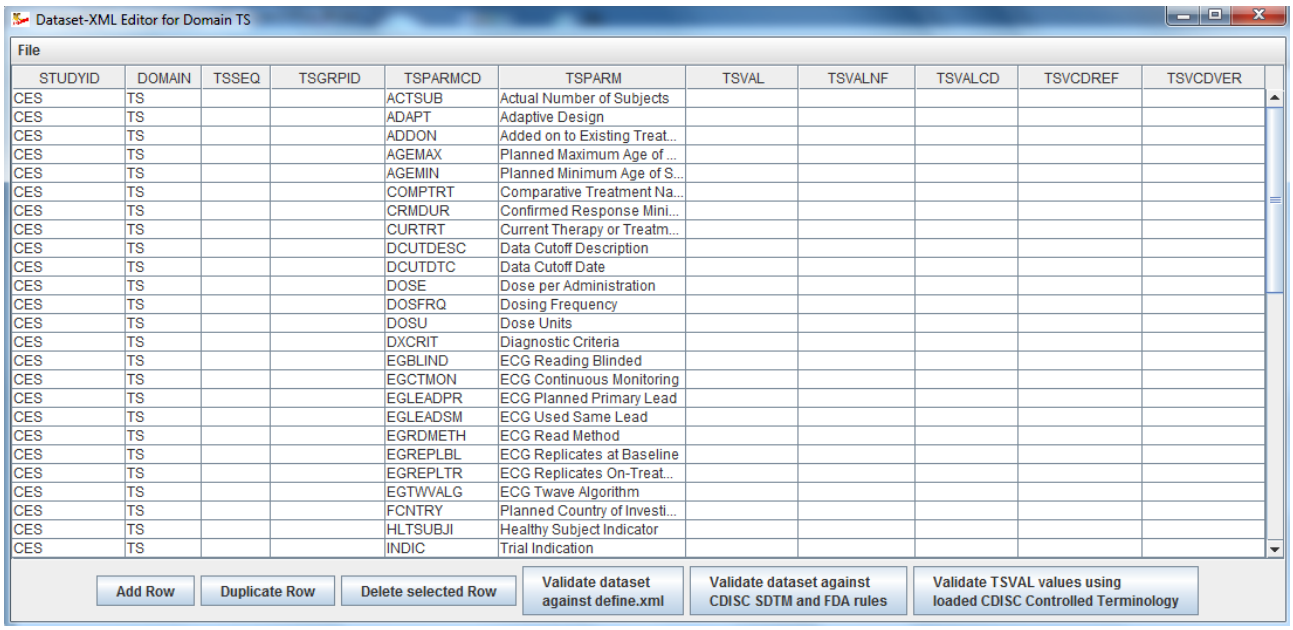
This is a suitable way to produce a TS table and dataset where the number of parameters is relative low.

The second strategy is to load all possible values for TSPARMCD, and generate a row for each of them, and then remove the ones that are not needed. This is usually the best strategy when you want to be sure that all by the FDA required "trial design parameters" are provided.

In order to do so, ensure that the checkbox "" is selected when starting to generate the TS table:



This will then result in the following table:



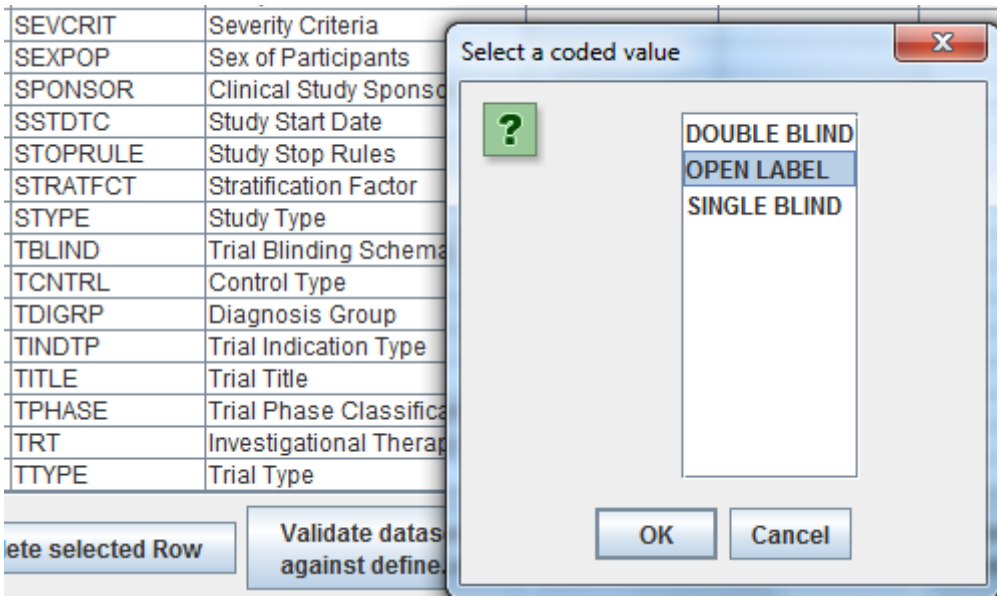
Also notice the extra button that has appeared at the bottom at the right stating "Validate TSVAL values using loaded CDISC controlled terminology". Its function will be explained further on.

One can now start adding information using the buttons "Add Row" and "Duplicate Row" (the latter for trial design parameters for which there is more than one value - e.g. "FCNTRY" ("country of planned investigation").

Some of the TSVAL values are coded. To find out, right-click the TSVAL cell. If the TSVAL for the TSPARMCD value is not coded, a message will displayed:

as no controlled terminology for "FCNTRY" has been defined by CDISC.

If however TSVAL is coded, for example for TBLIND ("Trial Blinding Scheme), the following dialog is popping up:

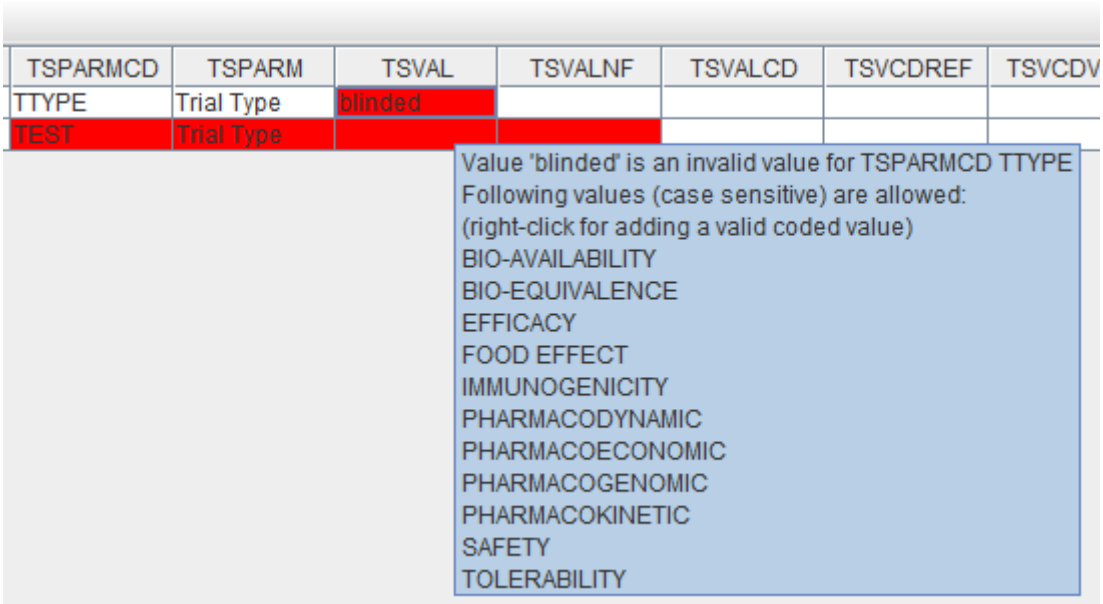


You can then select one of the values, and when clicking "OK", the value will be added to the TSVAL cell. Even then, you can still edit that cell and put another value (discouraged).

STYPE	Study Type	
TBLIND	Trial Blinding Schema	OPEN LABEL
TCNTRL	Control Type	

Please note that there are many "hidden" rules for TS for which no machine-executable rules have been defined yet, so looking into the SDTM-IG when filling the TS table is not a bad idea.

It is also always a good idea to do use the button "Validate TSVAL values using loaded CDISC controlled terminology". This will validate all TSVAL values against the codelists provided by CDISC. It also validates whether the value for TSPARMCD and TSPARM match. For example:



and:

TSPARMCD	TSPARM	TSVAL	TSVALNF	TSVALCD
TTYPE	Trial Type	blinded		
TEST	Trial Type			

Mismatch between TSPARMCD and TSPARM

or:

TSVAL	TSVALNF	TSVALCD	TSVCDR
blinded			

Either one of TSVAL or TSVALNF must be populated

Also here, do not forget to do a validation against the define.xml to check for completeness.

SDTM Validation

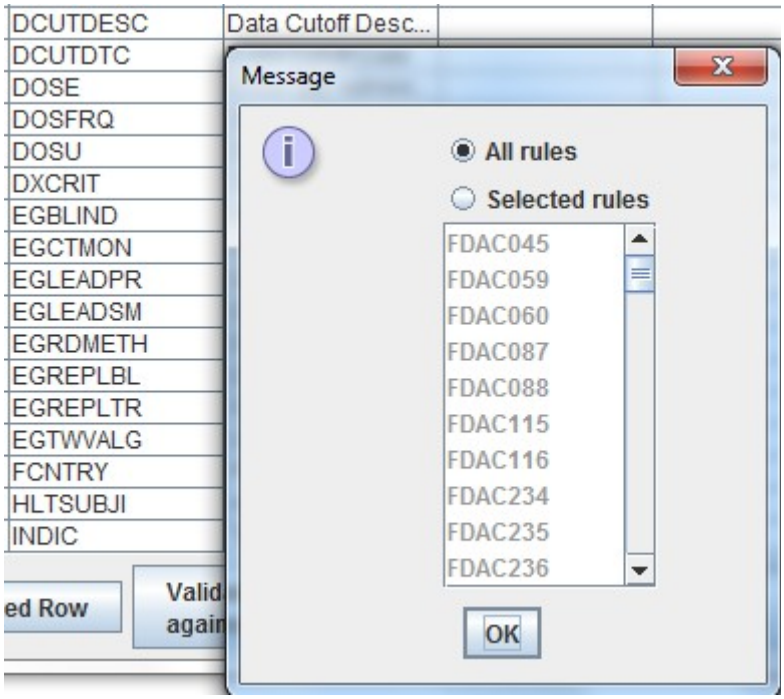
We have already seen the function "Validate dataset against define.xml", which does a simple validation on data types and whether a variable is a required variable or not.

However, trial design datasets have more complex rules that cannot be represented by define.xml alone. Even a simple rule that either TSVAL or TSVALNF must be populated cannot be expressed by define.xml.

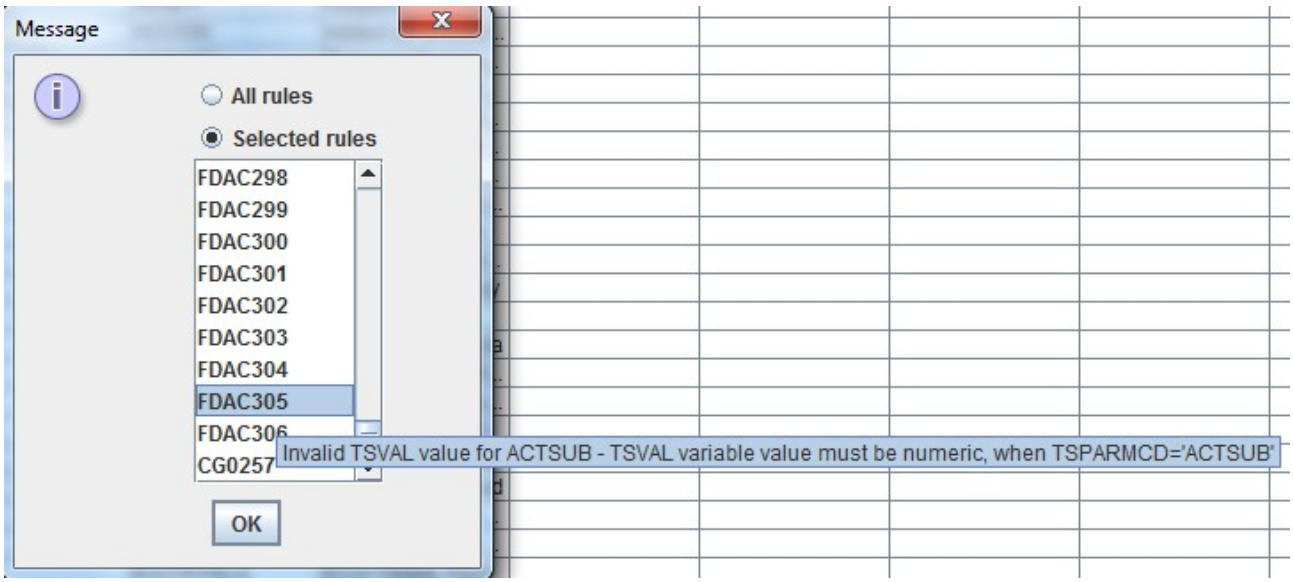
Recently, and in cooperation with CDISC, we started developing the FDA SDTM validation rules as open, human readable, machine-executable rules. They can be found at:
http://xml4pharmaserver.com/WebServices/XQueryRules_webservices.html.
These rules are later envisaged to become a part of CDISC eSHARE.

The set of rules is permanently be extended in cooperation with the "CDISC SDTM Validation Subteam".

The software allows to use these rules for validation of the TS datasets. When the button "Validate dataset against CDISC SDTM and FDA rules" is clicked, the software looks up all the rules for the specific domain and presents these for selection to the user. For example for TS (Trial Summary):



One can either decide to run all rules applicable to TS, or to do a selection. Each rule has a tooltip on it, so that the rule is explained when one hovers the mouse over the rule identifier. For example:



When the OK button is then clicked, the validation engine starts, and each of the rules is executed subsequently on the dataset. After a few seconds, a report in then displayed. For example:

Validation Messages for DomainTS

Validation messages for XQuery validation for domain TS

Date and time: 2015-09-13T14:11:30

Rule	Severity	Record number	Message
FDAC237	error		Invalid (non-ISO8601) TSVAL value=85 for AGEMAX in dataset=temp_TS.xml
FDAC234	error		Invalid (non-ISO8601) TSVAL value=18 for AGEMIN in dataset=temp_TS.xml
FDAC243	error		Invalid (non-ISO8601) TSVAL value=P36W for LENGTH in dataset=temp_TS.xml
FDAC252	error		Missing STOPRULE Trial Summary Parameter in dataset temp_TS.xml
FDAC255	error		Missing TDIGRP Trial Summary Parameter in dataset temp_TS.xml
FDAC260	error		Missing CURTRT Trial Summary Parameter in dataset temp_TS.xml
FDAC276	error		Missing REGID Trial Summary Parameter
FDAC277	error	27	Invalid TSVAL value for TRT in dataset temp_TS.xml: TSVAL for TRT record must be a valid preferred term from FDA Substance Registration System (SRS): value 'TEST PRODUCT XXX' is not a valid preferred term identifier from SRS
FDAC280	error	27	Invalid TSVCDREF value for TRT: TSVCDREF variable value must be 'UNII', when TSPARMCD='TRT', value found is ''

Please note that some of these rules use a RESTful webservice provided by the US "National Library of Medicine". So to be able to use these, your computer will need an internet connection. If no internet connection is available, the engine will simply skip the rule.

A great advantage of this new mechanism for performing SDTM validation is that the rules are "really open": anyone can inspect them. This is different from other validation tools, where the rules are hidden in the software (so intransparent), so that one cannot inspect how they have been implemented.
Furthermore, it allows organizations to develop company-internal validation rules. These can then simply be added to the software by copying them into one of the XML files of the directory "Validation_Rules_XQuery"[4].

Rules for other domains than the trial design datasets have already been developed, but they have not been implemented in the SDTM-ETL software. This will be started in the near future.

4 There is no additional license necessary to add company-specific rules to the software.