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Streamlining the Results Reporting for ClinicalTrials.gov and EudraCT

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ABSTRACT

Since ClinicalTrials.gov and EudraCT results disclosure requirements mandate the submission of clinical trial results in a specific structure, uniform across all trials and the ability to upload the results via XML (eXtensible Markup Language), it is possible to programmatically pull necessary information from existing databases to populate the results there by eliminating the need for manual entry which is time consuming and prone to errors. Programmers can make use of this capability to streamline the results reporting process across studies by developing standard templates for various results sections and set of generic macros to create standardized SAS datasets and converting them into XML format according to the required schemas which can be uploaded directly into the registry systems for posting in ClincialTrials.gov/EudraCT. This paper will discuss the results disclosure requirements and standard template for the Adverse Event summary dataset and applying the same approach to streamline the process for other results sections also.

INTRODUCTION

WHAT IS CLINICALTRIALS.GOV?

ClinicalTrials.gov is a Web-based resource that provides patients, their family members, health care professionals, researchers, and the public with easy access to information on publicly and privately supported clinical studies on a wide range of diseases and conditions. The Web site is maintained by the National Library of Medicine (NLM) at the National Institutes of Health (NIH). Information on ClinicalTrials.gov is provided and updated by the sponsor or principal investigator of the clinical study. Studies are generally submitted to the Web site (that is, registered) when they begin, and the information on the site is updated throughout the study. In some cases, results of the study are submitted after the study ends. This Web site and database of clinical studies is commonly referred to as a "registry and results database."

WHAT IS THE RESULTS DATABASE?

The ClinicalTrials.gov results database was launched in September 2008 to implement Section 801 of the Food and Drug Administration Amendments Act of 2007 (FDAAA), which requires the submission of "basic results" for certain clinical trials, generally no later than 1 year after their Completion Date. The submission of adverse event information was optional when the results database was first released but was required beginning in September 2009. Results information for registered and completed studies is submitted by the study sponsor or principal investigator in a standard, tabular format without discussions or conclusions. The information is considered summary information and does not include individual patient data. The "basic" results Scientific information is submitted as four separate modules:

- **Participant Flow.** A tabular summary of the progress of participants through each stage of a study, by study arm or comparison group. It includes the numbers of participants who started, completed, and dropped out of each period of the study based on the sequence in which interventions were assigned.
- **Baseline Characteristics.** A tabular summary of the data collected at the beginning of a study for all participants, by study arm or comparison group. These data include demographics, such as age and gender, and study-specific measures (for example, systolic blood pressure, prior antidepressant treatment).
- **Outcome Measures and Statistical Analyses.** A tabular summary of Outcome measure values, by study arm or comparison group. It includes tables for each prespecified Primary Outcome and Secondary Outcome and may also include other prespecified outcomes, post hoc outcomes, and any appropriate statistical analyses.

- **Adverse Events.** A tabular summary of all anticipated and unanticipated Serious adverse event and a tabular summary of anticipated and unanticipated other adverse events exceeding a specific frequency threshold. For each serious or other adverse event, the summary includes the adverse event term, affected organ system, number of participants at risk, and number of participants affected, by study arm or comparison group.

The Final Rule for Clinical Trials Registration and Results Information Submission (42 CFR Part 11), was issued in September 2016 and is effective in January 2017. It expands the scope of the results database by requiring the submission of results information for trials of unapproved products and additional information for summarizing trial results. Failure to comply with these requirements can result in civil penalties of up to $10,000 per day if required results are not submitted, and the withholding of grant funds for trials supported by federal agencies.

Similar to US requirements to post clinical trial results in public domain, on July 21st, 2014, the European Medicines Agency (EMA) has mandated the results disclosure for all interventional clinical trials conducted in the European Union (EU) and the European Economic Area (EEA), and all Pediatric studies irrespective of location. The EudraCT database has been established in accordance with Directive 2001/20/EC. Based on applicable business rules within EudraCT, Information of clinical trials in EudraCT database is posted to public via a website of EU Clinical Trials Register: www.clinicaltrialsregister.eu.

Table 1:

ClinicalTrials.gov – Studies and Timing		**EudraCT – Studies and Timing**	
Criteria	Timing	Criteria	Timing
Phase I/II and II – IV interventional studies that were either ongoing or started after September 27, 2007 and meet one or more of the following criteria: - At least one site in the United States - Conducted under an FDA investigational new drug application (IND) or investigational device exemption - Involves a drug, biologic, cell therapy or device that is manufactured in the United States or its territories and is exported for research ***Note*:** Studies conducted as part of a post-approval commitment are also required to have results posted. ***Note*:** Studies that were ongoing as of September 27, 2007 but ended by December 31, 2007 are not required. ***Note*:** Phase I studies are not required to have results posted on Clinical Trials.gov	For trials with a primary completion date (PCD) on or after 18 Jan 2017, study results must be posted within one year after the PCD unless a certificate of delay (COD) is submitted. If a COD has been submitted and the study is part of an initial U.S. approval, results must be submitted within 30 calendar days after the FDA approves, licenses or clears the drug or device for any indication OR within 2 years of the study's PCD. If a premarket notification is withdrawn and is not resubmitted within 210 calendar days, results must be posted within 30 days. ***Note*:** The maximum time a clinical trial results can be delayed is two years from the date the COD is submitted for a total of three years. ***Note*:** Any trial that includes an unapproved product with a PCD before January 18, 2017 is not required to have results posted.	All Phase I – IV interventional trials in adults that were conducted in at least one European Economic Area country or part of a pediatric investigational plan (PIP) and were either ongoing on or started after May 1, 2004. ***Note*:** Studies that are conducted entirely outside of the EU are also required to have results posted if they were part of a PIP.	Interventional studies in adults whose Study Completion Date (SCD) was on or after 21 July 2014 are required to have results posted within 12 months of the end of trial notification. Pediatric trials must have results posted within 6 months of the end of trial notification. ***Note*:** A pediatric trial is a trial that includes at least one subject below 18 years of age

CURRENT METHODS:

The ClinicalTrials.gov Protocol Registration and Results System (PRS) is a web-based tool used to submit clinical study information to ClinicalTrials.gov. Currently in many pharmaceutical companies, the clinical trial disclosure results are prepared manually by a designated group usually regulatory affairs or Clinical Trial Disclosure Lead based on the clinical study report outputs. The manual process is time consuming and error-prone, with many review cycles among different functional groups. The manual data entry is only feasible for a very small number of trials with a reasonable number of necessary entries.

Another method is uploading results via XML files that conform to PRS XML schemas. The XML file transfer (upload) capability facilitates the transfer of data into ClinicalTrials.gov from sponsor's computer system. The XML upload seems like a better choice compared to manual entry, however there are some challenges to be able to make use of this capability as the results are not readily available in a format that can be converted into XML format and significant technical expertise is required to structure the data according to the PRS XML schema. In the below steps we explain steps how sponsors can streamline the results disclosure process to achieve efficiency and accuracy across studies.

STREAMLINING THE PROCESS:

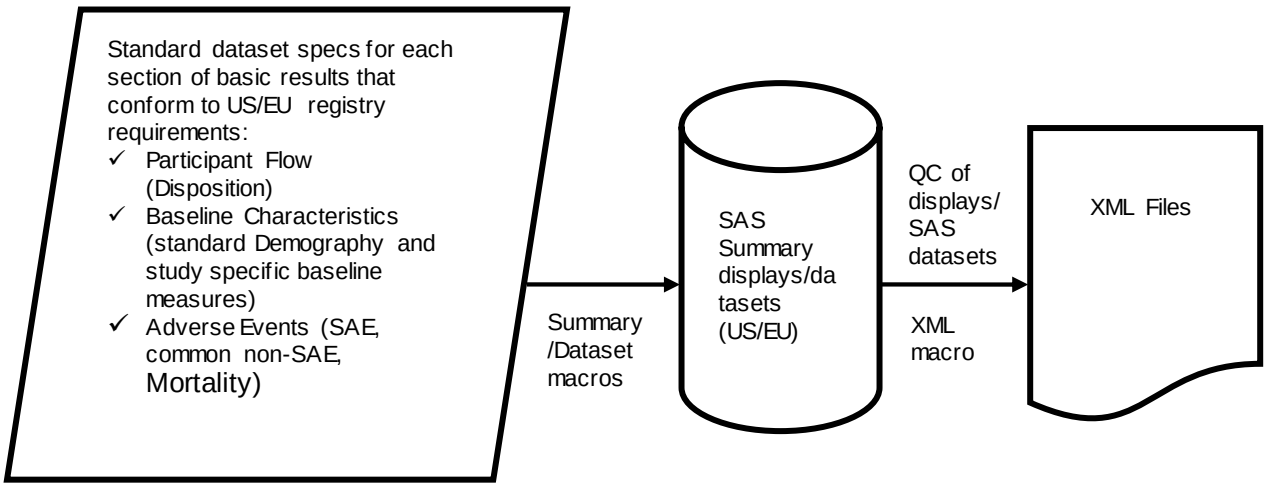
To simplify and streamline clinical data disclosure processes, SAS® can be used to gather the required information from existing databases and generate an XML file to be uploaded directly to ClinicalTrials.gov/EudraCT. In order to achieve this, the information needed for the registries need to be produced during the clinical trial reporting, at which these data elements are produced anyway, basically it comes down to having the required data displays as part of study analysis plans in the format that conform to regulatory standards for the US/EU study registers and convert to XML format to facilitate the transfer of data to company's internal registry systems and then release to public domain.

As a first step all the required information should to be specified in advance by defining standard templates for each section of basic results information. Once the standard templates are in place the data displays(tables) as well as corresponding output SAS datasets (these will be converted to XML files) will be produced using set of validated SAS macro tools. These steps will:

- Eliminate the need to manually transcribe summary results there by improving the accuracy, efficiency and consistency of the result posting.
- Eliminate the potential transcription errors.
- Simplify study team review of summary results process before they are released in the public domain.

PROPOSED METHOD

FIGURE 1



Above FIGURE 1 flow chart shows the flow of data in the proposed method where XML files are created that are ready to be uploaded onto the registries.

TABLE 2: AE SUMMARY RESULTS DATASET SPECIFICATION:

Below is the description of sample AE dataset variables for ClinicalTrials.gov.

SAS Field Name	XML tag	Definition
STUDYID		Identification of the Study to which the SAE/NONSAE/MORT is to be applied
TRT	reportingGroupID	Treatment group
TRTORD		Treatment Order
AEBODSYS	organSystemName	Body System or Organ Class Note: AEBODYS data will not be transferred when data value is "Total # participants affected" Note: Blank when AETYPE is "MORT"
AEDECOD	term	NONSAE or SAE preferred Term Note: Blank when AEBODSYS data value is "Total # participants affected") Note: Blank when AETYPE is "MORT"
AETYPE	frequentEvent = NONSAE SeriousAdverseEvent = SAE All-Cause Mortality = MORT	Identifies whether the event is NONSAE, SAE, or MORT.
MEDDRA	sourceVocabulary	Dictionary name and version. Example: MedDRA 20.0
N_ARM	partAtRiskSeriousEvents partAtRiskFrequentEvents partAtRiskAllCauseMort	Total number of Subjects in the Safety Population by Treatment Group
N_AE	numSubjectsFrequentEvents numSubjectsSeriousEvents numDeaths	Number of Subjects that experienced the defined Adverse Event (applies to SAE, NONSAE and MORT)

The datasets for both US and EU are very much like standard AE summary table. The core structure is one observation per treatment group (TRT, TRTORD), AE type (AETYPE), Preferred term (AEDECOD) within body system (AEBODSYS). An additional summary record for each TRT / AETYPE combination will be added to the dataset. Currently no macro code was presented in this paper as the code is similar to that of standard AE summary table by Body System and Preferred term.

A screenshot of the sample AE summary dataset and sample annotated Adverse Event results was presented in APPENDIX.

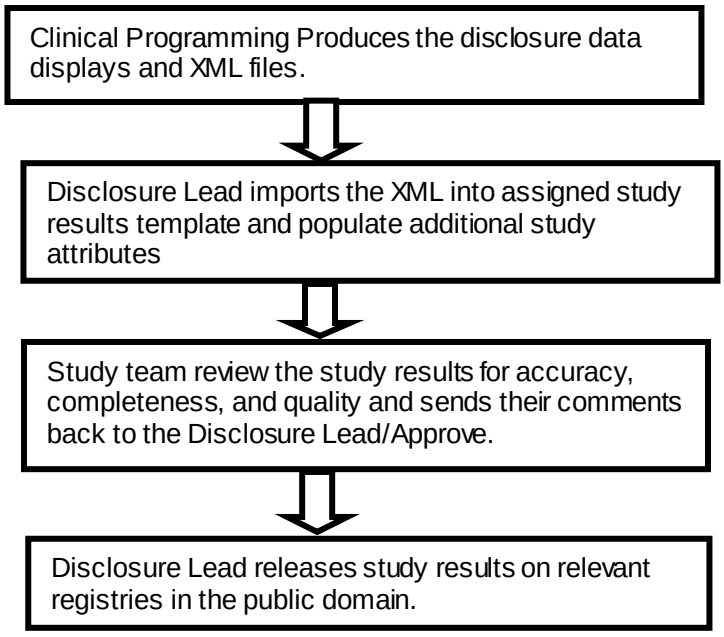
SAS TO XML CONVERSION:

Once the datasets are created using generic macro tools, next step would be conversion of the datasets into XML files using the accepted schemas, in some companies this step is performed by a different functional group such as IT systems, ideally the XML conversion also can be performed by programming group as there are several ways of generating XML from SAS (for example using PUT statements).

Similar to the AE summary results, specifications for other basic results sections can be established by working with study statistician and Results disclosure group lead. Validated generic macro tools should be developed to extract the required information from the existing databases for the remaining basic results sections. In order to extract results information for participant flow, baseline characteristics and outcome measures, the required data should exist in the form of datasets, this can be achieved by saving the reporting datasets (usually before the proc report step) at the time of creating summary tables for these data displays. This allows the mapping of the data into the format expected by the XML creation utility macro before finally creating the XML files. When developing these macro tools, care should be taken to account for variances from study to study such as number of treatment groups, multiple phases, CDISC vs legacy studies etc.

At a high level the entire process would be as below.

FIGURE 2



CONCLUSION

In the new proposed process programming group plays a major role as all required results will be produced and converted to XML format per the registry (US and EU) requirements at the same time along with clinical study report outputs. It is essential that the required data displays are included as part of study analysis plans. In the field of clinical trials where the prime focus is on attaining results with highest quality without effecting the integrity of the data, having a standardized process reduces effort and enhances the quality of the outputs delivered and which will eventually help in maintaining the accuracy and consistency of results, so it is prudent to opt for these new methodologies. Though there might be an initial flare in the departmental budgets to allocate programming resources to tasks associated in developing standard templates and macro tools but the return on investment in the longer run is great as we can save both time and money during the validation of the results as validated standard macro tools are used to generate the results.

REFERENCES

Food and Drug Administration Modernization Act (FDAMA Section 113)
http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126838.pdf

Food and Drug Administration Amendments Act of 2007 (FDAAA); also known as US Public Law 110-85,Title VIII, Section 801.
http://frwebgate.access.gpo.gov/cgibin/getdoc.cgi?dbname=110_cong_public_laws&docid=f:publ085.110.pdf

Final Rule for FDAAA 801 and NIH Policy on Clinical Trial Reporting: https://clinicaltrials.gov/ct2/managerecs/fdaaa

Clinical Trials Regulation EU No 536/2014: http://ec.europa.eu/health/human-se/clinicaltrials/regulation/index_en.htm

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RECOMMENDED READING

Information about the ClinicalTrials.gov database: http://prsinfo.clinicaltrials.gov

Information about How to Submit Results: https://clinicaltrials.gov/ct2/manage-recs/how-report#Overview

ClinicalTrials.gov Protocol Data Elements Definitions: http://prsinfo.clinicaltrials.gov/definitions.html

ClinicalTrials.gov Results Data Element Definitions for Interventional and Observational Studies:
https://prsinfo.clinicaltrials.gov/results_definitions.html

CONTACT INFORMATION

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APPENDIX:

FIGURE 4: AE SUMMARY DATASET

TRT	TRTORD	MEDDRA	AEBODSYS	AEDECOD	AETYPE	N_AE	N_ARM	RATIO
Group 1: 20 MG BID	1	MedDRA 20.0	Ear and labyrinth disorders	Ear pain	NONSAE	0	13	0
Group 1: 30 MG BID	2	MedDRA 20.0	Ear and labyrinth disorders	Ear pain	NONSAE	1	8	12.5
Group 2: 20 MG BID	3	MedDRA 20.0	Ear and labyrinth disorders	Ear pain	NONSAE	1	21	4.8
Group 1: 20 MG BID	1	MedDRA 20.0	Gastrointestinal disorders	Abdominal distension	NONSAE	1	13	7.7
Group 1: 30 MG BID	2	MedDRA 20.0	Gastrointestinal disorders	Abdominal distension	NONSAE	1	8	12.5
Group 2: 20 MG BID	3	MedDRA 20.0	Gastrointestinal disorders	Abdominal distension	NONSAE	3	21	14.3
Group 1: 20 MG BID	1	MedDRA 20.0	Gastrointestinal disorders	Abdominal pain	NONSAE	6	13	46.2
Group 1: 30 MG BID	2	MedDRA 20.0	Gastrointestinal disorders	Abdominal pain	NONSAE	1	8	12.5
Group 2: 20 MG BID	3	MedDRA 20.0	Gastrointestinal disorders	Abdominal pain	NONSAE	11	21	52.4
Group 1: 20 MG BID	1	MedDRA 20.0	Gastrointestinal disorders	Abdominal pain upper	NONSAE	2	13	15.4
Group 1: 30 MG BID	2	MedDRA 20.0	Gastrointestinal disorders	Abdominal pain upper	NONSAE	1	8	12.5
Group 2: 20 MG BID	3	MedDRA 20.0	Gastrointestinal disorders	Abdominal pain upper	NONSAE	4	21	19
Group 1: 20 MG BID	1	MedDRA 20.0	Total # participants affected		NONSAE	13	13	100
Group 1: 30 MG BID	2	MedDRA 20.0	Total # participants affected		NONSAE	7	8	87.5
Group 2: 20 MG BID	3	MedDRA 20.0	Total # participants affected		NONSAE	19	21	90.5
Group 1: 20 MG BID	1	MedDRA 20.0	Total # participants affected		SAE	0	13	0
Group 1: 30 MG BID	2	MedDRA 20.0	Total # participants affected		SAE	0	8	0
Group 2: 20 MG BID	3	MedDRA 20.0	Total # participants affected		SAE	0	21	0
Group 1: 20 MG BID	1				MORT	0	13	
Group 1: 30 MG BID	2				MORT	0	8	
Group 2: 20 MG BID	3				MORT	0	21	

FIGURE 5: ANNOTATED ADVERSE EVENT RESULTS

Other (Not Including Serious) Adverse Events — frequentEvent (if AETYPE='NONSAE')

Frequency Threshold for Reporting Other Adverse Events	5%	reportingGroupdID (TRT)	
	Group 1: 20 MG BID	**Group 1: 30 MG BID**	**Group 2 : 20 MG BID**
	Affected / at Risk (%)	Affected / at Risk (%)	Affected / at Risk (%)
Total	13/13 (100.00%)	7/8 (87.50%)	19/21 (90.48%)
Ear and labyrinth disorders	organSystemName (AEBODSYS)		
Ear pain †1	0/13 (0.00%)	1/8 (12.50%)	1/21 (4.76%)
Gastrointestinal disorders	term (AEDECOD)		
Abdominal distension †1	1/13 (7.69%)	numSubjectsFrequentEvents (N_AE) 1/8 (12.50%)	partAtRiskfrequentEvents (N_ARM) 3/21 (14.29%)
Abdominal pain †1	6/13 (46.15%)	1/8 (12.50%)	11/21 (52.38%)
Abdominal pain upper †1	2/13 (15.38%)	1/8 (12.50%)	4/21 (19.05%)