

A Regulatory Submission “DEFINE”d: The Who, Where and What

Robby Diseker, PPD, Wilmington, NC

Lindsay Dean, PPD, Wilmington, NC

ABSTRACT

A statistical SAS programmer assigned to work on a regulatory submission may not be aware of the scope of work involved. This could be particularly true where there may be teams assigned to each particular task involved in preparing a submission where only a few leaders might grasp the overall scope of work. This paper covers three basic elements of the FDA’s electronic submission format: 1) The Common Technical Document (eCTD), 2) the electronic case report tabulation (eCRT) and 3) the integrated study. The primary objective of this paper is to serve as an overview of where and what we are submitting, provide examples of the functionality of an eCRT and examples of subject profiles, as well as identifying key strategies for developing an integrated study including unifying structure and content, mapping datasets, variables, and formats, and unifying dictionary coding.

INTRODUCTION

The primary objective of this paper is to serve as an overview of where and what we are submitting to regulatory agencies for new drug applications. We will provide a background of the common technical document and examples of the primary deliverables produced in the biostatistics department, including the electronic case report tabulation known as the “Define” document and subject profiles. Also, key strategies for developing an integrated study will be discussed, including unifying structure and content, mapping datasets, variables, and formats, and unifying dictionary coding. People are generally better able to contribute when they are well informed. With a better understanding of what is involved in a regulatory submission from the biostatistics point of view, the SAS programmer can be more effective in contributing to the success of the final submission.

THE COMMON TECHNICAL DOCUMENT

One of the first steps in beginning submission work is to determine who, where and what to submit. There are four regions for submission that we regularly engage: USA, European Union, Australia, and Japan. In the USA, we submit to the US Department of Health and Human Service, Federal Drug Administration (FDA). Two of the common centers within the FDA that we submit to are the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER). When working with the European Union we submit to the European Agency for the Evaluation of Medicinal Products (EMA), the Human Medicines Evaluation Unit. In Australia, submissions go to the Department of Health and Aging, Therapeutic Goods Administration. Finally, in Japan we submit to the Ministry of Health, Labor and Welfare. For the purpose of this paper we will discuss submitting to the FDA, CDER agency.

The submission to CDER will be in the form of the Common Technical Document (CTD or electronic version eCTD.) The eCTD is a collection of documents in the form of datasets, reports, and forms. The eCTD specifications can be found on the FDA website, <http://www.fda.gov> (1). This paper will focus on the eCTD specifications outlined in the FDA Guidance for Industry (April 2006). The eCTD is organized into 5 modules by subject matter:

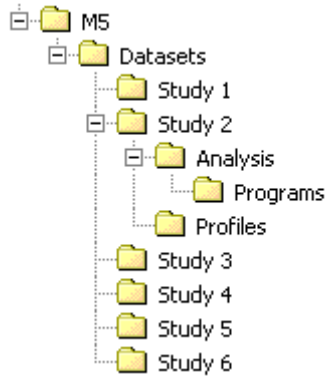
1. Administrative Information and Prescribing
2. Summary Folder (includes data from individual and integrated study Table, Listing and Figures)
3. Quality Folder
4. Safety Folder
5. Clinical Study Reports Folder (where eCRTs are stored)

Module 2 and module 5 are the two areas which require input from the statistical SAS programmer, however this paper will only discuss Module 5.

MODULE 5 OF THE CTD

Module 5 is the Clinical Study Reports folder. This folder is where the Electronic Case Report Tabulations (eCRT) and Subject/Patient Profiles will reside. Table 1 shows an example of the folder structure.

TABLE 1. MODULE 5 FOLDER STRUCTURE.



The eCRT consists of a document known as “Define” which is a bookmarked document containing an annotated Case Report Form (aCRF), datasets in transport format, and a format catalog if available. In the past, PDF has been the standard file type but as of January 2008 the FDA will request XML format for this document. In the Define document there are two types of Data Definition Tables (DDT) needed: the Data Table of Contents (DTC) as well as a DDT for each dataset. The DTC lists all datasets and the type of information contained in each dataset (dataset description) including the structure or unique keys for each dataset (Table 2). In the DTC there are a set of bookmarks with links to the DDT and links to the transport datasets. Transport datasets are required to be in SAS Version 5. This ensures variable names are a maximum of 8 characters, labels are a maximum of 40 characters, and character variables have a max length of 200.

TABLE 2. DATA TABLE OF CONTENTS (DTC), EXAMPLE.

Table of Contents of Data Sets

- Datasets
 - Adverse Events (AE)
 - Protocol Amendment (AMD)
 - Central Laboratory Collection (CLAB)
 - Concomitant Medications (CM)
 - Investigator Comment Log (COM)
 - Inclusion and Exclusion Criteria (CRIT)
 - Demographics (DEMO)
 - Demographics (DEMOGALL)
 - Drug Accountability Log (DLOG)
 - Discontinuation (DS)
 - 12-Lead Electrocardiogram (ECG)
 - Efficacy (EFF)
 - Fasting (FAST)
 - Hypoglycemic Events (HYPO)
 - Interactive Voice Response System (IVRS)
 - Unmasked Kit Schedule (KIT)
 - Laboratory Results (LABDATA)
 - Medical History (MH)
 - Physical Exam (PE)
 - Pharmacokinetic Data (PKDATA)
 - Pharmacokinetic and Pharmacodynamic Data (PKPD)
 - Reproductive Status and Urine Pregnancy Test (RST)
 - Site Examination (SITE)

Datasets for Study XXX-XXX

METHODOLOGY:
A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Determine the Efficacy and Safety of XXX-XXX (SYR-322) When Used in Combination with Metformin in Subjects with Type 2 Diabetes

Dataset	Description	Structure	Location
AE	Adverse Events	One record per subject per adverse event. (keys=PT AETERM AESTDT AEENDT)	AE.xpt
AMD	Protocol Amendment	One record per subject. (keys=PT)	AMD.xpt
CLAB	Central Laboratory Collection	One record per subject per visit. (keys=PT CPEVENT LBDDT)	CLAB.xpt
CM	Concomitant Medications	One record per subject per concomitant medication. (keys=PT CMTERM CMDOSE CMREAS CMSTDT CMENDT)	CM.xpt
COM	Investigator Comment Log	One record per subject per visit per comment. (keys=PT VST SECTION PAGE COMSEQ REPEATSN)	COM.xpt
CRIT	Inclusion and Exclusion Criteria	One record per subject per visit per page. (keys=PT VISIT PAGE)	CRIT.xpt
DEMO	Demographics	One record per subject. (keys=PT)	DEMO.xpt
DEMOGALL	Demographics	One record per subject for all subjects appearing on any data set except IVRS and LABDATA because it also contains screen failures. (keys=PT)	DEMOGALL.xpt
DLOG	Drug Accountability Log	One record per subject per dose. (keys=PT VST DSPER DSPDT RETDT MEDID REPEATSN)	DLOG.xpt

The DDT for each dataset contains all variables within the dataset and specific information about the variable such as variable type, format, and/or algorithm to derive the variable (Table 3). There will be links from the DDT to the aCRF for raw variables (Table 4), the transport datasets (Table 5), the variable decodes or format list (Table 6), as well as links to very detailed algorithms that were created in another dataset (Table 7).

TABLE 3: DATASET DEFINITION TABLE (DDT), EXAMPLE.

Within the DDT, there are links to format decodes, the aCRF page where the variable is first found and derived variable specifications.

Study XXX-XX - AMD Variables (Protocol Amendment)				
Variable	Label	Type	Code	Comments
ACCESSTS	Accessible Time Stamp	Number	8.	See CRF Page 1.
ACTEVENT	Actual Event	Number	8.	Derived by Data Management.
AGE	AGE IN YEARS	Number	8.	Derived. From DEMOGALLAGE .
AGECAT	AGE CATEGORY	Character	\$AGECAT	Derived. From DEMOGALLAGECAT .
AGECATN	AGE CATEGORY 75	Character	\$AGECATN	Derived. From DEMOGALLAGECATN .
AMEND	Amendment Visit Performed Under	Character	\$AMEND	See CRF Page 13A.
BASEDC	BASELINE ADD-ON THERAPY DOSE CATEGORY	Character	\$BASEDC	Derived. From DEMOGALLBASEDC .
BASEDOSE	BASELINE ADD-ON THERAPY DOSE	Number	8.	Derived. From DEMOGALLBASEDOSE .
BASEDT	BASELINE VISIT DATE	Number	DATE9	Derived. From DEMOGALLBASEDT .
BASE_TRT	BASELINE TREATMENT	Character	\$BTRT	Derived. From IVRS.BASE_TRT .
CPEVENT	CPE Name	Character	\$20.	See CRF Page 1.
DCMNAME	DCM Name	Character	\$16.	See CRF Page 1.
DCMSUBNM	DCM Subset Name	Character	\$8.	See CRF Page 1.
DMRCTX	Specify Other Race	Character	\$50.	Derived. From DEMO.DMRCTX .
DURDBY	DURATION OF DIABETES (YEARS)	Number	8.	Derived. From DEMOGALLDURDBY .
ETHNIC	Ethnicity	Character	\$ETHNIC	Derived. From DEMO.ETHNIC .
FSDOSDT	FIRST STABILIZATION DOSE DATE	Number	DATE9	Derived. From DEMOGALLFSDOSDT .

TABLE 4: ANNOTATED CASE REPORT FORM, EXAMPLE.

Variables collected on the aCRF have a link from the DDT to the first page of the aCRF where they were collected.

The screenshot shows a web-based form with the following fields and sections:

- Study Information:** STUDY C(8), Doc# R261759001, DCI Name/Shortname PAGE 01, FST1
- Visit Information:** Study Site INV C(10), Visit Name DAY-42 TO DAY-29, Status RECEIVED, CPEVENT C(20)
- Patient Information:** Patient 1001002, Visit# 1 VISIT, 0 SUBEVE, VISIT DATE (dd mon yyyy)
- FASTING Section:** FAST, FASTING, Has the subject fasted for at least 8 hours? No Yes, FASTSTA C(2) \$yn.
- Footer:**
 - HEADER INFORMATION WILL BE CAPTURED ON ALL DATASETS. ALL NUMERICS ARE IN 8 BYTES OF STORAGE; FORMATS SHOWN ARE FOR SAS.
 - ACCESS TS
 - DCMNAME C(10)
 - DCMSUBNM C(8)
 - LOGINTS
 - LSTCHGTS
 - PAGE C(10)
 - REPEATSN
 - SUBSETSN

TABLE 5: LINK TO SAS VERSION 5 TRANSPORT DATASET, EXAMPLE.

By clicking on the AMD.XPT link, the reviewer can open SAS viewer to take a close look at the data.

	AGE IN YEARS	AGE CATEGORY	AGE CATEGORY 75	EXTRACTION DATE	PHARMACOKINETIC SET FLAG	LAST TREATMENT DOSE DATE	RANDOMIZATION DATE	BASELINE HBATC CATEGORY	FULL ANALYSIS SET FLAG	RAND SET F
1	30	1		11JUL2007	1	08AUG2006	18APR2006	1	1	1
2	50	1		11JUL2007	1	19OCT2006	26APR2006	1	1	1
3	47	1		11JUL2007	1	20NOV2006	22MAY2006	1	1	1
4	21	1		11JUL2007	1	09OCT2006	22MAY2006	1	1	1
5	42	1		11JUL2007	1	04DEC2006	05JUN2006	2	1	1
6	50	1		11JUL2007	1	15JAN2007	17OCT2006	2	1	1
7	43	1		11JUL2007	1	20MAR2007	31OCT2006	2	1	1
8	46	1		11JUL2007	1	15MAY2007	15NOV2006	1	1	1
9	46	1		11JUL2007	1	14SEP2006	17MAR2006	1	1	1
10	22	1		11JUL2007	1	24OCT2006	26APR2006	2	1	1
11	65	2		11JUL2007	1	20NOV2006	23MAY2006	2	1	1
12	59	1		11JUL2007						
13	54	1		11JUL2007	1	10OCT2006	12APR2006	2	1	1
14	61	1		11JUL2007	1	02OCT2006	10AUG2006	1	1	1
15	65	2		11JUL2007	1	11FEB2007	14AUG2006	1	1	1
16	51	1		11JUL2007	1	25SEP2006	29MAR2006	1	1	1
17	54	1		11JUL2007		26APR2006	03APR2006	2	1	1
18	50	1		11JUL2007	1	21AUG2006	03APR2006	2	1	1
19	69	2		11JUL2007	1	04MAR2007	25OCT2006	1	1	1
20	56	1		11JUL2007	1	07MAR2007	04OCT2006	1	1	1
21	77	2	3	11JUL2007						
22	43	1		11JUL2007	1	04OCT2006	06APR2006	2	1	1
23	55	1		11JUL2007	1	17JUL2006	10MAY2006	2	1	1
24	33	1		11JUL2007	1	19JAN2007	22SEP2006	1	1	1
25	64	1		11JUL2007	1	25APR2007	13NOV2006	2	1	1
26	60	1		11JUL2007		06APR2006	20MAR2006	2	1	1
27	64	1		11JUL2007	1	26DEC2006	21JUN2006	1	1	1
28	48	1		11JUL2007	1	22NOV2006	22MAY2006	2	1	1

TABLE 6. DECODES OF FORMATS, EXAMPLE

By clicking on the \$DSREASN Code, the Define document links to the decode list for this variable at the end of the document.

Code Name-\$DSREASN	
Code	Decoded Value
1	Adverse Event
2	Major Protocol Deviation
3	Lost to Follow-up
4	Voluntary withdrawal
5	Study Termination
6	Pregnancy
7	Lack of Efficacy
9	PI Discretion
99	Other

TABLE 7 DDT, EXAMPLE OF DETAILED ALGORITHMS.

The DDT contains detailed specifications for how derived variables should be created.

Study XXX-XX - DEMOGALL Variables (Demographics)				
Variable	Label	Type	Code	Comments
AGE	AGE IN YEARS	Number	8.	Derived. Retain the integer portion of one more than the difference between the date of informed consent (CRIT.CONDT) and date of birth (DEMO.BRTHDT). Convert this value in days to years by dividing by 365.25.
AGECAT	AGE CATEGORY	Character	\$AGECAT	Derived. If AGE is greater than 0 and less than 65 then let set equal to '1'. If value is greater than or equal to 65 then let set equal to '2'.
AGECATN	AGE CATEGORY 75	Character	\$AGECATN	Derived. If AGE is greater than or equal to 75 then set equal to '3'.
BASEDC	BASELINE ADD-ON THERAPY DOSE CATEGORY	Character	\$BASEDC	Derived. If BASEDOSE is nonmissing and less than 10, set value to '1'. Else if between 10 and 15, inclusive, set value to '2'. Else if greater than 15, set value to '3'.
BASEDOSE	BASELINE ADD-ON THERAPY DOSE	Number	8.	Derived. For all subjects with non-missing DLOG.TOTDOSE, select the record closest to baseline (BASEDT), with non-missing dates (DLOG.DSPDT, BASEDT) and DLOG.DSPDT <= baseline date (BASEDT).
BASEDT	BASELINE VISIT DATE	Number	DATE9	Derived. Use the first treatment dose date (FTDOSDT).
BASE_TRT	BASELINE TREATMENT	Character	\$BTRT	Derived. Merge from IVRS data set.
DMRCTXT	Specify Other Race	Character	\$50.	Derived. Merge from DEMO data set.
DURDBY	DURATION OF DIABETES (YEARS)	Number	8.	Derived. First, calculate the difference between the month/year of screening (VIS.VISDTM and VIS.VISDTY where VIS.VISIT = '1') and the month/year of diabetes diagnosis (DEMO.DIAGDTM and DEMO.DIAGDTY) plus one. If the diagnosis month (DEMO.DIAGDTM) is missing, unknown, or invalid, use July. Next, divide this value by twelve to change the units to years.
ETHNIC	Ethnicity	Character	\$ETHNIC	Derived. Merge from DEMO data set.

In addition to the eCRT, the FDA may also request Subject Profiles. These are listings of CRF data for unique patients. These listings are limited to patients with serious adverse events, deaths, and those who discontinued study drug due to an adverse event (Table 8).

TABLE 8: SUBJECT PROFILES, EXAMPLE.

Investigator: 244		Protocol: XXX-XX		Page 1 of 655			
Birth Date: 21JAN19		Patient: 7001		Sex: Female			
		Race: White					
Demographics (DEMO)							
Page Number (PAGE)	Date of Birth (BERTDTC)	Sex (SEX)	Race (RACE)	Specify Other Race (DMRCTXT)	Ethnicity (ETHNIC)	Subject Initials (SUBJINIT)	Date Type II Diabetes Diag Month (DIAGDTM)
04	21JAN19	Female	White		Not Hispanic or Latino	FJA	JAN
Demographics (DEMO)							
Date Type II Diabetes Diag Year (DIAGDTY)	Number of Cigarettes (CIGRET)	Number of Cigars (CIGAR)	Number of Pipesful (PIPES)	Number of Years Subject Smoked (SMOKYRS)			
1997	0	0	0	30			
Adverse Events (AE)							
Check if no AEs (AENCNE)	Sequence Number (AENSEQ)	Page Number (PAGE)	Reported Term (ATERM)	Type of Adverse Event (AETYPE)	Adverse Event Start Date (AESTDTC)	Adverse Event Stop Date (AENEDTC)	AE Frequency (AEFREQ)
	1	39	WORSENING COPD / ASTHMA	Other	13JUN2006		Continuous
	2	40	ASTHMA EXACERBATION SECONDARY TO ACUTE BRONCHITIS.	Other	02OCT2006	06OCT2006	Continuous
	3	41	URINARY TRACT INFECTION	Lab	02OCT2006	07OCT2006	Continuous
	4	42	ELEVATED CPK LEVELS- HEART ATTACK RULED OUT.	Lab	02OCT2006	03OCT2006	Continuous
	5	43	ELEVATED BUN	Lab	03OCT2006	19OCT2006	Continuous
	6	44	WORSENING OF HYPERTENSION	Other	02OCT2006		Continuous
	7	45	WORSENING GERD	Other	02OCT2006		Intermittent
	8	46	SINUS BRADYCARDIA	ECG	18OCT2006		Continuous

THE INTEGRATED STUDY

The integrated study is a meta-analysis of some or all of the clinical protocols for a given drug used for reporting all the data together to examine broad trends in safety and efficacy. It can be a daunting task when faced with many protocols, different study designs and short timelines. This section will outline some of the key components of integration and give strategies for the work involved.

UNIFIED STRUCTURE: MAPPING DATASETS

The first task in creating a unified database is developing a list of data domains that will be integrated. This will often be determined by the sponsor and whether or not the integration will include efficacy along with safety results. The SAS programmer may begin with a simple Excel spreadsheet of databases and how they will be mapped to the final database name, Table 9. This spreadsheet can be converted to a SAS dataset that is then used to create macro variables in the analysis dataset program that the programmer can use to keep track of dataset names, Example 1.

TABLE 9. LIST OF DATASETS FOR EACH STUDY

STUDY	AE	CLAB	CM	DEMO	DLOG	DS	ECG	LABDATA	VS
#001	AE	.	MEDLOG	DEMO	DRUGADM	DISPOSIT	ECG	LAB	VITAL
#002	AE	CLAB	CM	DEMO	DLOG	DS	ECG	LAB	VS
#003	AE	CLAB	CM	DEMO	DLOG	DS	ECG	LAB	VS
#004	AE		MEDLOG	DEMOG	DRUGADM	STDYTERM	ECG	LAB	VITAL
#005	AE		MEDLOG	DEMOG	DRUGADM	STDYTERM	ECG	LAB	VITAL
#006	AE	CLAB	CM	DEMO	SMED	DS	ECG	LAB	VS
#007	AE	CLAB	CM	DEMO	DLOG	DS	ECG	LABDATA	VS
#008	AE	CLAB	CM	DEMO	DLOG	DS	ECG	LABDATA	VS
#009	AE	CLAB	CM	DEMO	DLOG	DS	ECG	LABDATA	VS

EXAMPLE 1. SAS CODE TO CREATE MACRO VARIABLES FOR DATASET REFERENCE

Using the SAS dataset domainlist, we select the main datasets for a particular study into macro variables. These macro variables can then be referenced instead of having to program each study differently.

```
%Macro GetDomains (sdy);
  %global AE CM DEMO DLOG DS ECG LABDATA VS;
  proc sql noprint;
    select AE, CM, DEMO, DLOG, DS, ECG, LABDATA, VS
    into :AE, :CM, :DEMO, :DLOG, :DS, :ECG, :LABDATA, :VS separated by ' '
    from status.domainlist
    where study = "&sdy";
  quit;
%mend GetDomains;
%GetDomains(#001)
```

UNIFIED CONTENT: MAPPING VARIABLES AND FORMATS

Identifying a data structure will be the next step in the process. Considerations for how to integrate different study designs such as parallel and crossover studies must be taken into account. With the FDA pushing toward CDISC compliant datasets, adopting the ADaM model must be considered as well. Another option may be to adopt the structure of a later phase study.

It is important to decide early what variables to keep: 1) all variables, 2) variables used in analysis plus their variable of origin or 3) variables used in the integrated analysis only. These options are listed in order of decreasing complexity and increasing order of efficiency. Generally, option 3 will be sufficient and provide the clearest presentation to the reviewer but communication between the sponsor and reviewer about the structure early on will help ensure success.

USING METADATA

Using the metadata for the datasets involved can help to facilitate the tedious job of mapping source data to the new structure. Using the Proc Contents in SAS, the programmer can generate an Excel spreadsheet of a side by side view of how the original study data will be mapped to the integrated data structure. Table 10 below shows the source data from datasets DEMO (studies 6,7,9,10) and DEMOG (study 8m) and the associated Subject ID for those datasets (PT and PATNO, respectively). Using PT for the final structure, PATNO in study 8m will be mapped to the new variable PT with a new length of 10 and new label, "Subject ID".

TABLE 10. METADATA OF SOURCE DATASETS MAPPED TO THE INTEGRATED ADSL DATASET.

4	Source Data							Output Dataset ADSL				
	Studies	Source Dataset	Source Variable	Type	Length	Format	Label	Output Variable	Type	Length	Format	Label
6	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----
7	#06, #07, #09, #10	DEMO	PT	Char	10		Subject ID	PT	Char	10		Subject ID
8	#08m	DEMOG	PATNO	Char	8		Patient Number					

USING FORMAT CATALOGS

One of the FDA recommendations is to use decoded variables instead of format catalogs for an integrated submission. If we take the example of the variable DSREAS, "Reason for Discontinuation", the final data structure would contain a numeric coded variable and a character variable containing the corresponding text for the codes. As we used the metadata to map study variable metadata characteristics, the format catalogs of all studies can be combined into an Excel spreadsheet to list common formats and compare their meanings. This can aid specification writing of the analysis database to ensure that correct values are mapped to integrated dataset variables. Table 11, below shows how this is done for the format for Reason for Discontinuation. Displayed are the different format names for each study and the underlying values that indicate "Lost to Follow-up". From here, the specification writer can decide the best way to unify all the codes in the integrated study.

TABLE 11. COMBINING FORMAT CATALOGS TO FACILITATE SPECIFICATION WRITING.

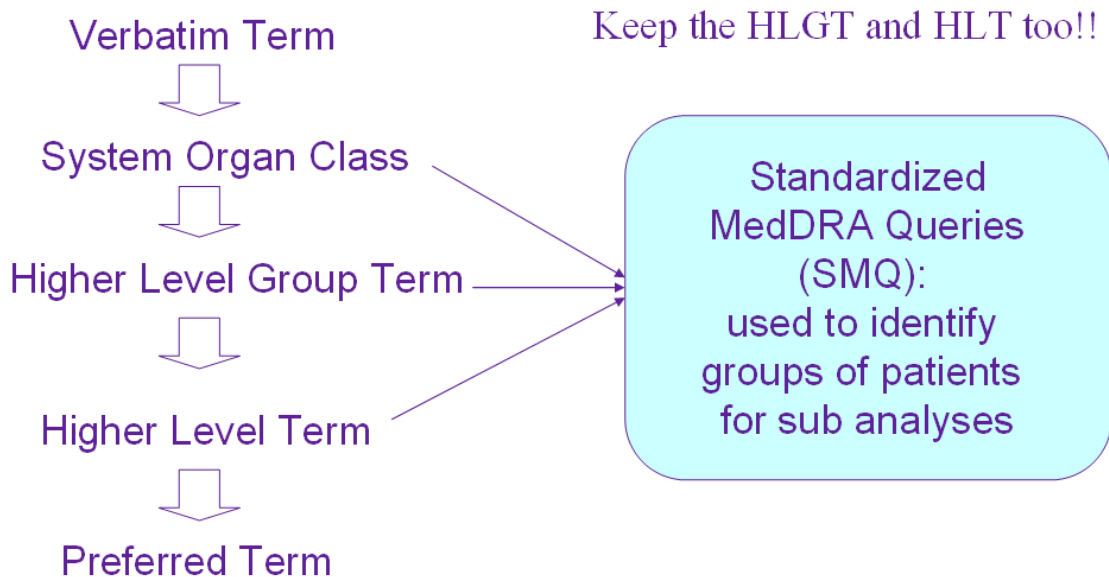
Format	Length	Source Study	label	start	end
DSREAS	\$0	#002, #003	Lost to follow up	5	5
DSREASN	\$37	#007, #008, #009, #010, #011, #012	Lost to Follow-up	3	3
RSNF	\$0	#014, #015, #016, #017, #018, #020, #021, #023	Lost to Follow-Up	3	3
REASON	\$0	#019	Lost to Follow-up	3	3
REASON	\$0	#001, #004, #005	Lost to Follow-up	5	5

UNIFIED CODING

It is common to be integrating studies that closed up to a year or more previously. When doing so, the dictionary used for Adverse Events, Medical History (MedDRA) and Medications (WHODRUG) may not be the current version and the coding will need to be updated to the most recent version based on the sponsor’s discretion. This is most easily accomplished by creating a set of unique terms that need to be mapped and running them through the coding process.

A relatively new system of codes, Standard MedDRA Queries (SMQs) has been used by the FDA to request analyses of sub populations of diseased patients. Often, the SMQs refer to Higher Level Group Terms and Higher Level Terms which are sometime not as familiar to programmers as the Preferred Terms and System Organ Class codes. It will be important to obtain these codes for the integrated study. Table 12, below, shows how these terms fit into the MedDRA coding schema.

TABLE 12. STANDARDIZED MEDRA QUERIES ARE COMPOSED OF HIGHER LEVEL GROUP TERMS AND HIGHER LEVEL TERMS.



CONCLUSIONS

When preparing for an FDA submission for a new drug application, it’s best to review the most current industry guidance to understand what is required. Experience is the best teacher and through this, we’ve tried to provide you with the major concepts of the eCTD “Define” document and the integrated study to provide some examples of what’s been done before so that the reader can compare that to their current project. Hopefully, these examples have provided insight into the biostatistical deliverables needed for a successful submission.

REFERENCES

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CONTACT INFORMATION

Robby Diseker
PPD
929 North Front Street
Wilmington, NC 28401
Work Phone: 910-558-2305
Fax: 919-654-0726
Email: Robert.Diseker@wilm.ppd.com

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