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A Practical Approach to Automating SDTM Using a Metadata-Driven Method That Leverages CRF Specifications and SDTM Standards

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ABSTRACT

Automated SDTM generation has several benefits, including efficiency, accuracy, compliance with regulatory requirements, and the speeding up of the data analysis process. However, due to the dissimilarity and varying complexity of different CRFs, SDTM domains, and eSource systems among different studies, development of a tool to automate SDTM has been a challenging task for sponsors, CROs, and EDC service providers.

We propose a new approach in automatic generation of SAS® code for SDTM. A SAS-based macro is developed based on CRF specifications from an EDC database and SDTM standards. Our approach is user-friendly with high transparency, easily scalable to multiple studies, and especially useful for relatively smaller sponsors and CROs, for there is no requirement to standardize CRFs and raw dataset variables' attributes (which is the best practice but can be too work-intensive) and no required expertise in other computer languages.

INTRODUCTION

SDTM automation streamlines the process of transforming raw clinical trial data into the standardized SDTM format. This process involves CRF annotations, SDTM specification writing, development of SAS code to generate SDTM data, validation, SDRG writing, and define.xml generation. SDRG and define.xml support regulatory submissions along with annotated CRFs and SDTM datasets in v5 Transport Format (XPORT) [1]. Automation offers several benefits, including efficiency, accuracy, compliance with regulatory requirements, and the speeding up of the data analysis process. However, it is not an easy task to achieve due to the complexity of different CRFs and eSource systems.

Sponsors, CROs, and EDC service providers can have many different approaches to automating SDTM, and the degree of automation can differ based on the initial data conditions and complexity. [2] details how Eli Lilly has been pursuing SDTM automation. It uses a car analogy to describe the concept: four wheels and an engine to drive. It states "*the four wheels are: a robust set of standards, a metadata repository to store and maintain those standards, a set of generic macros for data set creation, and a programming process to utilize those macros. The engine is metadata. By defining a metadata model that not only defines the source and target but also the logic to convert the source to the target, we can build out the rest of the components to make this vision a reality. A proof-of-concept project based on this idea achieved 96% automation of SDTM variables in a test study*" [2].

Automation is a hybrid process comprising of applications or tools plus manual parts involving CRF annotations and SDTM specification writing. Standardization of raw data collection can dramatically reduce the time spent on these manual parts. However, the resources needed for standardization are not always feasible for smaller sponsors or CROs.

This paper introduces a new approach in the automatic generation of SAS code for SDTM automation that strikes a balance between high-level automation and resource investment. A SAS-based macro named ***%SDTM_Code_Generator*** was developed based on CRF specifications from an EDC database and SDTM programming standards [3,4]. We provide details on the rationale and logic flow for this macro, its inputs and outputs, how to build a master-annotation spreadsheet to support SDTM automation, how to efficiently scale it up for new studies, how to handle external data, how to effectively validate its output datasets, and how to deal with EDC database changes.

Based on our working experience from applying this new approach to two different types of oncology studies, this paper is titled "**A Practical Approach to Automating SDTM**" for the following reasons:

1. High-quality delivery of SDTM datasets and operational efficiency through high-level automation

2. Flexibility for users to control the degree of automation and account for cost/timelines
3. Faster and solid validation due to not requiring double programming for all domains and a guarantee that all raw dataset variables are accounted for in SDTM programming
4. Scalability to multiple studies by leveraging existing CRF specifications, master-annotation spreadsheets, and macros
5. Transparency and user-friendliness as users can easily and directly review the inputs and outputs of the process so that they have very high confidence in the delivery of SDTM datasets
6. No requirement of huge efforts to standardize CRFs or raw dataset variable attributes
7. No requirement of expertise in other computer languages, such as Structured Query Language (SQL) for script creation

INTRODUCTION TO OUR SDTM PROGRAMMING PROCESS

In the past, we've written about our established SDTM programming process. [3] introduces our standard SDTM specification, which follows CDISC's standard. [4] presents a systematic approach to automating the SDTM programming process to ensure compliance with FDA Business Rules [5] and CDISC SDTMIG [6] for FDA submission. It details our SDTM programming standards consisting of the SDTM Programming Convention (SDTMPC) and the SDTM Programming Library (SDTMPL). The utilization of template SAS Programs for SDTM Mapping has been our standard practice, and they have been successfully applied to multiple clinical studies, including several FDA submissions and their approvals. Readers can refer to [4] for more information. The present goal is to replace our standard SDTM mapping templates with a macro for SDTM automation.

STANDARD SDTM PROGRAMMING WORKFLOW

Figure 1 below depicts the standard SDTM programming workflow. SDTM programmers start to develop SAS programs for the SDTM dataset generation ***only*** after CRF annotations and SDTM specifications are available. A SDTM programmer manually annotates each CRF either to set up the one-to-one mapping from each raw dataset variable specified in the CRF to its mapped SDTM domain variable or supplemental qualifier or to label it as "NOT SUBMITTED". The annotated case report form (aCRF) then guides the programmers to develop SAS programs for SDTM dataset generation. One also manually completes each SDTM domain specification to document and select the required SDTM variables and/or supplemental qualifiers in the final SDTM dataset.

The development of each SDTM mapping SAS program is both critical and integral to SDTM programming. However, it is time-consuming even with tools such as template SAS Programs for SDTM mapping or CRF annotation tools, which guide the programmers in annotating each CRF based on the applicable standards [7]. The amount of manual work required is high as well.

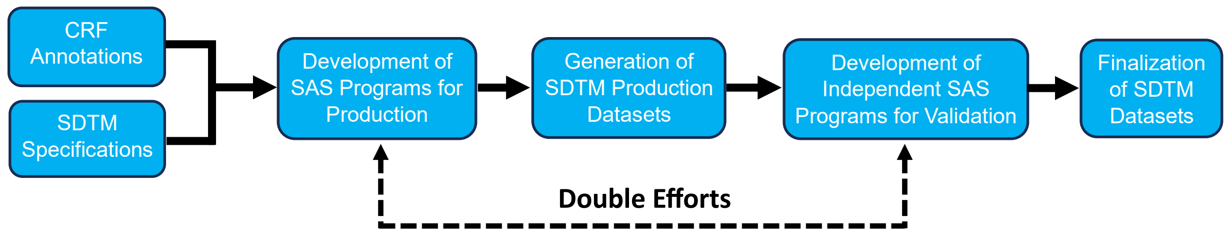

CRF Annotations
SDTM Specifications
Development of SAS Programs for Production
Generation of SDTM Production Datasets
Development of Independent SAS Programs for Validation
Finalization of SDTM Datasets
Double Efforts

Figure 1. Standard SDTM Programming Workflow

INTRODUCTION TO OUR NEW SDTM PROGRAMMING WORKFLOW

Figure 2 below shows our new SDTM programming workflow. In contrast to the standard workflow depicted in Figure 1, a master-annotation spreadsheet is created from CRF annotations and CRF specifications. The master-annotation spreadsheet contains metadata and variable attributes for the raw datasets combined with annotations mapping raw dataset variables to specific SDTM domain variables. SDTM specifications contain information on SDTM standards along with variable inclusion/exclusion and derivation. The master-annotation and SDTM specifications are the inputs of our new macro, ***%SDTM_Code_Generator***, which automatically generates SDTM mapping SAS programs. In contrast to the traditional double programming validation shown in Figure 1, our new programming validation process consists of the following three steps: code reviewing, real data testing, and developing an independent mapping SAS program to validate a SDTM dataset for some complicated domains as needed per the team's decision.

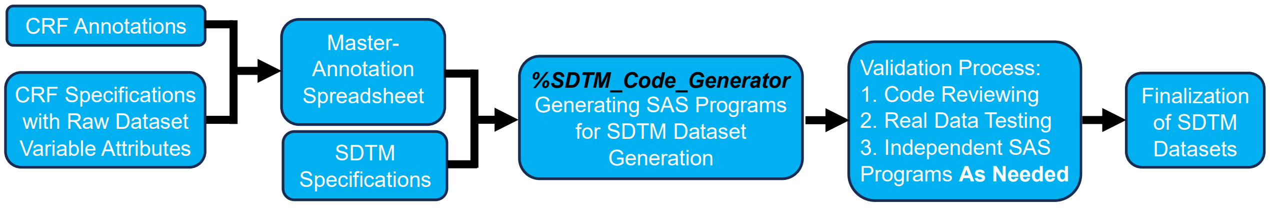

CRF Annotations
CRF Specifications with Raw Dataset Variable Attributes
Master-Annotation Spreadsheet
SDTM Specifications
%SDTM_Code_Generator Generating SAS Programs for SDTM Dataset Generation
Validation Process:
1. Code Reviewing
2. Real Data Testing
3. Independent SAS Programs As Needed
Finalization of SDTM Datasets

Figure 2. New SDTM Programming Workflow

RATIONALE FOR THE DEVELOPMENT OF A MACRO FOR SDTM AUTOMATION

Aside from trial design domains, there are typically over twenty SAS programs needed to read and map the data collected from CRFs for each study. From a quality assurance (QA) perspective, independently developed SAS programs for validation are designed to ensure the highest quality. However, that doubles the development work required. Some domains, such as LB or PR, may have hundreds of data blocks due to the numerous tests or procedures collected on CRF forms. The manual effort needed to ensure that all of these are correctly included in both production and validation programs is time-intensive and still prone to error.

Table 1 shows the advantages and benefits of a macro for SDTM automation over the SDTM mapping template SAS programs. A huge amount of work is needed to update template SAS programs for EDC database changes or new studies while a macro can automatically adapt to some of those changes and save development time.

Types of Changes	Specific Changes	SDTM Mapping Template SAS Programs	A Macro
eSource systems or EDC database changes	Raw dataset names, variable attributes, CRF annotations	Must make the corresponding updates/changes across over forty SAS programs from both production and validation by typing and/or copying, which is time-consuming and error-prone	No changes or minimal changes
New studies	New CRFs, domains, more changes, annotations, and specifications	Make the corresponding updates/changes to SAS programs	May need to update the macro correspondingly and update its input files if necessary

Table 1. Advantages of a Macro for SDTM Automation Over SDTM Mapping Template SAS Programs

INTRODUCTION TO THE MACRO'S SINGLE PARAMETER AND ITS OUTPUT FOR SDTM AUTOMATION

Table 2 below shows the macro's single parameter, its calls, and the outputs of the calls. Its single parameter is either a specific SDTM domain name or "ALL", and its call generates a SAS program for the specified domain or SAS programs for all domains, respectively. It requires that all CRF annotations (SDTM mapping), all raw dataset names, and their attributes (variable names, labels, and types) are stored in a single spreadsheet named as ***master-annotation***.xlsx. Further details for the master-annotation spreadsheet are included in a later section.

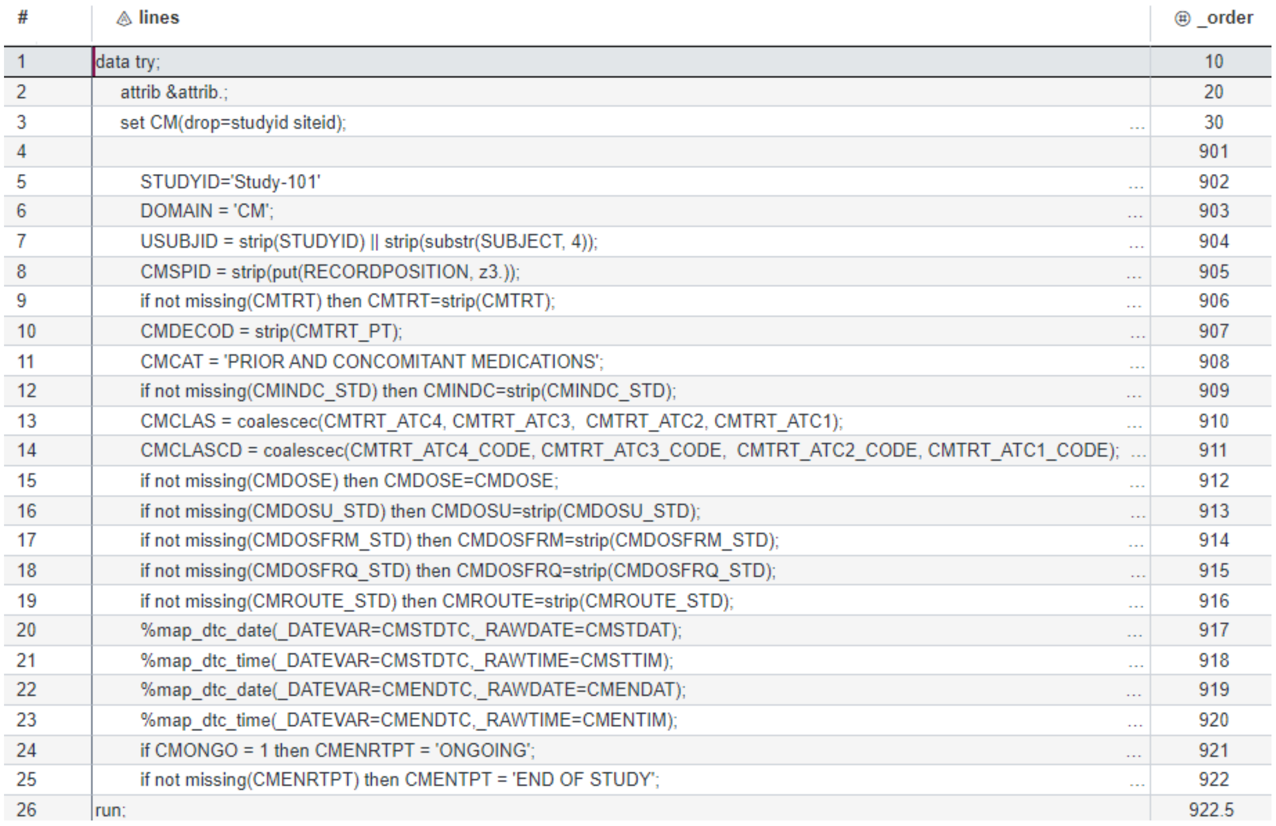
Of note, the subject visits (SV) domain is a special purpose domain that requires more complex derivations, many of which are different from ones of the original ***%SDTM_Code_Generator*** macro. To simplify the development of the macro and reduce the length of SAS code needed, we developed an additional macro named ***%SV_Code_Generator***, which leverages the output from the call of ***%SDTM_Code_Generator*** and extends it further. Please refer to [8] for more information.

Macro Call	Output of the Macro Call
%SDTM_Code_Generator(domain_=*Domain Name*) For example, % SDTM_Code_Generator(domain_=DM);	A SAS program with the domain name (e.g., DM.sas)
%SDTM_Code_Generator(domain_=ALL)	All SAS programs for the domains specified in master-annotation.xls

Table 2. *%SDTM_Code_Generator* Macro Calls and Outputs

HOW *%SDTM_CODE_GENERATOR* CREATES A SAS PROGRAM

Our macro generates SAS mapping code from its input files and writes that mapping code into a SAS dataset. Display 1 below is an example of that SAS dataset with 2 columns: ***lines*** and ***_order***. Using the code in Display 2 from ***%SDTM_Code_Generator***, we can output the contents of our final dataset into a SAS program file, CM.sas (Display 3). The lines of code contained in this output CM.sas file (Display 3) are identical to the contents of Display 1's ***lines*** column.

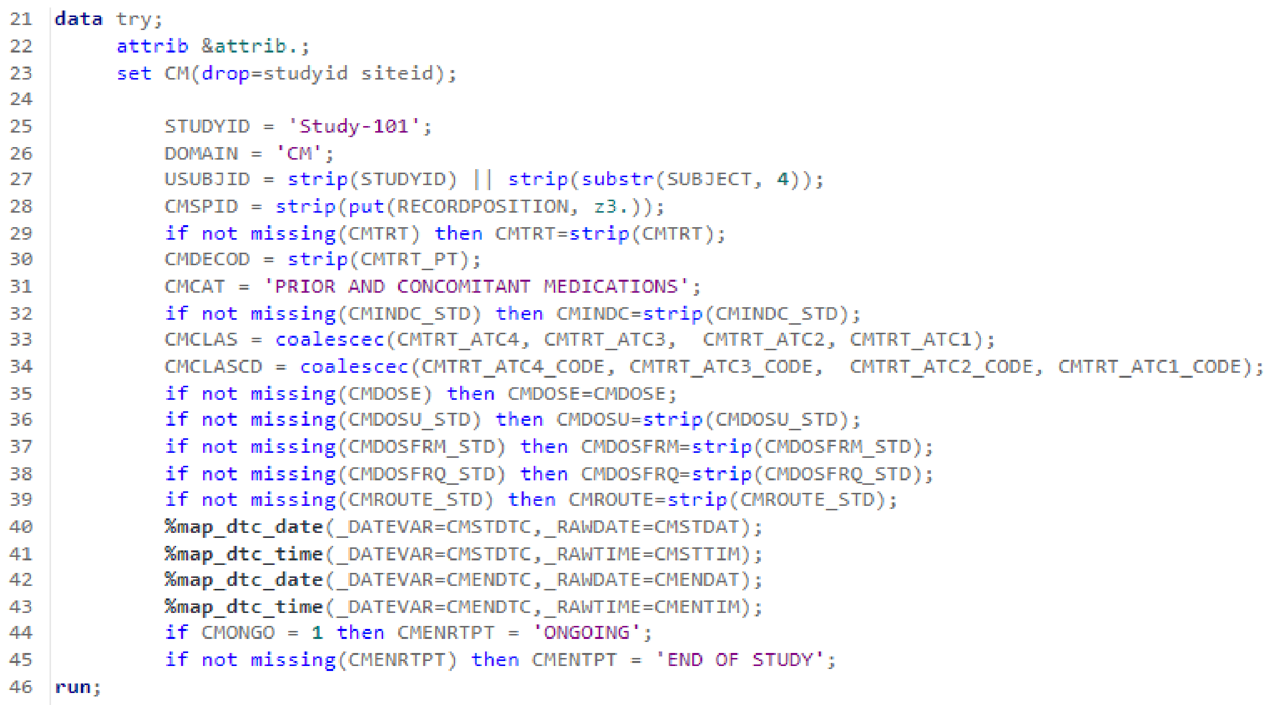


#	lines	_order
1	data try;	10
2	attrib &attrib.;	20
3	set CM(drop=studyid siteid);	30
4		901
5	STUDYID='Study-101'	902
6	DOMAIN = 'CM';	903
7	USUBJID = strip(STUDYID) || strip(substr(SUBJECT, 4));	904
8	CMSPID = strip(put(RECORDPOSITION, z3.));	905
9	if not missing(CMTRT) then CMTRT=strip(CMTRT);	906
10	CMDECOD = strip(CMTRT_PT);	907
11	CMCAT = 'PRIOR AND CONCOMITANT MEDICATIONS';	908
12	if not missing(CMINDC_STD) then CMINDC=strip(CMINDC_STD);	909
13	CMCLAS = coalescec(CMTRT_ATC4, CMTRT_ATC3, CMTRT_ATC2, CMTRT_ATC1);	910
14	CMCLASCD = coalescec(CMTRT_ATC4_CODE, CMTRT_ATC3_CODE, CMTRT_ATC2_CODE, CMTRT_ATC1_CODE);	911
15	if not missing(CMDOSE) then CMDOSE=CMDOSE;	912
16	if not missing(CMDOSU_STD) then CMDOSU=strip(CMDOSU_STD);	913
17	if not missing(CMDOSFRM_STD) then CMDOSFRM=strip(CMDOSFRM_STD);	914
18	if not missing(CMDOSFRQ_STD) then CMDOSFRQ=strip(CMDOSFRQ_STD);	915
19	if not missing(CMROUTE_STD) then CMROUTE=strip(CMROUTE_STD);	916
20	%map_dtc_date(_DATEVAR=CMSTDTC,_RAWDATE=CMSTDAT);	917
21	%map_dtc_time(_DATEVAR=CMSTDTC,_RAWTIME=CMSTTIM);	918
22	%map_dtc_date(_DATEVAR=CMENDTC,_RAWDATE=CMENDAT);	919
23	%map_dtc_time(_DATEVAR=CMENDTC,_RAWTIME=CMENTIM);	920
24	if CMONGO = 1 then CMENRTPT = 'ONGOING';	921
25	if not missing(CMENRTPT) then CMENTPT = 'END OF STUDY';	922
26	run;	922.5

Display 1. A SAS Dataset with Columns *lines* and *_order* Containing a Snippet of Code for SDTM CM.sas

```
%let outdir=.../&program_path.;
%let domain_=CM;
data _null_;
     set final;
     file "&outdir./_.&domain_..sas";
     put @1 lines $255.;
run;
```

Display 2. SAS Data _NULL_ Step to Output a SAS Program



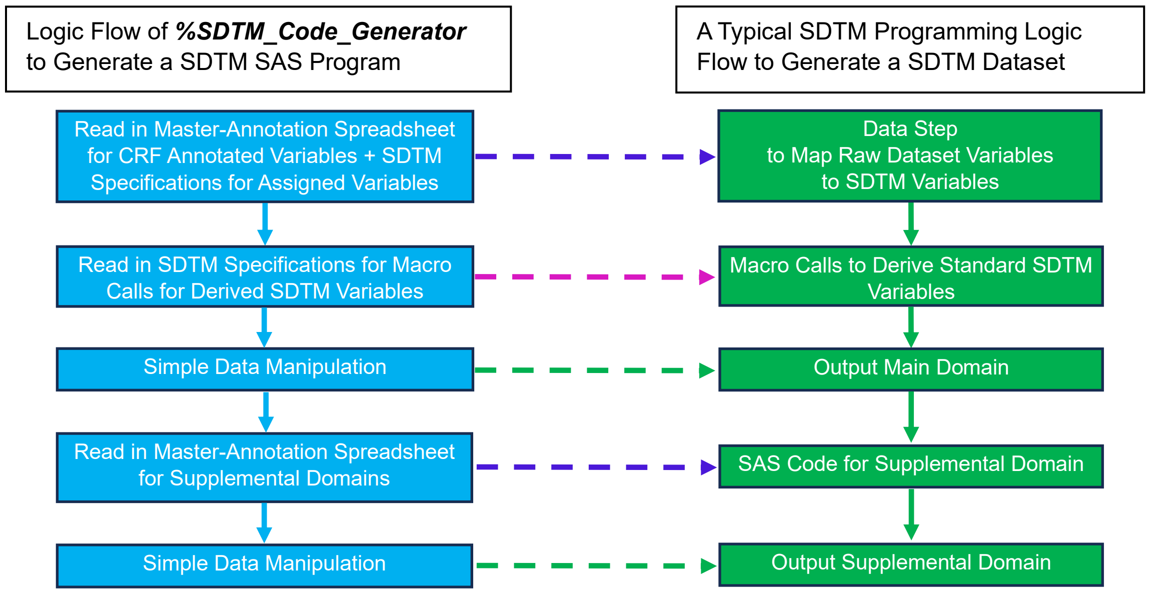
```
data try;
    attrib &attrib.;
    set CM(drop=studyid siteid);

        STUDYID = 'Study-101';
        DOMAIN = 'CM';
        USUBJID = strip(STUDYID) || strip(substr(SUBJECT, 4));
        CMSPID = strip(put(RECORDPOSITION, z3.));
        if not missing(CMTRT) then CMTRT=strip(CMTRT);
        CMDECOD = strip(CMTRT_PT);
        CMCAT = 'PRIOR AND CONCOMITANT MEDICATIONS';
        if not missing(CMINDC_STD) then CMINDC=strip(CMINDC_STD);
        CMCLAS = coalescec(CMTRT_ATC4, CMTRT_ATC3,  CMTRT_ATC2, CMTRT_ATC1);
        CMCLASCD = coalescec(CMTRT_ATC4_CODE, CMTRT_ATC3_CODE,  CMTRT_ATC2_CODE, CMTRT_ATC1_CODE);
        if not missing(CMDOSE) then CMDOSE=CMDOSE;
        if not missing(CMDOSU_STD) then CMDOSU=strip(CMDOSU_STD);
        if not missing(CMDOSFRM_STD) then CMDOSFRM=strip(CMDOSFRM_STD);
        if not missing(CMDOSFRQ_STD) then CMDOSFRQ=strip(CMDOSFRQ_STD);
        if not missing(CMROUTE_STD) then CMROUTE=strip(CMROUTE_STD);
        %map_dtc_date(_DATEVAR=CMSTDTC,_RAWDATE=CMSTDAT);
        %map_dtc_time(_DATEVAR=CMSTDTC,_RAWTIME=CMSTTIM);
        %map_dtc_date(_DATEVAR=CMENDTC,_RAWDATE=CMENDAT);
        %map_dtc_time(_DATEVAR=CMENDTC,_RAWTIME=CMENTIM);
        if CMONGO = 1 then CMENRTPT = 'ONGOING';
        if not missing(CMENRTPT) then CMENTPT = 'END OF STUDY';
run;
```

Display 3. A Snippet of the Output SAS Program for SDTM CM.sas

%SDTM_Code_Generator is designed to generate a SAS dataset first for each SDTM domain. Then, it uses the SAS code from Display 2 to output a SAS program for each SDTM domain.

INTRODUCTION TO THE LOGIC FLOW OF *%SDTM_CODE_GENERATOR*

Figure 3 below shows the logic flow of ***%SDTM_Code_Generator*** alongside a typical SDTM programming logic flow with arrows connecting corresponding blocks. The former outputs a SDTM SAS program while the latter outputs a SDTM dataset.



Logic Flow of %SDTM_Code_Generator to Generate a SDTM SAS Program
A Typical SDTM Programming Logic Flow to Generate a SDTM Dataset
Read in Master-Annotation Spreadsheet for CRF Annotated Variables + SDTM Specifications for Assigned Variables
Data Step to Map Raw Dataset Variables to SDTM Variables
Read in SDTM Specifications for Macro Calls for Derived SDTM Variables
Macro Calls to Derive Standard SDTM Variables
Simple Data Manipulation
Output Main Domain
Read in Master-Annotation Spreadsheet for Supplemental Domains
SAS Code for Supplemental Domain
Simple Data Manipulation
Output Supplemental Domain

Figure 3. The Logic Flow from *%SDTM_Code_Generator* vs. Typical SDTM Programming

Before developing SAS code for each SDTM domain, ***%SDTM_Code_Generator*** first reads in and subsets the master-annotation spreadsheet for the dedicated SDTM domain. Secondly, it reads the

Origin and our newly added ***Derivation/Assigned*** columns from SDTM specifications, which contain information on whether variables are directly mapped, assigned, or derived. Table 3 below shows the source of inputs for the macro's automation. When *Origin* is "CRF Page", the macro directly maps those variables from the master-annotation spreadsheet. When *Origin* is "Protocol", "Assigned", or "Derived", the *Derivation/Assigned* column in SDTM specifications can be utilized to further customize SAS macro code.

Origin of SDTM Variables	Input of a SAS-Based Macro	Source	Case
CRF	Master-Annotation Spreadsheet	Combination of CRF Specifications and CRF Annotations	All mapping variables
Protocol	SDTM Specifications	Derivation/Assigned column	Assignment, e.g., STUDYID='Study-101'
Assigned	SDTM Specifications	Derivation/Assigned column	Assignment, e.g., DOMAIN = 'CM' or DM.ARMCD from the call of %get_trt
Derived	SDTM Specifications	Derivation/Assigned column	A line of code or macro call(s)

Table 3. Sources of Inputs for *%SDTM_Code_Generator*

INTRODUCTION TO OUR STANDARD SDTM SPECIFICATIONS

Our standard SDTM specification [3] is based on CDISC's standard. See Table 4 below for an example of our DM domain specification with a sample of variables. The Variable, Label, Type, Controlled Terminology, and Core columns come directly from the SDTMIG v3.4. Per the SDTMIG [6], the sources of SDTM variables are categorized by the origin of the data source in the Define-XML document file, such as "CRF", "Protocol", "Assigned", or "Derived".

To support our SDTM automation, we've enhanced each SDTM specification with a new column, ***Derivation/Assigned***, to store either a simple line of SAS assignment code or a SAS macro name. This allows us to further customize code for the variables without needing to add extra code to ***%SDTM_Code_Generator***.

When *Origin* is "CRF Page xx", most SDTM variables (e.g., RFICDTC) can be directly mapped from raw dataset variables. When *Origin* is "Protocol", "Assigned", or "Derived", the *Derivation/Assigned* column can be utilized to further customize SAS macro code. In the case when one line of code is sufficient (e.g., STUDYID, USUBJID, etc.), we write the code directly in the *Derivation/Assigned* column, and the macro reads that in.

However, some other standard SDTM variables require more lines of code. They may need additional lines of code and/or data steps to derive from other variables either within the same raw dataset or across multiple raw datasets. Examples of these are --DTC, --STDTC, --ENDTC, --DY, --STDY, --ENDY, --BLFL, --LOBXFL, --SEQ, RFSTDTC, RFENDTC, RFXSTDTC, RFXENDTC, RFPENDTC, ARMCD, ARM, etc. For coding efficiency, the derivation of these variables is generalized and grouped into a utility macro, and the name of that specific utility macro is included in the SDTM specifications (e.g., ***%get_trt***).

While the SDTM variables that require utility macros usually have *Origin* as "Protocol", "Assigned", or "Derived", there is one exception: the variable *RACE*. Since multiple races are collected in a study and the multiple race-related SDTM guidelines [6] should be followed, we had to develop a ***%map_race*** utility macro, and that utility macro name is written in the ***Derivation/Assigned*** column in SDTM specifications for automation as shown in Table 4.

Variable	Label	Type	Length	Controlled Terminology	Origin	Core	Derivation/Assigned
STUDYID	Study Identifier	Char	20		Protocol	Req	STUDYID='Study-101';
DOMAIN	Domain Abbreviation	Char	2	DOMAIN	Assigned	Req	DOMAIN='DM';
USUBJID	Unique Subject Identifier	Char	40		Derived	Req	USUBJID=strip(STUDYID)|| strip(substr(SUBJECT,4));
SUBJID	Subject Identifier for the Study	Char	20		CRF Page 267	Req	SUBJID=strip(substr(SUBJECT,5));
RFSTDTC	Subject Reference Start Date/Time	Char	20	ISO 8601	Derived	Exp	%get_rfstdtc
RFENDTC	Subject Reference End Date/Time	Char	20	ISO 8601	Derived	Exp	%get_rfendtc
RFXSTDTC	Date/Time of First Study Treatment	Char	20	ISO 8601	Derived	Exp	%get_rfxstdtc
RFXENDTC	Date/Time of Last Study Treatment	Char	20	ISO 8601	Derived	Exp	%get_rfxendtc
RFICDTC	Date/Time of Informed Consent	Char	20	ISO 8601	CRF Page 5	Exp	
RFPENDTC	Date/Time of End of Participation	Char	20	ISO 8601	Derived	Exp	%get_rfpendtc
RACE	Race	Char	50	RACE	CRF Page 7	Exp	%map_race
ETHNIC	Ethnicity	Char	40	ETHNIC	CRF Page 7	Perm	
ARMCD	Planned Arm Code	Char	20		Assigned	Exp	%get_trt

Variable	Label	Type	Length	Controlled Terminology	Origin	Core	Derivation/Assigned
ARM	Description of Planned Arm	Char	200		Assigned	Exp	%get_trt
ACTARMCD	Actual Arm Code	Char	20		Assigned	Exp	%get_trt
ACTARM	Description of Actual Arm	Char	200		Assigned	Exp	%get_trt
ARMNRS	Reason Arm and/or Actual Arm is Null	Char	80		Assigned	Exp	%get_trt
ACTARMUD	Description of Unplanned Actual Arm	Char	200		Assigned	Exp	%get_trt

Table 4. DM Domain Specification With a Sample of Variables

INTRODUCTION TO OUR SAS UTILITY MACROS

Table 5 lists five of our SAS utility macros dedicated to SDTM variables: --DTC, RACE, RACE1, …, RACE5, --SEQ, and --DY. Please refer to Appendix 1 for a more comprehensive list of our utility macros. A centralized SAS dataset named ***macrocalls*** stores all macro calls located in the macro library, except for %map_dtc_date and %map_dtc_time, which are directly called by ***%SDTM_Code_Generator***. Table 6 shows examples of the records in the macrocalls dataset for domains AE, DM, and LB.

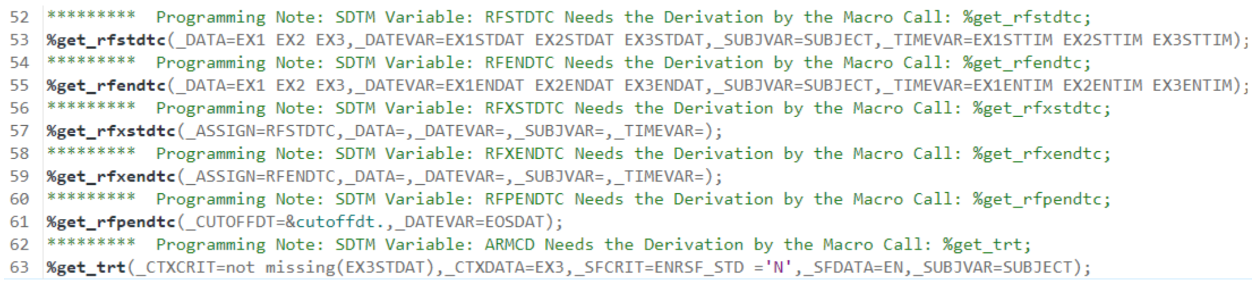
SDTM Variable	Macro Name	Description	SDTM Domains	Example Macro Call
--DTC	map_dtc_date and map_dtc_time	Derive –DTC variables when there are partial dates	All Domains except for DM and SV	%map_dtc_date(_DATEVAR=AESTDTC, _RAWDATE=AESTDAT); %map_dtc_time(_DATEVAR=AESTDTC, _RAWTIME=AESTTIM);
RACE, RACE1, …, RACE5	map_race	Derive RACE variables for DM and SUPPDM	DM, SUPPDM	%map_race(_NUMFL=Y,_VAR=RACE1 RACE2 RACE3 RACE4 RACE5 RACE6);
--SEQ	get_seq	Derive --SEQ variables based on provided key variables	All Domains except for DM and SV	%get_seq(_DOMAIN=LB, _SORTKEYS=STUDYID USUBJID LBCAT LBTESTCD VISITNUM LBDTC);
--DY	get_dy	Derive --DY variables based on provided --DTC variables	All Domains	%get_dy(_DATEVAR=LBDTC, _DAYVAR=LBDY);

Table 5. Examples of SAS Utility Macros for SDTM Automation

MACRO	MORD	DOMAIN	VARIABLE	MCALL
%get_seq	100	AE	AESEQ	%get_seq(_DOMAIN=AE,_SORTKEYS=STUDYID USUBJID AESTDTC AEDECOD AESPID);
%get_dy	102	AE	AEENDY	%get_dy(_DATEVAR=AEENDTC,_DAYVAR=AEENDY);
%get_dy	102	AE	AESTDY	%get_dy(_DATEVAR=AESTDTC,_DAYVAR=AESTDY);
%get_aetrtem	111	AE	AETRTEM	%get_aetrtem();
%map_race	2	DM	RACE	%map_race(_NUMFL=Y,_VAR=RACE1 RACE2 RACE3 RACE4 RACE5 RACE6);
%get_rfstdtc	105	DM	RFSTDTC	%get_rfstdtc(_DATA=EX1 EX2 EX3,_DATEVAR=EX1STDAT EX2STDAT EX3STDAT,_SUBJVAR=SUBJECT, _TIMEVAR=EX1STTIM EX2STTIM EX3STTIM);
%get_rfendtc	106	DM	RFENDTC	%get_rfendtc(_DATA=EX1 EX2 EX3,_DATEVAR=EX1ENDAT EX2ENDAT EX3ENDAT,_SUBJVAR=SUBJECT, _TIMEVAR=EX1ENTIM EX2ENTIM EX3ENTIM);
%get_rfxstdtc	107	DM	RFXSTDTC	%get_rfxstdtc(_ASSIGN=RFSTDTC,_DATA=,_DATEVAR=, _SUBJVAR=,_TIMEVAR=);
%get_rfxendtc	108	DM	RFXENDTC	%get_rfxendtc(_ASSIGN=RFENDTC,_DATA=,_DATEVAR=, _SUBJVAR=,_TIMEVAR=);
%get_rfpendtc	109	DM	RFPENDTC	%get_rfpendtc(_CUTOFFDT=&cutoffdt.,_DATEVAR=EOSDAT);
%get_trt	110	DM	ARMCD	%get_trt(_DRGCRIT=not missing(EX3STDAT),_DRGDATA=EX3, _SFCRIT=ENRSF_STD='N',_SFDATA=EN,_SUBJVAR=SUBJECT);
%get_seq	100	LB	LBSEQ	%get_seq(_DOMAIN=LB,_SORTKEYS=STUDYID USUBJID LBCAT LBTESTCD VISITNUM LBDTC);
%get_dy	102	LB	LBDY	%get_dy(_DATEVAR=LBDTC,_DAYVAR=LBDY);
%get_lobxfl	103	LB	LBLOBXFL	%get_lobxfl(_DATEVAR=LBDTC,_DAYVAR=LBDY,_DOMAIN=LB, _LASTVAR=LBTESTCD,_RESVAR=LBSTRESC, _SORTVARS=USUBJID LBCAT LBTESTCD LBDTC);
%get_blfl	104	LB	LBBLFL	%get_blfl(_DATEVAR=LBDTC,_DAYVAR=LBDY,_DOMAIN=LB, _LASTVAR=LBTESTCD,_RESVAR=LBSTRESC, _SORTVARS=USUBJID LBCAT LBTESTCD LBDTC);

Table 6. Examples of Records From SAS Dataset *Macrocalls* for SDTM Domains: AE, DM, and LB

%SDTM_Code_Generator merges the ***macrocalls*** data with the ***Derived/Assigned*** column in SDTM specifications by domain, variable name, and macro name. Then it generates the macro calls for each domain's SDTM mapping program using the ***MCALL*** variable. Display 4 shows the generated macro calls for DM.sas along with the programming comments.



```
*********  Programming Note: SDTM Variable: RFSTDTC Needs the Derivation by the Macro Call: %get_rfstdtc;
%get_rfstdtc(_DATA=EX1 EX2 EX3,_DATEVAR=EX1STDAT EX2STDAT EX3STDAT,_SUBJVAR=SUBJECT,_TIMEVAR=EX1STTIM EX2STTIM EX3STTIM);
*********  Programming Note: SDTM Variable: RFENDTC Needs the Derivation by the Macro Call: %get_rfendtc;
%get_rfendtc(_DATA=EX1 EX2 EX3,_DATEVAR=EX1ENDAT EX2ENDAT EX3ENDAT,_SUBJVAR=SUBJECT,_TIMEVAR=EX1ENTIM EX2ENTIM EX3ENTIM);
*********  Programming Note: SDTM Variable: RFXSTDTC Needs the Derivation by the Macro Call: %get_rfxstdtc;
%get_rfxstdtc(_ASSIGN=RFSTDTC,_DATA=,_DATEVAR=,_SUBJVAR=,_TIMEVAR=);
*********  Programming Note: SDTM Variable: RFXENDTC Needs the Derivation by the Macro Call: %get_rfxendtc;
%get_rfxendtc(_ASSIGN=RFENDTC,_DATA=,_DATEVAR=,_SUBJVAR=,_TIMEVAR=);
*********  Programming Note: SDTM Variable: RFPENDTC Needs the Derivation by the Macro Call: %get_rfpendtc;
%get_rfpendtc(_CUTOFFDT=&cutoffdt.,_DATEVAR=EOSDAT);
*********  Programming Note: SDTM Variable: ARMCD Needs the Derivation by the Macro Call: %get_trt;
%get_trt(_CTXCRIT=not missing(EX3STDAT),_CTXDATA=EX3,_SFCRIT=ENRSF_STD ='N',_SFDATA=EN,_SUBJVAR=SUBJECT);
```

Display 4. SAS Code Generated by *%SDTM_Code_Generator* for the Macro Calls of the DM Domain

INTRODUCTION TO MEDIDATA'S ARCHITECT LOADER SPECIFICATION (ALS)

Medidata's Rave EDC (Electronic Data Capture) is widely used to build the EDC database for a clinical study. The Architect Loader Specification (ALS) is the document that Rave uses with metadata systems, and it provides information about how the database has been set up. One can duplicate the structure in another study database simply by customizing a pre-existing ALS and then importing the modified ALS into the new study database. Rave users can export an ALS directly from the Rave database. Table 7 shows an example of the *Forms* sheet from a study's ALS. The *OID* column shows the form names (EDC dataset names), and the *DraftFormName* column shows the label of each form.

OID	Ordinal	DraftFormName
SUBJ	1	Subject Registration
SV	2	Subject Visit
IC	3	Informed Consent
DM	4	Demographics
IE	5	Inclusion and Exclusion
EN	6	Enrollment
DIA	7	Diagnosis
MH	8	Medical History
RADPRE	9	Prior Radiation Therapy
THERPRE	10	Prior Anti-Cancer Therapy
MR	14	Modified Rai Clinical Stage
VS	18	Vital Signs
EG	22	12- Lead ECG - Single Timepoint
PK	25	Study Product PK
BIONON	31	Exploratory Biomarkers
LBCHEM	35	Local Lab - Chemistry
UV	491	Unscheduled Subject Visit
EOS	494	End of Study

Table 7. An Example of the *Forms* Sheet From an ALS

Table 8 below shows an example of the *Fields* sheet from a study's ALS. The *FieldOID* column shows the variable names for the EOS form, along with their formats (*DataFormat*) and labels (*SASLabel*). Of note, the last column *VARIABLE TYPE* is added by the user and derived from column *DataFormat*. It is directly used for the derivation inside ***%SDTM_Code_Generator***.

FormOID	Ordinal	FieldOID	SASLabel / VARIABLE LABEL	DataFormat	VARIABLE TYPE
EOS	1	EOSDAT	End of Study Date	dd MMM yyyy	Date
EOS	2	EOSSTAT	Subject Disposition at the End of Study	$15	char
EOS	3	EOSREAS	Reason for End of Study	$40	char
EOS	4	EOSOTSP_O	Other, Specify	$200	char
EOS	5	EOSDEADT	Death Date	dd MMM yyyy	Date
EOS	6	PRCDTH	Primary Cause of Death	$20	char
EOS	7	EOSAESP_O	Adverse Event, Specify	$200	char
EOS	8	EOSNSRSP_O	Not Study Related, Specify	$200	char
EOS	9	EOSOTSPY_O	Other, Specify	$200	char

Table 8. An Example of the *Fields* Sheet for the EOS Form From an ALS

An ALS is the repository for all raw dataset names and variable attributes for a study, which are some of the inputs for SDTM programming. SDTM programmers manually annotate CRFs at the beginning of SDTM programming. The aCRF then guides programmers to develop SAS programs for SDTM datasets. Moreover, it is one of the required documents for regulatory submission. Each annotation sets up the one-to-one mapping from each raw dataset variable in a CRF to its mapped SDTM domain variable or supplemental qualifier in each SDTM mapping program. If this could be directly used as the logic/mapping rules by a SAS macro, it would be more beneficial to the programming, and automation could be achieved. Hence, we store these annotations along with the metadata for raw datasets as described above in a single spreadsheet called "**master-annotation**", which is "**semi-automatically**" developed per the availability of a study's ALS. This allows a SAS macro to simultaneously import all the mapping rules for all domains and utilize them in the SDTM automation macro, instead of having multiple programmers individually annotate and develop programs for different SDTM domains.

INTRODUCTION TO OUR MASTER-ANNOTATION SPREADSHEET

As described above, we developed a spreadsheet file named **master-annotation.xlsx** as the repository of all raw dataset names and variable attributes (variable name, label, and type) as specified in the ALS along with CRF annotations mapping raw dataset variables to SDTM domains and their variables. Furthermore, extra columns are added to the file to aid the macro in automating SAS code generation.

We start with variables (EDC DATASET NAME – VARIABLE LABEL) derived directly from the ALS as the foundation for the master-annotation as the ALS includes raw dataset names, variable names, labels, types, formats, and orders. Additional columns (SDTM DOMAIN – DECOD/TRT) are added in the master-annotation to facilitate mapping those raw dataset variables to the corresponding SDTM domains. These columns generally come from CRF Annotations. Extra columns (QLABEL – TRT ASSIGN) are designed to assist the automation for certain SDTM variables. Please see Table 9 below for an example of how the RADPOST (Post-Treatment Radiation Therapy) form is annotated in the master-annotation and Table 10 for a summary of these key columns (variables) in the master-annotation.

From ALS **From CRF Annotation**

EDC DATASET NAME	EDC DATASET LABEL	ORD.	VARIABLE TYPE	VARIABLE NAME	VARIABLE LABEL	SDTM DOMAIN	SDTM VARIABLE	CATEGORY	SUB CATE GORY	DECOD/TRT
RADPOST	Post-Treatment Radiation Therapy	1	char	RADPOSTYN_STD	Post-Treatment Radiation Therapy?	PR	[NOT SUBMITTED]	CONCURRENT RADIOTHERAPY		RADIOTHERAPY
RADPOST	Post-Treatment Radiation Therapy	2	Date	RADPOSTSTDAT	Date of First Dose	PR	PRSTDTC			
RADPOST	Post-Treatment Radiation Therapy	3	Date	RADPOSTENDAT	Date of Last Dose	PR	PRENDTC			
RADPOST	Post-Treatment Radiation Therapy	4	Numeric	RADPOSTTD	Total Dose	PR	PRDOSE			
RADPOST	Post-Treatment Radiation Therapy	5	char	RADPOSTTDU_STD	Total Dose Unit	PR	PRDOSU			
RADPOST	Post-Treatment Radiation Therapy	6	char	RADPOST_O	Other, Specify	PR	DOSSPEC in SUPPPR			
RADPOST	Post-Treatment Radiation Therapy	7	char	RADPOSTSR_STD	Site of Radiation	PR	PRLOC			
RADPOST	Post-Treatment Radiation Therapy	8	char	RADPOSTS_O	Other, Specify	PR	LOCSPEC in SUPPPR			
RADPOST	Post-Treatment Radiation Therapy	9	char	RADPOSTPU_STD	Purpose	PR	PURPOSE in SUPPPR			

Assisting the Macro to Automate the SAS Code Generation

EDC DATASET NAME	ORDER	QLABEL	QORIG	QEVAL	GRPID	TRT ASSIGN
RADPOST	1					
RADPOST	2					
RADPOST	3					
RADPOST	4					
RADPOST	5					
RADPOST	6	Total Dose, Other, Specify	CRF			
RADPOST	7					
RADPOST	8	Site of Radiation, Other, Specify	CRF			
RADPOST	9	Purpose	CRF			

Table 9. An Example of the Master-Annotation for the PR Domain (With Raw Dataset: RADPOST)

Column	Column Content		Origin	Manual?
EDC DATASET NAME	Raw dataset name		ALS	
EDC DATASET LABEL	Raw dataset label		ALS	
ORDER	The order of variables specified in CRFs, one of the key variables used to sort intermediate datasets generated by ***%SDTM_Code_Generator***		ALS	
VARIABLE TYPE	Variable type in raw dataset: Numeric, char, Date, Time, or Date & Time		ALS	Derived
VARIABLE NAME	Variable name in raw dataset		ALS	
VARIABLE LABEL	Variable label in raw dataset		ALS	
SDTM VARIABLE	SDTM variable name, SDTM variable name for a specific test, QNAM in supplemental domain, or not submitted		CRF Annotation	Y
CATEGORY	Text to assign –CAT. Applicable to domains: DS, EG, FA, LB, QS, TR, VS		CRF Annotation	Y
SUB CATEGORY	Text to assign --SCAT/FAOBJ. Applicable to domains: DS, EG, FA, LB, QS, TR		CRF Annotation	Y
DECOD/TRT	Text to assign --TRT/--TEST/DSTERM/DSDECOD. Applicable to domains: DS, FA, PR, TR		CRF Annotation	Y
QLABEL	Assign QLABEL in supplemental domains	Triplet to help map raw dataset variables in supplemental domains	User input (intended to assist ***%SDTM_Code_ Generator*** with SAS code generation)	Y
QORIG	Assign QORIG in supplemental domains, with values: CRF, Derived, or Assigned.			
QEVAL	Assign QEVAL in supplemental domains, e.g., "CLINICAL STUDY SPONSOR"			
GRPID	Column to define the group (block) within a raw dataset indicating that variables in the same group will be mapped to a specific intervention, occurrence, event, measurement, or finding. Applicable to domains: DS, FA, PR, QS, TR, TU			
TRT ASSIGN	Column to aid automation and indicate extra coding is needed for the mapping of the variables. Applicable to all finding domains along with DS, FA, PR, and SV			

Table 10. Summary of the Key Variables in the Master-Annotation

The macro uses the variables above as its inputs to derive SDTM SAS programs. Table 11 shows an example of SDTM date variables --DTC, --STDTC, or –ENDTC along with raw dataset variables used to derive them.

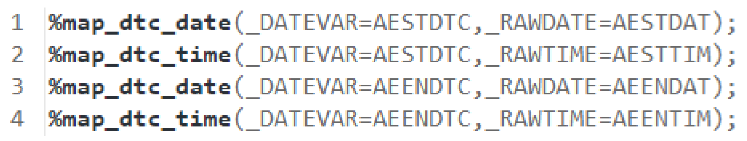
EDC DATASET NAME	EDC DATASET LABEL	ORDER	VAR. TYPE	VARIABLE NAME	VARIABLE LABEL	SDTM DOMAIN	SDTM VARIABLE
AE	Adverse Events	3	Date	AESTDAT	Start Date	AE	AESTDTC
AE	Adverse Events	4	Time	AESTTIM	Start Time	AE	AESTDTC
AE	Adverse Events	5	Date	AEENDAT	End Date	AE	AEENDTC
AE	Adverse Events	6	Time	AEENTIM	End Time	AE	AEENDTC
EOS	End of Study	1	Date	EOSDAT	End of Study Date	DS	DSSTDTC
EOS	End of Study	5	Date	EOSDEADT	Death Date	DM	DTHDTC
EX1	Lymphodepleting Chemotherapy: Fludarabine	8	Date	EX1STDAT	What was the treatment start date?	EX	EXSTDTC
EX1	Lymphodepleting Chemotherapy: Fludarabine	10	Date	EX1ENDAT	What was the treatment stop date?	EX	EXENDTC
LBCHEM	Local Lab - Chemistry	2	Date	LBDAT	Date of Collection	LB	LBDTC
VS	Adverse Events	2	Date	VSDAT	Date of Collection	VS	VSDTC

Table 11. A Sample of Raw Dataset Date/Time Variables and Their Mapped SDTM Variable Names From the Master-Annotation

Display 5 shows SAS code from ***%SDTM_Code_Generator*** that is used to generate the SAS code for AE.AESTDTC and AE.AEENDTC in AE.sas. Of note, *SDTM VARIABLE* was renamed as *variable* for convenience inside the macro as shown on lines 4 and 6. Display 6 shows the output SAS code generated by Display 5 for AESTDTC and AEENDTC.

```
1 if (strip(variable_type)='Date' and index(variable_label,'Date')) or
2    (strip(variable_type)='Time' and index(variable_label,'Time')) then do;
3    if substr(reverse(strip(variable_name)),1,3)='TAD' then
4       lines='        '||'%map_dtc_date(_DATEVAR='||strip(variable)||',_RAWDATE='||strip(variable_name)||');';
5    else if substr(reverse(strip(variable_name)),1,3)='MIT' then
6    lines='        '||'%map_dtc_time(_DATEVAR='||strip(variable)||',_RAWTIME='||strip(variable_name)||');';
7 end;
```

Display 5. SAS Code from *%SDTM_Code_Generator* Used to Generate SAS Code Inside AE.sas for AESTDTC and AEENDTC



```
%map_dtc_date(_DATEVAR=AESTDTC,_RAWDATE=AESTDAT);
%map_dtc_time(_DATEVAR=AESTDTC,_RAWTIME=AESTTIM);
%map_dtc_date(_DATEVAR=AEENDTC,_RAWDATE=AEENDAT);
%map_dtc_time(_DATEVAR=AEENDTC,_RAWTIME=AEENTIM);
```

Display 6. SAS Code to Map Raw Dataset Variables to AESTDTC and AEENDTC Inside AE.sas

From the example above, the macro uses the columns from the master-annotation for derivation, instead of needing to specify individual variable names from the raw datasets. This allows for the macro to be used in multiple studies, even if their EDC databases are built from different vendors.

INTRODUCTION TO MASTER-ANNOTATION COLUMN *TRT ASSIGN*

Column *TRT ASSIGN* is used to indicate additional derivation rules for certain SDTM variables. It is restricted to one of the following keywords: Blank, "Y", "TEST", "COMBINE", or a subset condition for different classes of the SDTM domains. When combined with the columns *SDTM VARIABLE*, *CATEGORY*, *SUB CATEGORY*, and *DECOD/TRT*, it helps set up the logic for the derivation of SDTM domain variables and supplemental qualifiers: --CAT, --SCAT, --TEST, --TESTCD, --ORRES, --ORRESU, QNAM, QLABEL, QORIG, QVAL, etc. Table 12 shows examples of how *TRT ASSIGN* is combined with these other columns and the logic for the mapping and derivations of the relevant SDTM variables.

#	Class of the Domains (Example)	TRT ASSIGN	SDTM VARIABLE	CATEGORY	SUB CATEGORY	DECOD/ TRT	Logic for Mapping and Derivation
1.1	ALL Domains	Blank	[NOT SUBMITTED]	NA	NA	NA	No mapping
1.2	ALL Domains	Blank	Variable in main domain	NA	NA	NA	Map VARIABLE NAME to Domain Variable
1.3	Findings (EG, VS, TR)	Blank	--ORRESU when --TESTCD = ZZZ	NA	NA	NA	Map VARIABLE NAME to --ORRESU where --TESTCD = ZZZ
1.4	ALL Domains	Blank	QNAM in Supplemental Domain	NA	NA	NA	Map QNAM to SUPP--.QNAM, Map QLABEL to SUPP--.QLABEL, Map QORIG to SUPP--.QORIG, Map VARIABLE NAME to SUPP--.QVAL
2.1	Interventions (PR)	Y	[NOT SUBMITTED]	PRCAT	-	PRTRT	Map CATEGORY to PRCAT, Map DECOD/TRT to PRTRT
2.2	Findings About (FA)	Y	[NOT SUBMITTED]	FACAT	FAOBJ	-	Map CATEGORY to FACAT, Map SUB CATEGORY to FAOBJ
2.3	Findings (LB, QS, RS, TR, TU)	Y	[NOT SUBMITTED]	--CAT	--SCAT	-	Map CATEGORY to --CAT, Map SUB CATEGORY to --SCAT
3	Findings (EG, LB, PE, VS, QS, RS, TR, TU), Findings About (FA)	TEST	--ORRES when --TESTCD = ZZZ			--TEST	Map DECOD/TRT to --TEST, Map ZZZ to --TESTCD, Map VARIABLE NAME to --ORRES
4	Supplemental (SUPPSV)	COMBINE	QNAM in Supplemental Domain	NA	NA	NA	Concatenate the values of raw dataset variables by "," before outputting them into QVAL for QNAM = "UNSAPERF". Please refer to [8]
5	Supplemental (SUPPPR)	A Subset Condition	QNAM in Supplemental Domain	NA	NAA	NA	Output the records into supplemental domain ONLY when a subset condition is satisfied

Table 12. Examples of How *TRT ASSIGN* is Combined With Other Columns to Derive Certain SDTM Variables

There are five main scenarios according to the values of column *TRT ASSIGN*, and the following five tables provide examples of these scenarios.

Scenario 1: Column *TRT ASSIGN* is Blank.

EDC DATASET NAME	EDC DATASET LABEL	ORD.	VAR. TYPE	VARIABLE NAME	VARIABLE LABEL	SDTM DOMAIN	SDTM VARIABLE	QLABEL	QORIG	TRT ASSIGN
AE	Adverse Events	1	char	AEYN_STD	Any AE	AE	[NOT SUBMITTED]			
AE	Adverse Events	2	char	AETERM	AE Term	AE	AETERM			
AE	Adverse Events	12	char	AESITYP_STD	AESI Type	AE	AESITY in SUPPAE	AESI Type	CRF	
VS	Vital Signs	1	char	VSPERF_VSALL_STD	Vital Signs Collected	VS	[NOT SUBMITTED]			
VS	Vital Signs	2	Date	VSDAT	Date of Collection	VS	VSDTC			
VS	Vital Signs	12	char	VSMETHOD_OXYSAT	Oxygen Saturation Method	VS	OXYSAT in SUPPVS	Oxygen Saturation Method	CRF	
VS	Vital Signs	14	char	VSORRES_OXYSATU	Oxygen Saturation Units	VS	VSORRESU when VSTESTCD = OXYSAT			

Table 13. An Example of a Master-Annotation Where *TRT ASSIGN* is Set to Blank

Scenario 2: Column *TRT ASSIGN* = "Y".

EDC DATASET NAME	EDC DATASET LABEL	ORD.	VAR. TYPE	VARIABLE NAME	VARIABLE LABEL	SDTM DOMAIN	SDTM VARIABLE	CATEGORY	SUB CATEGORY	DECOD /TRT	TRT ASSIGN
CP	Concomitant Procedures and Treatment	1	char	CPYN_STD	Surgical Therapeutic Diag Procedure	PR	[NOT SUBMITTED]	CONCOMITANT PROCEDURES AND TREATMENT			Y
RADPRE	Prior Radiation Therapy	1	char	RADPREYN _STD	Any Prior Radiation Therapy Performed?	PR	[NOT SUBMITTED]	PRIOR RADIOTHERAPY		RADIOTHERAPY	Y
ECHO	Echocardiogra m	1	char	ECHOYN _STD	Was ECHO Performed?	FA	[NOT SUBMITTED]	ECHOCARDIOGRAM STATUS	ECHOCARDIO GRAM		Y
LBCHEM	Local Lab - Chemistry	1	char	LBPERF_STD	Was sample collected?	LB	[NOT SUBMITTED]	CHEMISTRY	LOCAL LABORATORY		Y
LBHM	Local Lab - Hematology	1	char	LBPERF_STD	Was sample collected?	LB	[NOT SUBMITTED]	HEMATOLOGY	LOCAL LABORATORY		Y

Table 14. An Example of a Master-Annotation Where *TRT ASSIGN* is Set to "Y"

Scenario 3: Column *TRT ASSIGN* = "TEST"

EDC DATASET NAME	EDC DATASET LABEL	ORDER	VAR. TYPE	VARIABLE NAME	VARIABLE LABEL	SDTM DOMAIN	SDTM VARIABLE	CATEGORY	SUB CATEGORY	DECOD /TRT	TRT ASSIGN
LBCHEM	Local Lab - Chemistry	3	Numeric	GLUCOSE _ORRES	Glucose	LB	LBORRES when LBTESTCD = GLUC			Glucose	TEST
LBCHEM	Local Lab - Chemistry	6	Numeric	BILITOT _ORRES	Total Bilirubin	LB	LBORRES when LBTESTCD = BILI			Bilirubin	TEST
ECHO	Echocardiogra m	3	char	ECHOORRES	Ejection Fraction	FA	FAORRES when FATESTCD = LVEF			Ejection Fraction	TEST
LS	Lugano Staging	4	char	LSSTAGE _STD	Lugano Staging at Study Entry	FA	FAORRES when FATESTCD = STAGE			Lugano Staging at Study Entry	TEST

Table 15. An Example of a Master-Annotation Where *TRT ASSIGN* is Set to "TEST"

Scenario 4: Column *TRT ASSIGN* = "COMBINE"

This is a special case to handle the concatenation of raw dataset variables prior to inclusion in SUPPSV with QNAM = "UNSAPERF" and QLABEL = "Unscheduled Assessments Performed". Please refer to APPENDIX 3 in [8] for the resulting SAS code.

EDC DATASET NAME	EDC DATASET LABEL	ORD.	VAR. TYPE	VARIABLE NAME	VARIABLE LABEL	SDTM DOMAIN	SDTM VARIABLE	QLABEL	QORIG	TRT ASSIGN
UV	Unscheduled Subject Visit	15	Numeric	EG	ECG	SV	UNSAPERF in SUPPSV	Unscheduled Assessments Performed	CRF	COMBINE
UV	Unscheduled Subject Visit	32	Numeric	CHEM	Local Lab Chemistry	SV	UNSAPERF in SUPPSV	Unscheduled Assessments Performed	CRF	COMBINE
UV	Unscheduled Subject Visit	33	Numeric	COAG	Local Lab Coagulation	SV	UNSAPERF in SUPPSV	Unscheduled Assessments Performed	CRF	COMBINE
UV	Unscheduled Subject Visit	35	Numeric	HEM	Local Lab Hematology	SV	UNSAPERF in SUPPSV	Unscheduled Assessments Performed	CRF	COMBINE
UV	Unscheduled Subject Visit	37	Numeric	PG	Local Lab Pregnancy Test	SV	UNSAPERF in SUPPSV	Unscheduled Assessments Performed	CRF	COMBINE
UV	Unscheduled Subject Visit	51	Numeric	VS	Vital Signs	SV	UNSAPERF in SUPPSV	Unscheduled Assessments Performed	CRF	COMBINE

Table 16. An Example of a Master-Annotation Where *TRT ASSIGN* is Set to "COMBINE"

Scenario 5: Column *TRT ASSIGN* specifies a subset condition.

This is another special case to output raw dataset variables to supplemental datasets per a subset condition. In the example below (Table 17), one CRF (Bone Marrow Aspirate/Biopsy – Lymphoma) collects data for both PRTRT = "BONE MARROW ASPIRATION" and PRTRT = "BONE MARROW BIOPSY" in the same record. PR.sas must separate them in SUPPPR for each category; otherwise, there will be duplicate records. Therefore, a condition for the differentiation is added. Display 7 shows the SAS code from PR.sas for generating different SUPPPR data blocks with QLABEL = "Morphology" by adding the condition from the *TRT ASSIGN* column.

EDC DATASET NAME	EDC DATASET LABEL	ORD.	VAR. TYPE	VARIABLE NAME	VARIABLE LABEL	SDTM DOMAIN	SDTM VARIABLE	QLABEL	QORIG	TRT ASSIGN
LBBMLYM	Bone Marrow Aspirate/Biopsy - Lymphoma	4	char	BMAORRES_BMINTP_STD	Morphology	PR	BMINTP in SUPPPR	Morphology	CRF	PRTRT='BONE MARROW ASPIRATION'
LBBMLYM	Bone Marrow Aspirate/Biopsy - Lymphoma	5	char	BMAORRES_IHCRES_STD	IHC Result	PR	IHCRES in SUPPPR	IHC Result	CRF	PRTRT='BONE MARROW ASPIRATION'
LBBMLYM	Bone Marrow Aspirate/Biopsy - Lymphoma	7	char	BMAORRES_DISSTATE_STD	Evidence Of Disease	PR	DISSTATE in SUPPPR	Evidence of Disease	CRF	PRTRT='BONE MARROW ASPIRATION'
LBBMLYM	Bone Marrow Aspirate/Biopsy - Lymphoma	11	char	BMBORRES_BMINTP_STD	Morphology	PR	BMINTP in SUPPPR	Morphology	CRF	PRTRT='BONE MARROW BIOPSY'
LBBMLYM	Bone Marrow Aspirate/Biopsy - Lymphoma	12	char	BMBORRES_IHCRES_STD	IHC Result	PR	IHCRES in SUPPPR	IHC Result	CRF	PRTRT='BONE MARROW BIOPSY'
LBBMLYM	Bone Marrow Aspirate/Biopsy - Lymphoma	14	char	BMBORRES_DISSTATE_STD	Evidence Of Disease	PR	DISSTATE in SUPPPR	Evidence of Disease	CRF	PRTRT='BONE MARROW BIOPSY'

Table 17. An Example of a Master-Annotation Where *TRT ASSIGN* Specifies a Subset Condition

```
if not missing(BMAORRES_BMINTP_STD) and PRTRT='BONE MARROW ASPIRATION' then do;
     qnam='BMINTP';
     qlabel='Morphology';
     qval=strip(BMAORRES_BMINTP_STD);
     qorig='CRF';
     qeval='';
     output;
end;
if not missing(BMBORRES_BMINTP_STD) and PRTRT='BONE MARROW BIOPSY' then do;
     qnam='BMINTP';
     qlabel='Morphology';
     qval=strip(BMBORRES_BMINTP_STD);
     qorig='CRF';
     qeval='';
     output;
end;
```

Display 7. SAS Code From *PR*.sas for Generating Different SUPPPR Data Blocks With QLABEL = "Morphology"

INTRODUCTION TO MASTER-ANNOTATION COLUMN *GRPID*

For findings domains, we often see cases where a raw dataset collects multiple types of findings horizontally within the same record. However, for SDTM, that horizontal dataset is converted to a vertical format with one type of finding per record. To account for these blocks of data, we added *GRPID* to the master-annotation to indicate which variables need to be grouped together. ***%SDTM_Code_Generator*** utilizes *GRPID* to output different blocks for different values of *GRPID*. Table 18 shows an example of a master-annotation where *GRPID* aids SDTM automation. The same CRF SCTPOST ("Stem Cell Transplant Post Treatment") collects data from both "Autologous Stem Cell Transplant" and "Allogeneic Stem Cell Transplant". Display 8 shows SAS code from PR.sas that correctly maps the two different transplant types into two separate blocks.

EDC DATASET NAME	EDC DATASET LABEL	ORDER	GRPID	VARIABLE TYPE	VARIABLE NAME	VARIABLE LABEL	SDTM DOMAIN	SDTM VARIABLE
SCTPOST	Stem Cell Transplant Post Treatment	1	1			Autologous Stem Cell Transplant	PR	
SCTPOST	Stem Cell Transplant Post Treatment	2	1	char	SCTAUTOYN_STD	Autologous Stem Cell Transplant Post	PR	[NOT SUBMITTED]
SCTPOST	Stem Cell Transplant Post Treatment	3	1	Date	SCTAUTODAT	Date of Autologous Stem Cell Transplant	PR	PRSTDTC
SCTPOST	Stem Cell Transplant Post Treatment	4	1	char	SCTAUTOREL_STD	Progressed/Relapsed After the Transplant	PR	RELAPYN in SUPPPR
SCTPOST	Stem Cell Transplant Post Treatment	5	1	Date	SCTAUTORELDAT	Date of Progression/Relapse	PR	RELAPDTC in SUPPPR
SCTPOST	Stem Cell Transplant Post Treatment	6	2			Allogeneic Stem Cell Transplant	PR	
SCTPOST	Stem Cell Transplant Post Treatment	7	2	char	SCALLOTYN_STD	Allogeneic Stem Cell Transplant After	PR	[NOT SUBMITTED]
SCTPOST	Stem Cell Transplant Post Treatment	8	2	Date	SCTALLODAT	Date of Allogeneic Stem Cell Transplant	PR	PRSTDTC
SCTPOST	Stem Cell Transplant Post Treatment	9	2	char	SCTALLOPREL_STD	Progressed/Relapsed After the Transplant	PR	RELAPYN in SUPPPR
SCTPOST	Stem Cell Transplant Post Treatment	10	2	Date	SCTALLORELDAT	Date of Progression/Relapse	PR	RELAPDTC in SUPPPR

Table 18. An Example of a Master-Annotation Where *GRPID* Indicates the Variables That Need Grouping

```
if strip(SCTAUTOYN_STD)='Y' and _SCTPOST then PRCAT='STEM CELL TRANSPLANT POST-CTX112 TREATMENT';
if strip(SCTAUTOYN_STD)='Y' and _SCTPOST then PRTRT='AUTOLOGOUS STEM CELL TRANSPLANT';
%map_dtc_date(_DATEVAR=PRSTDTC,_RAWDATE=SCTAUTODAT);
if _SCTPOST and not missing(PRSTDTC) then output;

call missing (PRCAT,PRTRT,PRSTDTC);
if strip(SCALLOTYN_STD)='Y' and _SCTPOST then PRCAT='STEM CELL TRANSPLANT POST-CTX112 TREATMENT';
if strip(SCALLOTYN_STD)='Y' and _SCTPOST then PRTRT='ALLOGENIC STEM CELL TRANSPLANT';
%map_dtc_date(_DATEVAR=PRSTDTC,_RAWDATE=SCTALLODAT);
if _SCTPOST and not missing(PRSTDTC) then output;
```

Display 8. SAS Code from PR.sas With Two Separate Blocks for Mapping Data From "Autologous Stem Cell Transplant" and "Allogeneic Stem Cell Transplant"

RATIONALE FOR THE STRUCTURE OF THE MASTER-ANNOTATION SPREADSHEET

From the examples above, it is easy to understand that the master-annotation provides the macro with directions to directly map raw dataset variables to SDTM variables. The key variables/columns specified in Table 10 are the "pillars" of the macro, and SDTM standards are the "rules/logic" to be followed. The macro uses all of these to generate SAS code. The relevant rows of the master-annotation are processed by the macro to generate the SAS code for each SDTM mapping SAS program. However, the "pillars" and "rules/logic" are seldom changed (except for the up-versioning of the SDTMIG) while the rows of the master-annotation change from study to study. Once the macro is very well developed, it can be adapted for other studies with some new or updated directions while keeping most of the existing framework.

However, the master-annotation must be updated to account for new study CRFs. This update can lead to macro modifications to incorporate new additional domains or new annotations due to CRF changes intended to meet a new requirement, which can occur constantly in oncology studies. For example, SDTM TR domain (Tumor/Lesion Results) is applied to both liquid tumor studies and solid tumor studies. However, the lesion assessments for these two types of oncology studies have totally different data collection, leading to different CRFs and annotations.

The vertical structure of raw dataset variable names and their attributes in a master-annotation provides the macro with an advantage over SDTM mapping templates. The macro uses a single column ***VARIABLE NAME*** to read each raw dataset variable name one by one to generate a SDTM SAS program for a domain. When the raw dataset variable names change, there is very little impact on the macro as the changes are automatically reflected in the master-annotation's *VARIABLE NAME* column. In contrast, raw dataset variable name changes have a negative impact on SDTM mapping templates as the user needs to manually update variable names within a template program. This further shows a benefit of this new approach.

Furthermore, all SDTM variables and their annotations are more accessible to users in the form of the master-annotation spreadsheet compared to an annotated case report form (aCRF). Users can utilize spreadsheet functionalities, such as sorting and filtering, to quickly locate specific variables and their annotations. Users can easily review variables for a specific form or SDTM domain without needing to scroll through or go back and forth between multiple pages of an aCRF. This master-annotation spreadsheet is not only a wonderful tool for SDTM automation and programming but can also serve as a great resource for ADaM programming.

BALANCING BETWEEN HIGH LEVEL AUTOMATION FROM A MACRO AND COST/TIMELINES

Due to the dissimilarity and varying complexity of different CRFs from different studies, it is an unreasonable expectation that the macro can achieve 100% automation for different studies, even if these studies are from same compound within the same company.

The more standardized CRFs and raw dataset variable attributes become, the higher the level of automation that can be achieved from the macro! While that standardization is the best practice, it requires much more work to achieve. Even with a high degree of standardization, there are still minor deviations in clinical trials.

The challenging question is what the expected level of automation is and what cost the organization is willing to pay–the cost being the risk of missing timelines and the amount of resource investment. Striking the right balance is vital to the team for short-term and long-term achievement. The more the macro development aims to future-proof, the more time and resources it will take. If the development of the macro were only dedicated to the current study, it would require fewer resources and could meet the timelines. In our case, 100% automation is not expected, and the output SAS programs can still be modified and updated by the users, especially for handling external datasets. This requires less effort to develop the macro and makes it easier to meet the timelines, and the simplicity of the macro makes it easily adaptable for new studies as well. This is our strategic approach with an adaptive mindset! This approach is very feasible for relatively small sponsors and CROs, who have fewer resources and tight timelines, for there is no requirement of huge efforts to standardize CRFs or raw dataset variable attributes nor any requirement of expertise in other computer languages, such as Structured Query Language (SQL) for script creation. This is the reason why our paper is titled as “***A Practical Approach to Automating SDTM***”.

HOW TO HANDLE EXTERNAL DATASETS

A clinical trial usually has some external data, e.g., central safety lab, biomarkers, imaging data (MRI/CT, PET scan) from Central Imaging Services, etc. They are typically stored outside the EDC database, and their metadata are specified by Data Transfer Agreements (DTA) from different vendors. The finalization of DTAs and the first data transfer usually come much later than the first EDC raw data extract.

The approach in this paper focuses on dealing with CRF data, not external data. The main reasons to exclude external data for SDTM automation are the timing of its availability (for both metadata and actual data) and simplifying the development of the macro to balance the level of automation with the cost of meeting timelines.

Once the DTAs are finalized and the external data are available, the related SDTM mapping SAS programs can be updated by inserting some code to the existing SAS programs for the inclusion of external data. Please refer to [8] for an example of how external data are handled for the subject visits (SV) domain programming.

When the external datasets are ready for inclusion, the team can decide if the new programming should be added to either the ***%SDTM_Code_Generator*** or the related individual SDTM SAS program. The decision requires balancing the generalization of the macro for future use with the spending of more time/resources in updating the macro and its potential impact of timelines.

HOW TO LEVERAGE THE EXISTING MASTER-ANNOTATION FOR A NEW STUDY

One can leverage the existing master-annotation as an automation template for new studies. We will explain the process from our working experience with two oncology studies.

We completed SDTM programming for two studies, and their EDC databases were both built by Medidata's Rave. Let us name them as Study-101 and Study-102, respectively.

SDTM programming for Study-101 was first completed at the very early stage of the study. Hence, its master-annotation-101.xlsx and ***%SDTM_Code_Generator*** had been fully developed. Before starting to work on SDTM automation for Study-102, we compared its ALS with Study-101's and got the following five output files shown in Table 19.

Output File Name	Output File Label	Function
F1	Common variable names from common datasets	Identify discrepancies in variable attributes, which could potentially impact the macro for Study-102. e.g., the raw dataset variable IE.IETESTCD is a character variable in Study-101 but numeric in Study-102. Raw dataset variable IETESTCD being numeric is problematic for SDTM programming since IETESTCD is a standard SDTM variable that should be character.
F2	All variable names only included in Study-101	Identify variables potentially being omitted from Study-102. e.g., Raw variables UV.UVREAS and UV.UVREAS_O ("Reason for Unscheduled Visit" and "Other, Specify") were in Study-101 but not in Study-102.
F3	All variable names only included in Study-102	Identify variables that need new annotations. e.g., CM.CMDOSFRM, ICE.ICETOTAL ("ICE Total Score") were added to the CM and ICE forms in Study-102.
F4	All variable names only included in Study-101 among common datasets	Identify variables with different variable names from the same CRF. e.g., ICE.IAYN ("Was ICE Assessment performed?") from Study-101 vs. ICE. ICEPERF from Study-102.
F5	All variable names only included in Study-102 among common datasets	

Table 19. Five Outputs from the Comparison of ALSs between These Two Studies

Per these five files, the summary tables are shown by Table 20 and Table 21, which show the similarities (same CRF names and same variable names from the same CRF) and dissimilarities of CRFs for these two studies. Out of 80 CRFs in Study-101 and 67 CRFs in Study-102, there were 50 common CRFs between the two studies, and a sample of these common forms is shown in Table 22. Not surprisingly, they are from standard safety domains.

Study Number	Number of CRFs	Number of Common CRFs	Number and Percentage of Unique CRFs	Total Number of Variables
Study-101	80	50 (62.5%)	30 (37.5%)	906
Study-102	67	50 (74.6%)	17 (25.4%)	678

Table 20. Tabulation of CRFs From Two Studies

Study	Total Number of Variables	Number and Percentage of Common Variables	Number and Percentage of Unique Variables
Study-101	906	410 (45%)	496 (55%)
Study-102	678	410 (60%)	268 (40%)

Table 21. Tabulation of CRF Variables From Two Studies

EDC DATASET NAME	EDC DATASET LABEL	SDTM DOMAIN
AE	Adverse Events	AE
CM	Prior and Concomitant Medications	CM
DM	Demographics	DM
ECHO	Echocardiogram / MUGA	FA
EG	12- Lead ECG - Single Timepoint	EG
EN	Enrollment	DS
EOS	End of Study	DS
IC	Informed Consent	DS
IE	Inclusion and Exclusion	IE
MH	Medical History	MH
SS	Survival Status	SS
SUBJ	Subject Registration	DM
VS	Vital Signs	VS

Table 22. Examples of Common CRFs From Two Studies

The **EDC DATASET NAME** (*FormOID*) and **VARIABLE NAME** (*FieldOID*) were combined as the key to merge the ALS of Study-102 with master-annotation-101.xlsx, bringing in the other columns (CRF annotations and other variables as specified in Table 10) of master-annotation-101.xlsx for CRFs and variable names that were common to these two studies. This newly augmented file was used as a starting point to complete master-annotation-102.xlsx, and users only needed to fill in the other columns (e.g., CRF annotations) for new CRFs and variables that were unique to Study-102. Table 23 below shows an example of master-annotation-102.xlsx with the first column indicating the variables that need additional manual work to complete their master-annotation record.

Need New Annotation	EDC DATASET NAME	SDTM DOMAIN	EDC DATASET LABEL	Order	VARIABLE NAME	VARIABLE LABEL	SDTM VARIABLE
	EN	DS	Enrollment	1	ENRSF_STD	Was Subject Enrolled?	[NOT SUBMITTED]
	EN	DS	Enrollment	3	ENRDAT	Enrollment Date	DSSTDTC
	EN	DS	Enrollment	4	ENPHASE_STD	Study Phase	PHASEENR in SUPPDS
	EN	DS	Enrollment	5	ENPART_STD	Study Part	PARTENR in SUPPDS
Y	EN	DS	Enrollment	6	ENCOHRT_STD	Study Cohort	COHORT in SUPPDS
	EN	DS	Enrollment	8	ENSFDAT	Screen Fail Date	DSSTDTC
	EN	DS	Enrollment	9	ENRSP_STD	Screen Failure Reason	DSTERM
	EN	DS	Enrollment	10	ENRESCR_STD	Was Subject Re Screened?	SUBJRESC in SUPPDS
	ECHO	FA	Echocardiogram / MUGA	1	ECHOYN_STD	Was ECHO or MUGA performed?	[NOT SUBMITTED]
Y	ECHO	FA	Echocardiogram / MUGA	2	ECHOMETH_STD	If Yes, method of assessment performed?	ECHOMETH in SUPPFA
	ECHO	FA	Echocardiogram / MUGA	3	ECHODAT	Test Date	FADTC
	ECHO	FA	Echocardiogram / MUGA	4	ECHOORRES	Ejection Fraction	FAORRES when FATESTCD = LVEF
	ECHO	FA	Echocardiogram / MUGA	5	ECHOORESU_STD	Ejection Fraction Units	FAORRESU

Table 23. An Example of Master-Annotation-102.xlsx

Per Table 21, we had 410 variables that were in both Study-101 and Study-102 and 268 variables unique to Study-102 that needed manual work to complete master-annotation-102.xlsx. Thus, 60% of all variables for Study-102 were “borrowed” from Study-101, and only 40% of the variables required extra manual work for master-annotation completion. (The majority of that 40% was from the CRFs for efficacy data.) By utilizing the existing master-annotation for Study-101, huge time savings and high efficiency were achieved for Study-102! Higher standardization of CRFs could contribute to even more high-quality programming efficiency across studies!

HOW TO LEVERAGE THE EXISTING %SDTM_CODE_GENERATOR FOR A NEW STUDY

For a new study, once the master-annotation and SDTM specifications are finalized by leveraging the method introduced in the previous section, ***%SDTM_Code_Generator*** can then be adapted to the new study for SDTM automation.

The five outputs from Table 19 should be carefully reviewed. The SAS code for ***%SDTM_Code_Generator*** should be carefully checked for mentions of the variables identified from the review, especially those from F1, F4, and F5 which could potentially require some SAS coding updates. Special attention should also be paid to the variables flagged as “***Need New Annotation***” from F3 (see Table 23 for some examples) as these might require updates to the macro’s SAS code. Variables from F2 should not have any impact.

The macro’s output files (i.e., SDTM mapping SAS programs) should also be carefully reviewed, especially for SAS code pertaining to variables in F3. The programming validation process should be strictly followed. Please refer to the following section for the scalability of this new approach.

Our working experience is that there was almost no change of the macro for the safety domains (except for IEDTC in IE.sas due to the difference between two EDC database builds), but some changes had been made to the efficacy domains such as RS, TR, and TU. While we were finalizing the macro for the second study, we also updated the macro for the first study to make it more generalized to both studies. It has been an adaptive process.

INTRODUCTION TO THE SCALABILITY OF OUR NEW PRACTICAL APPROACH

So far, we have illustrated this new practical approach to automating SDTM. For the first study, one needs to develop the master-annotation spreadsheet (but can leverage existing CRF specifications) and the ***%SDTM_Code_Generator*** macro from scratch. However, it is still a more efficient and less error-prone process than the SAS template programs suggested in Table 1. Once one has fully developed the master-annotation and macro for a clinical study, one can adapt them for new studies.

The ease of adaptability depends on the similarity of CRF designs and specifications of new studies compared to the first study. Table 24 below lists different scenarios of what new studies' EDC or CRF setup may be like relative to the first study.

Scenario of A New Study Per An EDC Vendor	**CRF Specifications of An EDC Database**	**Similarity and Dissimilarity of Safety and Efficacy Data**
Same EDC vendor	Similar CRF Specifications	Similar CRF designs and CRF specifications for safety data but dissimilar CRF specifications for efficacy data if different indications
		Similar CRF designs and CRF specifications for both safety data and efficacy data if the same indication
Different EDC vendors	Different CRF Specifications	Similar CRF design for safety data but dissimilar CRF design for efficacy data if different indications
		Similar CRF design for both safety data and efficacy data if the same indication

Table 24. Different Scenarios of a New Study's EDC or CRF Setup

In the case where new studies use the same EDC vendor, we'd expect CRF form design and specifications to be relatively similar, especially for safety data. Thus, we can easily leverage and adapt the existing master-annotation and ***%SDTM_Code_Generator*** for those new studies. Table 25 provides suggestions on how to adapt our SDTM automation tools for new studies with similar CRF specifications due to using the same EDC vendor.

Scenario of A New Study	**Master-Annotation**	***%SDTM_Code_Generator***
Similar CRF Specifications for safety data but dissimilar CRF design for efficacy data	Leverage the existing master-annotation from the first study	Add new programming to account for new/different efficacy data
Similar CRF Specifications for both safety data and efficacy data		May need a little tweaking

Table 25. Suggestions for Adaptation to New Studies With EDC Databases Built by the Same Vendor

In the case where new studies use a different EDC vendor, we'd expect CRF form design to be somewhat similar but the actual CRF specifications to be different. More manual work will need to be done to update the SDTM automation tools, in particular the master-annotation spreadsheet, to account for the different CRF specifications. Table 26 provides suggestions on how to adapt our SDTM automation tools for new studies with different CRF specifications due to using different EDC vendors.

Scenario of A New Study	**Master-Annotation**	***%SDTM_Code_Generator***
Different CRF Specifications: Similar CRF design for safety data but dissimilar CRF design for efficacy data	Consider as a new study. Leverage CRF specifications and annotations for master-annotation. However, need to manually fill in key columns from Table 10 where the origin is not "ALS".	Add new programming to account for new/different efficacy data
Different CRF Specifications: Similar CRF design for both safety data and efficacy data		May need a little tweaking

Table 26. Suggestions for Adaptation to New Studies With EDC Databases Built by Different Vendors

INTRODUCTION TO OUR VALIDATION PROCESS FOR SDTM PROGRAMMING

The development of ***%SDTM_Code_Generator*** starts only after CRF annotations and SDTM specifications pass the review and validation process as they are the inputs of the macro as shown in Figure 2.

The traditional approach for SDTM dataset validation requires programmers to develop an independent mapping SAS program. This double programming requires more resources and time since it essentially doubles development efforts.

Our SDTM programming validation consists of the following three steps: code reviewing, real data testing, and developing independent mapping SAS programs to validate relatively complicated SDTM datasets as needed per the team's decision. This validation process validates both the macro and each SDTM mapping SAS program. Figure 4 below depicts the new validation process.

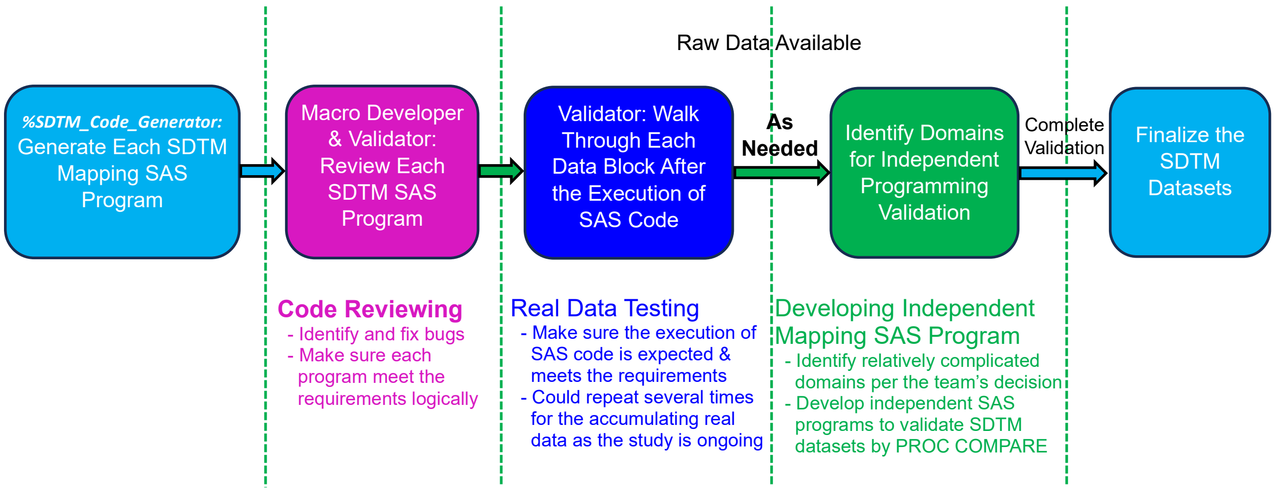

%SDTM_Code_Generator: Generate Each SDTM Mapping SAS Program
Macro Developer & Validator: Review Each SDTM SAS Program
Validator: Walk Through Each Data Block After the Execution of SAS Code
Raw Data Available
As Needed
Identify Domains for Independent Programming Validation
Complete Validation
Finalize the SDTM Datasets
Code Reviewing
- Identify and fix bugs
- Make sure each program meet the requirements logically
Real Data Testing
- Make sure the execution of SAS code is expected & meets the requirements
- Could repeat several times for the accumulating real data as the study is ongoing
Developing Independent Mapping SAS Program
- Identify relatively complicated domains per the team's decision
- Develop independent SAS programs to validate SDTM datasets by PROC COMPARE

Figure 4. The Logic Flow of Our SDTM Programming Validation Process

When each SDTM mapping SAS program (e.g., DM.sas) is generated from the macro call, the macro developer and users work together to review the code to identify bugs before the testing phase until they make certain that the coding logic meets domain requirements.

Once raw data are available, each SDTM mapping SAS program is tested by using real data. Users walk through each data block to make sure that the execution is as expected and meets the requirement. This step also includes retesting after bug fixing, and this could repeat several times for the accumulating real data while the study is ongoing until the user ensures that the SAS program is thoroughly tested and meets the requirements of the domain.

The team also identifies and decides which SDTM domains need traditional totally independent programming validation. For example, the TR (Tumor/Lesion Results) domain from one study included data from 13 CRFs, which had 190 variables in total (Table 27), so we developed an independent SAS program to validate the TR domain.

CRF Name	EDC Raw Data Label
INL	Lesion Assessment - New Lesion - CLL/SLL
INTL1	Lesion Assessment - Non-Target Lesions - Baseline - CLL/SLL
INTL2	Lesion Assessment - Non-Target Lesions - Post-Baseline - CLL/SLL
ITL1	Lesion Assessment - Target Lesions - Baseline - CLL/SLL
ITL2	Lesion Assessment - Target Lesions - Post-Baseline - CLL/SLL
NL	Lesion Assessment - New Lesion
NTL1	Lesion Assessment - Non-Target Lesions – Baseline
NTL2	Lesion Assessment - Non-Target Lesions - Post-Baseline
ORG	Organ Enlargement Assessment
PET1	PET Scan- Baseline
PET2	PET Scan- Post-Baseline

CRF Name	EDC Raw Data Label
TL1	Lesion Assessment - Target Lesions - Baseline
TL2	Lesion Assessment - Target Lesions - Post-Baseline

Table 27. An Example of 13 Source CRFs for the TR Domain

Solid SDTM programming expertise and working experience from the macro developer and the users can shorten the development process and is the key to high quality delivery of SDTM datasets. This new approach to automating SDTM is user-friendly as users can directly review the output code (instead of facing a "black box") and test it with real data, ensuring that each SDTM dataset they produce is of the highest quality. Since only a fraction of SDTM datasets need independently developed SAS programs for programming validation, a lot of time and resources are saved compared to the traditional way of validating all SDTM datasets or the situation where a sponsor must have an in-house or outsourced SDTM programming team independently develop SDTM SAS programs to validate the automated SDTM datasets provided by vendors.

HOW TO GUARANTEE ALL RAW DATASET VARIABLES ARE MAPPED INTO SDTM

How does one avoid accidental omissions of raw dataset variables from SDTM, which would be a failure of SDTM programming? Given limited resources and timelines, it is not feasible to manually review each raw dataset variable against the targeted SDTM SAS mapping program(s). Therefore, automation to detect these omissions is the key to the solution for success. Once the omitted variables are detected, the errors can be fixed. Hence, this step guarantees all raw dataset variables are accounted for in SDTM programming.

Another functionality of the macro ***%SDTM_Code_Generator*** is that it can automatically detect any raw dataset variables unmapped in SDTM. As mentioned in an earlier section, the SAS code generated by our macro is saved in a SAS dataset before it is output to a SDTM mapping SAS program. This SAS dataset contains all variables from the master-annotation specified in Table 10 in addition to the previously mentioned *lines* and *_order* variables. Each call of the macro merges this dataset with the master-annotation by *EDC DATASET NAME* and *VARIABLE NAME* for a specific domain. Any records that have non-missing values for *EDC DATASET NAME* and *VARIABLE NAME* but are missing *lines* are warning signs that those raw dataset variables may not have been mapped or included in the SDTM mapping SAS program. One exception would be the records where *SDTM VARIABLE* = “[NOT SUBMITTED]”, which marks raw dataset variables that are intentionally not submitted. Table 28 shows an example of raw dataset variable AENOW from the AE form, whose omission was detected by the macro. However, as indicated by its *SDTM VARIABLE* column, AENOW was intentionally not mapped to any SDTM datasets.

EDC DATASET NAME	EDC DATASET LABEL	VARIABLE NAME	VARIABLE LABEL	SDTM DOMAIN	SDTM VARIABLE
AE	Adverse Events	AENOW	Form last updated (derived for edit check)	AE	[NOT SUBMITTED]

Table 28. An Example of Raw Dataset Variable(s) That Are Not Mapped to SDTM AE as Identified by *%SDTM_Code_Generator*

HOW TO HANDLE EDC DATABASE CHANGES

It is very typical for the EDC database to change due to a variety of reasons, such as protocol changes, EDC database build errors, etc. The newly updated ALS or CRF specifications are provided along with a document, such as a “**Database Change Request Form**”. The simple solution is to use SAS programming to compare the new CRF specifications to the original one. The output file can help the team pinpoint the changes to examine the impact on SDTM programming. The worst-case scenario is to consider it as a new study. The previous sections present how to leverage the existing master-annotation and ***%SDTM_Code_Generator*** for a new study.

We experienced a situation where one study’s ALS was updated three months after the EDC database was in place. The comparison between these two ALS files showed that two safety lab tests had been added and one variable’s label had been changed. We manually added these tests into master-annotation and reran the macro to generate LB.sas. After reviewing the mapping sections for these two tests in the output LB.sas and confirming that they met our requirements, we finished our update process for SDTM LB programming.

This is another example that further illustrates what a powerful tool CRF specifications are for SDTM automation.

HOW TO HANDLE THE SITUATION WHERE CRF SPECIFICATIONS FROM AN EDC DATABASE ARE UNAVAILABLE

As introduced above, CRF specifications from an EDC database (or an ALS) serve as the repository of all raw dataset names and their variable attributes in a study. If the CRF specifications from an EDC database or the ALS were not available for any reason, one would need to use the SAS PROC CONTENTS or PROC DATASETS procedure to retrieve the metadata from the validated test data or the first production transferred data. However, there are typically a lot of variables beyond those collected on CRFs, e.g., intermediate variables dedicated to database setup. Hence, one would have to spend some time in manually identifying which variables should be included in a file serving as simulated CRF specifications by cross-checking CRF annotations one-by-one. Once the simulated CRF specifications are finalized, one can generate a master-annotation spreadsheet and follow the approach introduced in the previous sections for SDTM automation.

CONCLUSION

This paper presented a new approach to automating SDTM using a metadata-driven method that leverages CRF specifications and SDTM standards. We compared the workflow between our new approach and the standard one. We introduced our master-annotation spreadsheet, which leverages CRF specifications from an EDC database (in particular, the Architect Loader Specification of Medidata’s Rave EDC), and our macro ***%SDTM_Code_Generator***. We discussed our experience on two different types of oncology studies and demonstrated the practicality of our new approach through its efficiency, flexibility, transparency, and scalability.

We are confident that the macro will become more mature as our new approach is applied to more studies down the road. The intent of this presentation is to share our ideas with readers to aid them in automating SDTM with much more efficiency and higher quality that is applicable across multiple clinical studies within an organization.

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APPENDIX 1. SUMMARY OF MACROS CALLS USED BY *%SDTM_CODE_GENERATOR*

SDTM Variable	Macro Name	Description	SDTM Domains	Example Macro Call
--DTC	map_dtc_date and map_dtc_time	Derive –DTC variables when there are partial dates	All Domains except for DM and SV	%map_dtc_date(_DATEVAR=AESTDTC,_RAWDATE=AESTDAT); %map_dtc_time(_DATEVAR=AESTDTC,_RAWTIME=AESTTIM);
RACE, RACE1, …, RACE5	map_race	Derive RACE variables for DM and SUPPDM	DM, SUPPDM	%map_race(_NUMFL=Y,_VAR=RACE1 RACE2 RACE3 RACE4 RACE5 RACE6);
--SEQ	get_seq	Derive --SEQ variables based on provided key variables	AE, CE, CM, DS, EG, EX, FA, HO, IE, LB, MH, PC, PR, QS, SS, VS	%get_seq(_DOMAIN=LB,_SORTKEYS=STUDYID USUBJID LBCAT LBTESTCD VISITNUM LBDTC);
--DY	get_dy	Derive --DY variables based on provided --DTC variables	AE, CE, CM, DS, EG, EX, FA, HO, IE, LB, MH, PC, PR, QS, SS, VS	%get_dy(_DATEVAR=LBDTC,_DAYVAR=LBDY);
--LOBXFL	get_lobxfl	Derive the Last Observation Before Exposure Flag	EG, FA, LB, PC, QS, VS	%get_lobxfl(_DATEVAR=LBDTC,_DAYVAR=LBDY,_DOMAIN=LB, _LASTVAR=LBTESTCD,_RESVAR=LBSTRESN, _SORTVARS=USUBJID LBCAT LBTESTCD LBDTC);
--BLFL	get_blfl	Derive the Baseline Flag	EG, FA, LB, PC, QS, VS	%get_blfl(_DATEVAR=LBDTC,_DAYVAR=LBDY,_DOMAIN=LB, _LASTVAR=LBTESTCD,_RESVAR=LBSTRESN, _SORTVARS=USUBJID LBCAT LBTESTCD LBDTC);
RFSTDTC	get_rfstdtc	Derive RFSTDTC	DM	%get_rfstdtc(_DATA=EX1 EX2 EX3,_DATEVAR=EX1STDAT EX2STDAT EX3STDAT, _SUBJVAR=SUBJECT,_TIMEVAR=EX1STTIM EX2STTIM EX3STTIM);
RFENDTC	get_rfendtc	Derive RFENDTC	DM	%get_rfendtc(_DATA=EX1 EX2 EX3,_DATEVAR=EX1ENDAT EX2ENDAT EX3ENDAT, _SUBJVAR=SUBJECT,_TIMEVAR=EX1ENTIM EX2ENTIM EX3ENTIM);
RFXSTDTC	get_rfxstdtc	Derive RFXSTDTC	DM	%get_rfxstdtc(_ASSIGN=RFSTDTC,_DATA=,_DATEVAR=,_SUBJVAR=,_TIMEVAR=);
RFXENDTC	get_rfxendtc	Derive RFXENDTC	DM	%get_rfxendtc(_ASSIGN=RFENDTC,_DATA=,_DATEVAR=,_SUBJVAR=,_TIMEVAR=);
RFPENDTC	get_rfpendtc	Derive RFPENDTC	DM	%get_rfpendtc(_CUTOFFDT=&cutoffdt.,_DATEVAR=EOSDAT);
TRT	get_trt	Derive ARM-related variables in DM	DM	%get_trt(_DRGCRIT=not missing(EX3STDAT),_DRGDATA=EX3, _SFCRIT=ENRSF_STD='N',_SFDATA=EN,_SUBJVAR=SUBJECT);
AETRTEM	get_aetrtem	Derive the TEAE Flag to be included in SUPPAE	SUPPAE	%get_aetrtem();
IEDTC	get_dtc_dov	Derive --DTC using date of visit from raw data when a specific form is missing a date field	IE	%get_dtc_dov(_DATEVAR=IEDTC,_DOVDATA=SV,_DOVDATE=VISDAT, _SORTVARS=SUBJECT FOLDER);