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A Practical Approach to Preparing Documentation for Clinical Registries

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ABSTRACT

Clinical trial sponsors must comply with a wide variety of legal requirements. The focus of this paper is the requirement to publicly register and post clinical trial information, including trial results. Depending on where the trial is conducted, there are different clinical registries that need to be supported. The processes are documented on the corresponding websites where the trials must be registered. While it is possible to manually calculate and enter trial results into the registry, that information must be accurate and manual entry increases the review burden and the risk of human error. Programming support can make the process safer and easier. More specifically, for some content it is possible to directly upload validated content, avoiding the risks associated with manual entry. In other cases, manual entry and review can be facilitated with validated tables that specifically target entry needs. In this paper, we will provide case studies and examples illustrating our current process for creating and validating content designed to support population of clinical trial results in clinical registries.

INTRODUCTION

Many programmers versed in clinical trials will be aware of the Title 21 Code of Federal Regulations, Part 11: Electronic Records and Electronic Signatures. These regulations define the criteria under which electronic data and associated signatures are considered trustworthy and reliable. This paper will be discussing a lesser-known Part 11, of Title 42: Clinical Trials Registration and Results Information Submission. Conduction of a clinical trial includes compliance with legal aspects, specifically providing required information at designated timepoints of the study. Among those requirements is registering and posting clinical information, such as certain, specific trial results. Applicable registry references should be documented in the SDTM Trial Summary domain (TS). More specifically, TS should contain a row for each applicable registry reference in TSVAL where TSPARMCD = 'REGID'. Different registries are required depending on where the trial is conducted, such as ClinicalTrials.gov (United States), and EudRACT (Europe). The processes for publicly sharing these results are documented on the respective websites. This paper will discuss our experience supporting entry and upload of clinical trial results on ClinicalTrials.gov.

LEGAL OBLIGATIONS AND REGISTRY RESTRICTIONS

There are two very important deadlines to keep in mind when a trial will need to be registered on ClinicalTrials.gov, and these requirements are fully explained in the text describing Title 42, Part 11, on the Code of Federal Regulations website. The first deadline is regarding the actual registration of the trial, and it is stated that this information must be posted on the clinical trial registry no later than 30 calendar days after the responsible party has submitted information for drug approval. Once the trial is registered, there remains one more important deadline, which is the posting of trial results. It is stated that the clinical trial results will be publicly posted on the registry no later than 1 year from the completion date of the clinical trial. These regulations do fully apply to any trials initiated after September 27, 2007, and additionally to any trials that initiated on or before September 27, 2007, but were ongoing on December 26, 2007.

It could be a costly mistake to not comply with the federal regulations outlined above. In 2021, the FDA issued a Notice of Noncompliance to a pharmaceutical company for failing to submit required trial summary information to a clinical registry. The notice provided a 30-day deadline for submitting these select results, with failure to do so potentially resulting in civil penalties.

Clinical registries require an electronic upload of the information—that is, whether by creating a reference for manual entry of individual terms or a consolidated file designed to be directly uploaded, trial results must be added into this digital registry. There are certain limitations on which results can be uploaded and which require manual entry, which are illustrated in the table below. For example, while both adverse

event and demographic information is required to be included in ClinicalTrials.gov, only the adverse events content can be uploaded in a file at this time. On the other hand, EudRACT allows for a file upload or manual entry for both adverse event and demographic information. While we will not discuss the creation of materials for EudRACT, with slight modifications to the process followed for ClinicalTrials.gov, the XML files for EudRACT can be easily produced.

Table 1 describes the different methods of entry available on EudRACT and ClinicalTrials.gov when electronically uploading the trial results.

Registry	Demographic Information	Adverse Event Information
ClinicalTrials.gov	Manual Entry	Manual Entry/Automatic Upload of XLSX file
EudRACT	Manual Entry/Automatic Upload of XML file	Manual Entry/Automatic Upload of XML file

Table 1. Loading Clinical Trial Results: Digital Upload Options

Considering this information, and the variability of certain efficacy variables to be included in demographics registration data, we prioritized generation of the upload file for the adverse event data and still rely on manual entry of the demographic data (supported by validated outputs that match the format expected in the registry). Since the adverse event related-data comprises the bulk of what is required for the registry, we have successfully mitigated the potential for data-entry issues.

NAVIGATING THE REGISTRY

When navigating the ClinicalTrials.gov website, there are multiple tabs that can be selected for each specific study: Study Details, Tabular View, and Study Results.

Figure 1 is an example of what you may see after selecting a specific study on the registry.

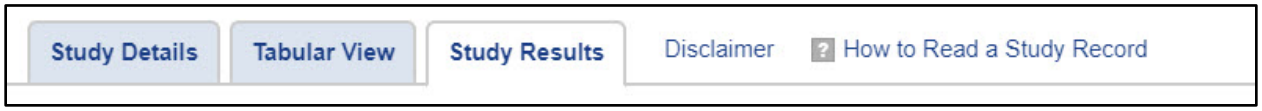

Figure 1. Screenshot of ClinicalTrials.gov Study tabs

The first tab (Study Details) contains Study Description, Arms and Interventions, Outcome Measures, Eligibility Criteria, Contacts and Locations, and More Information. This tab is updated by Corporate Communications, or the otherwise assigned Responsible Party, and our programmers do not enter these results.

The second tab (Tabular View) contains Tracking Information, Descriptive Information, Recruitment Information, and Administrative Information. The information on this tab is updated by the Responsible Party.

The third tab (Study Results) will display as 'No Results Posted' if the results have not been uploaded to the registry yet. When populated, this tab contains Participant Flow, Baseline Characteristics, Outcome Measures, Adverse Events, Limitations and Caveats, and More Information. This tab is the focus of our programming support, with validated tables specifically designed to support manual entry of Baseline Characteristics and validated files designed for direct upload for Adverse Events.

ADVANTAGES TO DIRECT UPLOAD

Specifically for the demographics section, as we have discussed above, there is a limitation on how the data can be uploaded. Demographics still requires a manual entry of certain, specific data points. However, the demographics section also requires, where possible, statistics on the primary efficacy parameter. The efficacy parameter is study specific and is summarized separately from demographics in clinical study reports.. Thus, if we were not to create a ClinicalTrials.gov-specific demographic output, the Responsible Party may have to search the CSR to source the required values from multiple different tables.

Similarly, other, slight modifications to demographics tables may be required. For example, on some studies, we include all the required statistics by treatment group, but we do not include an overall column.

When this is the case, we do modify the demographics datasets to include this Overall column, since it is required by ClinicalTrials.gov.

Though the data must still be manually entered, we have created a process that will produce a single data-source for all demographic required information. Additionally, if the ability for digital upload ever becomes possible, we need only to adjust the formatting of our demographic output to allow for the upload. We will not need to create the program from scratch at that time.

Regarding the adverse events section, the benefit of programmatic support is even more clear as the validated content can be directly uploaded. The registry requires values that come from 4 very similar tables in our CSR outputs. Rather than individually entering each record of an Adverse Event, it saves time and improves accuracy to upload validated data results for each of the outputs. Additionally, since each of the files requires the same, specific formatting within Excel, it is logical to use a macro as part of the process.

DEMOGRAPHICS

Baseline Characteristics

	Arm/Group Title	Bardoxolone Methyl - ADPKD	Bardoxolone Methyl - IgAN	Bardoxolone Methyl - T1D
	▼ Arm/Group Description	Participants with autosomal polycystic kidney disease (ADPKD) who received bardoxolone methyl capsules at a starting dose of 5 mg and titrate up to a maximal dose of 20 mg (participants with UACR less than or equal to 300 mg/g) or 30 mg (participants with UACR greater than 300 mg/g) daily. Bardoxolone methyl capsules: Bardoxolone 5 mg capsules	Participants with IgA nephropathy (IgAN) who received bardoxolone methyl capsules at a starting dose of 5 mg and titrate up to a maximal dose of 20 mg (participants with UACR less than or equal to 300 mg/g) or 30 mg (participants with UACR greater than 300 mg/g) daily. Bardoxolone methyl capsules: Bardoxolone 5 mg capsules	Participants with Type 1 diabetes (T1D) who received bardoxolone methyl capsules at a starting dose of 5 mg and titrate up to a maximal dose of 20 mg (participants with UACR less than or equal to 300 mg/g) or 30 mg (participants with UACR greater than 300 mg/g) daily. Bardoxolone methyl capsules: Bardoxolone 5 mg capsules
	Overall Number of Baseline Participants	31	26	28
	▼ Baseline Analysis Population Description	All participants who received any amount of study drug		
Age, Continuous Mean (Standard Deviation) Unit of measure: Years				
	Number Analyzed	31 participants	26 participants	28 participants
		47.4 (9.49)	48.5 (9.53)	49 (9.91)

Figure 2. Example of Baseline Characteristics from ClinicalTrials.gov

Figure 2 is an example of what the Baseline Characteristics section on ClinicalTrials.gov looks like. A picture of the full content of the site is hard to read, so we have selected a subset of the cohorts to provide an example of what the registry looks like, and have also transformed the results into a more readable format in Figure 3. Displayed in each of the figures is an example study, PHOENIX, containing 4 different treatment cohorts.

Arm/Group Title	Bardoxolone Methyl ADPKD	Bardoxolone Methyl IgAN	Bardoxolone Methyl T1D	Bardoxolone Methyl FSGS	Total
Overall Number of Baseline Participants	31	26	28	18	103
Baseline Analysis Population Description: All participants who received any amount of study drug					
Age, Continuous *Mean (Standard Deviation)* *Unit of measure: Years* Number Analyzed	 31 participants 47.4 (9.49)	 26 participants 48.5 (9.53)	 28 participants 49 (9.91)	 18 participants 48.6 (12.79)	 103 participants 48.3 (10.12)
Sex: Female, Male *Measure Type: Count of Participants* *Unit of measure: Participants* Number Analyzed Female Male	 31 participants 21 (67.7%) 10 (32.3%)	 26 participants 11 (42.3%) 15 (57.7%)	 28 participants 21 (75.0%) 7 (25.0%)	 18 participants 10 (55.6%) 8 (44.4%)	 103 participants 63 (61.2%) 40 (38.8%)
Ethnicity (NIH/OMB) *Measure Type: Count of Participants* *Unit of measure: Participants* Number Analyzed Hispanic or Latino Not Hispanic or Latino Unknown or Not Reported	 31 participants 3 (9.7%) 28 (90.3%) 0 (0.0%)	 26 participants 2 (7.7%) 24 (92.3%) 0 (0.0%)	 28 participants 2 (7.1%) 26 (92.9%) 0 (0.0%)	 18 participants 1 (5.6%) 17 (94.4%) 0 (0.0%)	 103 participants 8 (7.8%) 95 (92.2%) 0 (0.0%)
Race (NIH/OMB) *Measure Type: Count of Participants* *Unit of measure: Participants* Number Analyzed American Indian or Alaska Native Asian Native Hawaiian or Other Pacific Islander Black or African American White More than one race Unknown or Not Reported	 31 participants 1 (3.2%) 1 (3.2%) 0 (0.0%) 4 (12.9%) 25 (80.6% 0 (0.0%) 0 (0.0%)	 26 participants 0 (0.0%) 4 (15.4%) 0 (0.0%) 0 (0.0%) 22 (84.6%) 0 (0.0%) 0 (0.0%)	 28 participants 0 (0.0%) 0 (0.0%) 0 (0.0%) 1 (3.6%) 27 (96.4%) 0 (0.0%) 0 (0.0%)	 18 participants 1 (5.6%) 1 (5.6%) 0 (0.0%) 5 (27.8%) 11 (61.1%) 0 (0.0%) 0 (0.0%)	 103 participants 2 (1.9%) 6 (5.8%) 0 (0.0%) 10 (9.7%) 85 (82.5% 0 (0.0%) 0 (0.0%)
Baseline estimated glomerular filtration rate (eGFR) *Mean (Standard Deviation)* *Unit of measure: mL/min/1.73 m^2* Number Analyzed	 31 participants 47.69 (13.630)	 26 participants 46.19 (12.576)	 28 participants 67.52 (17.059)	 18 participants 51.66 (18.144)	 103 participants 53.39 (17.427)
Baseline urine albumin-to-creatinine ratio (UACR) *Mean (Full Range)* *Unit of measure: Mg/g* Number Analyzed	 31 participants 44.4 (2.4 to 1824.5)	 26 participants 104.03 (5.2 to 1288.0)	 28 participants 30.88 (2.5 to 1208.0)	 18 participants 184.3 (3.5 to 1006.5)	 103 participants 63.95 (2.4 to 1824.5)

Figure 3. ClinicalTrials.gov Demographic information converted to readable format

We have identified the demographic tables from the CSR that contain these results. For the sake of a complete explanation, and due to the way analysis was done, the results required for this table will span 5 datasets: one for each cohort, and one for the overall treatment group. We have included each below.

Figure 4 is the table dataset supporting the production of demographics for patients in the ADPKD group. Multiple variables are included in this output, so we will take one as an example, and review *AGE*. Based on the output dataset, there were 31 subjects in the ADPKD cohort, with a mean age of 47.4 and standard deviation of (9.49).

	column_c	parameter	class	class_ord	result_c
1	Bardoxolone Methyl~(N=31)	AGE	N	100	31
2	Bardoxolone Methyl~(N=31)	AGE	Median	600	46.0
3	Bardoxolone Methyl~(N=31)	AGE	Min, Max	700	26, 69
4	Bardoxolone Methyl~(N=31)	AGE	Q1, Q3	400	41, 52
5	Bardoxolone Methyl~(N=31)	AGE	Mean (SD)	200	47.4 (9.49)

Figure 4. Demographics table dataset for ADPKD patients

Figure 5 is the table dataset supporting the production of demographics for patients in the IgAN group. IgAN contained 26 subjects in the cohort, where the mean and standard deviation for age were 48.5 (9.53).

	column_c	parameter	class	class_ord	result_c
1	Bardoxolone Methyl~(N=26)	AGE	N	100	26
2	Bardoxolone Methyl~(N=26)	AGE	Median	600	50.0
3	Bardoxolone Methyl~(N=26)	AGE	Min, Max	700	27, 66
4	Bardoxolone Methyl~(N=26)	AGE	Q1, Q3	400	42, 56
5	Bardoxolone Methyl~(N=26)	AGE	Mean (SD)	200	48.5 (9.53)

Figure 5. Demographics table dataset for IgAN patients

Figure 6 is the table dataset supporting the production of demographics for patients in the T1D group. Below, T1D contained 28 subjects, with mean and standard deviation of 49.0 (9.91) in the cohort.

	column_c	parameter	class	class_ord	result_c
1	Bardoxolone Methyl~(N=28)	AGE	N	100	28
2	Bardoxolone Methyl~(N=28)	AGE	Median	600	52.5
3	Bardoxolone Methyl~(N=28)	AGE	Min, Max	700	29, 64
4	Bardoxolone Methyl~(N=28)	AGE	Q1, Q3	400	39, 57
5	Bardoxolone Methyl~(N=28)	AGE	Mean (SD)	200	49.0 (9.91)

Figure 6. Demographics table dataset for T1D patients

Figure 7 is the table dataset supporting the production of demographics for patients in the FSGS group. The FSGS-specific dataset contains 18 subjects in the cohort, with a mean of 48.6 and standard deviation of 12.79.

	column_c	parameter	class	class_ord	result_c
1	Bardoxolone Methyl~(N=18)	AGE	N	100	18
2	Bardoxolone Methyl~(N=18)	AGE	Median	600	52.5
3	Bardoxolone Methyl~(N=18)	AGE	Min, Max	700	21, 65
4	Bardoxolone Methyl~(N=18)	AGE	Q1, Q3	400	37, 59
5	Bardoxolone Methyl~(N=18)	AGE	Mean (SD)	200	48.6 (12.7...

Figure 7. Demograpics table dataset for FSGS patients

Figure 8 is the table dataset supporting the production of demographics for all patients. Finally, the overall table contains 31 + 26 + 28 + 18 (or 103) subjects. When considering the groups as a whole, the mean and standard deviation are 48.3 (10.12). In addition to checking the counts, we can also verify the

minimum and maximum values. The smallest minimum value in any of the contributing datasets is from the cohort T1D, which is 21. The largest maximum value in any of the contributing datasets is from the cohort ADPKD, which is 69. The values displayed in our overall table for minimum and maximum age are 21, 69, so these counts are also as expected.

	column_c	parameter	class	class_ord	result_c
1	Bardoxolone Methyl~(N=103)	AGE	Median	600	49.0
2	Bardoxolone Methyl~(N=103)	AGE	N	100	103
3	Bardoxolone Methyl~(N=103)	AGE	Min, Max	700	21, 69
4	Bardoxolone Methyl~(N=103)	AGE	Q1, Q3	400	41, 57
5	Bardoxolone Methyl~(N=103)	AGE	Mean (SD)	200	48.3 (10.12)

Figure 8. Demographics table dataset for all patients

The values from each of these datasets in Figure 4, Figure 5, Figure 6, Figure 7, and Figure 8 (including additional parameters that are not displayed in the example subset) are what has been provided for upload to ClinicalTrials.gov, (the data from Figure 3), and therefore match what is posted there. This exercise has confirmed that the posted results do match the counts we are claiming in the CSR.

This exercise can be performed with each of the contributing variables for the Baseline Characteristics section, though slight modification may be required to include the primary efficacy variable. As discussed above, we do recommend including this in the output. Additional modifications to the programs may be needed, such as including a specific age group that may not be considered in the CSR program. These slight modifications should be reviewed on a study-by-study basis, to ensure all pertinent data has been submitted to the clinical registry. The modifications needed for these programs contribute to why we elect to validate this table output again, when we produce the excel file containing the results.

The file we ultimately produce outputs Summary Statistics on one sheet and Frequency Counts on another. Figure 9 is an example of the demographic output.

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Demographic Characteristics
Safety Population

	Bardoxolone Methyl - ADPKD	Bardoxolone Methyl - IgAN	Bardoxolone Methyl - T1D	Bardoxolone Methyl - FSGS	Overall (N=103)
Age at Screening (years)					
n	31	26	28	18	103
Mean (SD)	47.4 (9.49)	48.5 (9.53)	49.0 (9.91)	48.6 (12.79)	48.3 (10.12)
Median	46	50	52.5	52.5	49
Min, Max	26, 69	27, 66	29, 64	21, 65	21, 69

Summary Statistics | Frequency Counts

Figure 9. Sample of Demographics ClinicalTrials.gov file for upload to registry

Please note that ClinicalTrials.gov supports calculation of the overall values, based on the groups, in the case that Frequency Counts are being provided. For this reason, the overall column is not strictly required, but we do choose to include it for consistency with our summary statistics output. Summary Statistics, by group, provided to ClinicalTrials.gov, on the other hand, cannot be used to automatically calculate the overall column, and thus these values should be provided in the demographic output.

ADVERSE EVENTS

As done with Demographics, we can produce and validate tables to provide the information required for the Adverse Events section. What is additionally helpful in this case, is that these files, if produced in the correct format, can be directly uploaded to the registry without a need for manual entry. While all of the Adverse Events sections contain similar information and can be produced in the same way, we have selected a single example for clarity in the explanation. Figure 10 is an example of what the Adverse

Events section looks like on ClinicalTrials.gov. Displayed in each of the figures is an example study, MOTOR, containing 6 different treatment groups, and a placebo group.

Adverse Events Go to

Time Frame	16 weeks
Adverse Event Reporting Description	Significant adverse events are collected from the time of the first dose of study drug until the final visit or 30 days following final study dose for patients who terminated early. Both investigator assessment/questioning (systematic) and patient self reporting (non-systematic) are used in this study but were reported by the investigators as a consolidated number and are reported below as systematic.

Arm/Group Title	Placebo	Omaveloxolone Capsules 2.5 and 5 mg	Omaveloxolone Capsules 10 mg	Omaveloxolone Capsules 20 mg	Omaveloxolone Capsules 40 mg	Omaveloxolone Capsules 80 mg	Omaveloxolone Capsules 160 mg
▼ Arm/Group Description	Placebo capsules administered orally once daily for 12 weeks	Omaveloxolone (RTA 408) 2.5 mg capsules administered orally once daily for 2 weeks then 5 mg administered orally once daily for 10 weeks	Omaveloxolone (RTA 408) 10 mg capsules administered orally once daily for 12 weeks	Omaveloxolone (RTA 408) 20 mg capsules administered orally once daily for 12 weeks	Omaveloxolone (RTA 408) 40 mg capsules administered orally once daily for 12 weeks	Omaveloxolone (RTA 408) 80 mg capsules administered orally once daily for 12 weeks	Omaveloxolone (RTA 408) 160 mg capsules administered orally once daily for 12 weeks

All-Cause Mortality

	Placebo	**Omaveloxolone Capsules 2.5 and 5 mg**	**Omaveloxolone Capsules 10 mg**	**Omaveloxolone Capsules 20 mg**	**Omaveloxolone Capsules 40 mg**	**Omaveloxolone Capsules 80 mg**	**Omaveloxolone Capsules 160 mg**
	Affected / at Risk (%)	Affected / at Risk (%)	Affected / at Risk (%)	Affected / at Risk (%)	Affected / at Risk (%)	Affected / at Risk (%)	Affected / at Risk (%)
Total	0/13 (0.00%)	0/6 (0.00%)	0/6 (0.00%)	0/6 (0.00%)	0/6 (0.00%)	0/6 (0.00%)	0/10 (0.00%)

Figure 10. Example of Adverse Events from ClinicalTrials.gov

As was the case for Baseline Characteristics, a picture of the full content of the site is hard to read, so we have also transformed these results into a more readable format in Figure 11. Please note that while an Overall column is required for the Demographics section of the site, the Adverse Events section does not contain one. If the CSR tables you currently produce are only run on the overall population, further modifications are needed before running them through the conversion macro.

Arm/Group Title	**Placebo**	**Omaveloxolone Capsules 2.5 and 5 mg**	**Omaveloxolone Capsules 10 mg**	**Omaveloxolone Capsules 20 mg**	**Omaveloxolone Capsules 40 mg**	**Omaveloxolone Capsules 80 mg**	**Omaveloxolone Capsules 160 mg**
Serious Adverse Events	*Affected / at Risk (%)*	*Affected / at Risk (%)*	*Affected / at Risk (%)*	*Affected / at Risk (%)*	*Affected / at Risk (%)*	*Affected / at Risk (%)*	*Affected / at Risk (%)*
Total	1/13 (7.69%)	0/6 (0.00%)	1/6 (16.67%)	0/6 (0.00%)	1/6 (16.67%)	1/6 (16.67%)	1/10 (10.00%)
Cardiac disorders							
Wide complex tachycardia	0/13 (0.00%)	0/6 (0.00%)	1/6 (16.67%)	0/6 (0.00%)	0/6 (0.00%)	0/6 (0.00%)	0/10 (0.00%)
Atrioventricular dissociation	0/13 (0.00%)	0/6 (0.00%)	0/6 (0.00%)	0/6 (0.00%)	0/6 (0.00%)	0/6 (0.00%)	1/10 (10.00%)
Ventricular tachycardia	0/13 (0.00%)	0/6 (0.00%)	0/6 (0.00%)	0/6 (0.00%)	0/6 (0.00%)	0/6 (0.00%)	1/10 (10.00%)
General disorders							
Exacerbated fatigue	0/13 (0.00%)	0/6 (0.00%)	0/6 (0.00%)	0/6 (0.00%)	0/6 (0.00%)	1/6 (16.67%)	0/10 (0.00%)
Nervous system disorders							
Tonic epileptic seizure	1/13 (7.69%)	0/6 (0.00%)	0/6 (0.00%)	0/6 (0.00%)	0/6 (0.00%)	0/6 (0.00%)	0/10 (0.00%)
Optic neuritis	0/13 (0.00%)	0/6 (0.00%)	0/6 (0.00%)	0/6 (0.00%)	1/6 (16.67%)	0/6 (0.00%)	0/10 (0.00%)
Right sided hemiparesis	0/13 (0.00%)	0/6 (0.00%)	0/6 (0.00%)	0/6 (0.00%)	1/6 (16.67%)	0/6 (0.00%)	0/10 (0.00%)

Figure 11. ClinicalTrials.gov Adverse Event information converted to readable format

To illustrate the starting point, before creating any additional registry documents, below is the table for Serious, Treatment-Emergent Adverse Events that we included in the CSR, and the associated, supporting table dataset.

Table 14.4.1.5 Serious Treatment-emergent Adverse Events by System Organ Class and Preferred Term
Safety Population

Body System or Organ Class Preferred Term	5 MG (N=6) n (%)	10 MG (N=6) n (%)	20 MG (N=6) n (%)	40 MG (N=6) n (%)	80 MG (N=6) n (%)	160 MG (N=10) n (%)	Pooled 408 (N=40) n (%)	Placebo (N=13) n (%)
Number of Subjects with Serious TEAE	0	1 (16.7)	0	1 (16.7)	1 (16.7)	1 (10.0)	4 (10.0)	1 (7.7)
Cardiac disorders	0	1 (16.7)	0	0	0	1 (10.0)	2 (5.0)	0
Atrioventricular dissociation	0	0	0	0	0	1 (10.0)	1 (2.5)	0
Tachycardia	0	1 (16.7)	0	0	0	0	1 (2.5)	0
Ventricular tachycardia	0	0	0	0	0	1 (10.0)	1 (2.5)	0
Nervous system disorders	0	0	0	1 (16.7)	0	0	1 (2.5)	1 (7.7)
Hemiparesis	0	0	0	1 (16.7)	0	0	1 (2.5)	0
Optic neuritis	0	0	0	1 (16.7)	0	0	1 (2.5)	0
Tonic convulsion	0	0	0	0	0	0	0	1 (7.7)
General disorders and administration site conditions	0	0	0	0	1 (16.7)	0	1 (2.5)	0
Fatigue	0	0	0	0	1 (16.7)	0	1 (2.5)	0

Figure 12. CSR Output for MOTOR: Serious, Treatment-Emergent Adverse Events

column_c	termvar	result_c	disp_pct
Pooled 408~(N=40)	Atrioventricular dissociation	1 (2.5)	-0.025
Pooled 408~(N=40)	Tachycardia	1 (2.5)	-0.025
Pooled 408~(N=40)	Ventricular tachycardia	1 (2.5)	-0.025
Pooled 408~(N=40)	General disorders andnadministration site con...	1 (2.5)	-0.025
Pooled 408~(N=40)	Fatigue	1 (2.5)	-0.025
Pooled 408~(N=40)	Nervous system disorders	1 (2.5)	-0.025
Pooled 408~(N=40)	Hemiparesis	1 (2.5)	-0.025
Pooled 408~(N=40)	Optic neuritis	1 (2.5)	-0.025
Placebo~(N=13)	Number of Subjects with Serious TEAE	1 (7.7)	-0.077
Placebo~(N=13)	Nervous system disorders	1 (7.7)	-0.077
Placebo~(N=13)	Tonic convulsion	1 (7.7)	-0.077
160 MG~(N=10)	Number of Subjects with Serious TEAE	1 (10.0)	-0.1
160 MG~(N=10)	Cardiac disorders	1 (10.0)	-0.1
160 MG~(N=10)	Atrioventricular dissociation	1 (10.0)	-0.1
160 MG~(N=10)	Ventricular tachycardia	1 (10.0)	-0.1
10 MG~(N=6)	Number of Subjects with Serious TEAE	1 (16.7)	-0.167
10 MG~(N=6)	Cardiac disorders	1 (16.7)	-0.167
10 MG~(N=6)	Tachycardia	1 (16.7)	-0.167
40 MG~(N=6)	Number of Subjects with Serious TEAE	1 (16.7)	-0.167
40 MG~(N=6)	Nervous system disorders	1 (16.7)	-0.167
40 MG~(N=6)	Hemiparesis	1 (16.7)	-0.167
40 MG~(N=6)	Optic neuritis	1 (16.7)	-0.167
80 MG~(N=6)	Number of Subjects with Serious TEAE	1 (16.7)	-0.167
80 MG~(N=6)	General disorders andnadministration site con...	1 (16.7)	-0.167
80 MG~(N=6)	Fatigue	1 (16.7)	-0.167
Pooled 408~(N=40)	Cardiac disorders	2 (5.0)	-0.05
Pooled 408~(N=40)	Number of Subjects with Serious TEAE	4 (10.0)	-0.1

Figure 13. Supporting table dataset for MOTOR CSR Output

Figure 12 contains all the adverse events that occurred, and the number and percentage of subjects affected. Figure 13, the table dataset, shows that only 5 treatment groups are represented, in addition to the pooled, overall analysis. This is because the subjects in the 5 MG capsule group and the 20 MG capsule group did not experience any adverse events over the course of the study. Reviewing these outputs, we can anticipate what counts we would expect to see uploaded to the clinical registry. For example, both the 10 MG capsule group and the 160 MG capsule group contained a single subject who experienced a cardiac disorder. This is in alignment with our pooled group which indicates that 2 subjects experienced cardiac disorders.

Therefore, based on these CSR documents, we would anticipate our ClinicalTrials.gov results to match what we have populated in Table 2.

Table 2. Compilation of serious adverse events, per treatment group, in MOTOR

Placebo group	1 serious adverse event, tonic convulsion, occurring in 1 subject
5 MG group	0 serious adverse events
10 MG group	1 serious adverse event, tachycardia, occurring in 1 subject
20 MG group	0 serious adverse events
40 MG group	2 serious adverse events, hemiparesis and optic neuritis, occurring in 1 subject
80 MG group	1 serious adverse event, fatigue, occurring in 1 subject
160 MG group	2 serious adverse events, atrioventricular dissociation and ventricular tachycardia, occurring in 1 subject

At this point we have defined the information that needs to be uploaded to ClinicalTrials.gov. We have identified where that information can be found in our final table programs, and in this case, we already have a single program including all of the treatment groups, so there is no need to refer to multiple datasets as was the case with PHOENIX and the demographics table. We need only to convert the output to a validated XLSX file for upload. We have displayed only the placebo group in the resulting excel file in Figure 14 to improve readability, but for the sake of completion, we have also included Figure 15, which converts the treatment values into a more readable format.

This file of "Serious" or "Other" adverse events was generated by the ClinicalTrials.gov Protocol Registration and Results System (PRS)
CAUTION: Do not change the column headers (names or placement) or a subsequent upload will not work.
Column A (adverseEventType) must contain either "Serious" in every row or "Other" in every row.
Column B (assessmentType) may be blank (indicates use table default) or "Systematic Assessment" or "Non-systematic Assessment".
Column C (additionalDescription) may be blank.
Column D (organSystemName) must contain one of the Organ System options listed in http://prsinfo.clinicaltrials.gov/results_definitions.html#OrganSystem
Column E (sourceVocabulary) may be blank (indicates use table default).
Column F (term) - should not be blank and should contain the name of the adverse event
Column G (truncated-arm-name{numEvents}) - may be blank
Column H (truncated-arm-name{numSubjectsAffected}) - should not be blank and should contain a number
Column I (truncated-arm-name{numSubjectsAtRisk}) - may be blank (indicates use table default)
etc... previous three columns repeated for each Arm/Group.
Upon upload, the contents of this file will completely replace the corresponding adverse event table in the PRS.
#

adverseEventType	assessmentType	additionalDescription	organSystemName	sourceVocabulary	term	Placebo {numEvents}	Placebo {numSubjectsAffected}	Placebo {numSubjectsAtRisk}
Serious	Systematic Assessment		*TOTAL	MedDRA (14.1)		1	1	13
Serious	Systematic Assessment		Cardiac disorders	MedDRA (14.1)	Atrioventricular dissociation	0	0	13
Serious	Systematic Assessment		Cardiac disorders	MedDRA (14.1)	Tachycardia	0	0	13
Serious	Systematic Assessment		Cardiac disorders	MedDRA (14.1)	Ventricular tachycardia	0	0	13
Serious	Systematic Assessment		General disorders and administration site conditions	MedDRA (14.1)	Fatigue	0	0	13
Serious	Systematic Assessment		Nervous system disorders	MedDRA (14.1)	Hemiparesis	0	0	13
Serious	Systematic Assessment		Nervous system disorders	MedDRA (14.1)	Optic neuritis	0	0	13
Serious	Systematic Assessment		Nervous system disorders	MedDRA (14.1)	Tonic convulsion	1	1	13

Figure 14. Example of XLSX file for upload to ClinicalTrials.gov

	{numEvents}	{numSubjectsAffected}	{numSubjectsAtRisk}	{numEvents}	{numSubjectsAffected}	{numSubjectsAtRisk}	{numEvents}	{numSubjectsAffected}	{numSubjectsAtRisk}	{numEvents}	{numSubjectsAffected}	{numSubjectsAtRisk}
term	Placebo	Placebo	Placebo	5 MG	5 MG	5 MG	10 MG	10 MG	10 MG	20 MG	20 MG	20 MG
	1	1	13	0	0	6	1	1	6	0	0	6
Atrioventricular dissociation	0	0	13	0	0	6	0	0	6	0	0	6
Tachycardia	0	0	13	0	0	6	1	1	6	0	0	6
Ventricular tachycardia	0	0	13	0	0	6	0	0	6	0	0	6
Fatigue	0	0	13	0	0	6	0	0	6	0	0	6
Hemiparesis	0	0	13	0	0	6	0	0	6	0	0	6
Optic neuritis	0	0	13	0	0	6	0	0	6	0	0	6
Tonic convulsion	1	1	13	0	0	6	0	0	6	0	0	6

term	40 MG	40 MG	40 MG	80 MG	80 MG	80 MG	160 MG	160 MG	160 MG
	2	1	6	1	1	6	2	1	10
Atrioventricular dissociation	0	0	6	0	0	6	1	1	10
Tachycardia	0	0	6	0	0	6	0	0	10
Ventricular tachycardia	0	0	6	0	0	6	1	1	10
Fatigue	0	0	6	1	1	6	0	0	10
Hemiparesis	1	1	6	0	0	6	0	0	10
Optic neuritis	1	1	6	0	0	6	0	0	10
Tonic convulsion	0	0	6	0	0	6	0	0	10

Figure 15. Modified output of file for upload to registry, reformatted for readability

Note that the XLSX format requirement displayed in Figure 17 is specifically regarding files for upload to ClinicalTrials.gov. A similar file can be created for automatic upload to EudRACT, but it will need to be in XML format.

INTRODUCING THE MACRO

A key piece to this automation is the utilization of a macro, ***%ctgovxls***. SAS macros are very powerful tools and are typically used when you are doing a repetitive task and want to ensure consistency. In our

case, we use this SAS macro for the main purpose of ensuring accurate and consistent outputs. Based on our process at Reata, every TLF that is created for the CSR has an associated SAS dataset with a specific, pre-defined structure that contains the relevant information. The macro relies on this pre-defined structure of these TFL datasets to produce the desired XLSX output for ClinicalTrials.gov. In addition, it will produce a dataset that contains the information from the XLSX file, only for the purpose of validating the data in the final document. We have illustrated the process in Figure 16.

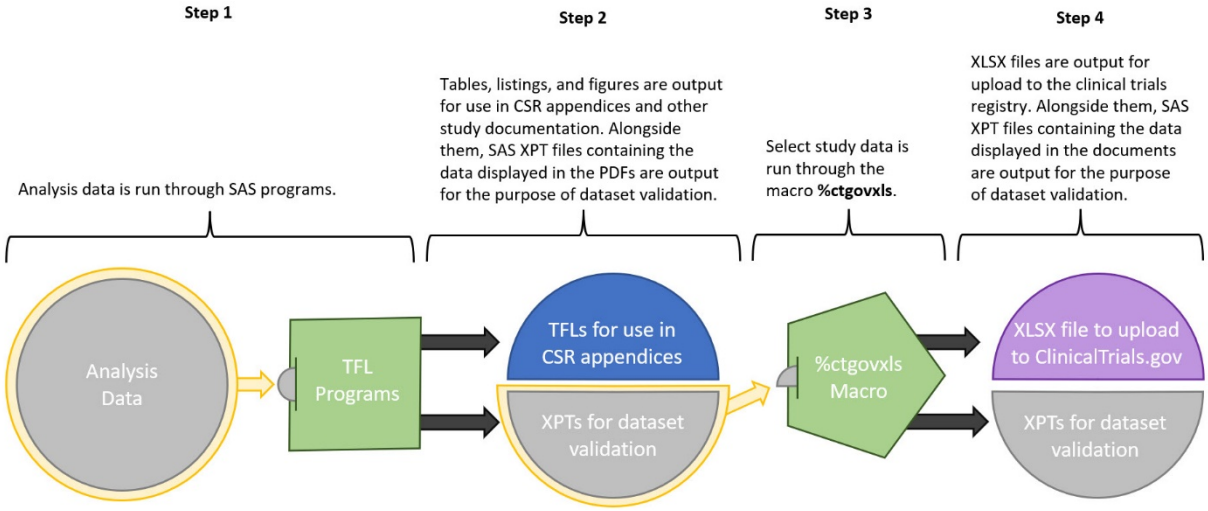


Figure 16. Process flow for creation of files for a clinical registry

Please note that we anticipate (and hope for) the ability to utilize this macro for demographic tables as well, if it becomes possible to automate the results. At this present time, we only run it on our Adverse Events outputs, to prepare them for direct upload to the registry. Therefore, moving forward, the discussion of the macro will be Adverse Event-specific.

The macro we have discussed above is used to produce each of the necessary adverse events tables in file formats that can be directly uploaded to the site. The required adverse events information can be broken up into 4 tables:

1. All-Cause Mortality,
2. Treatment-Emergent, Serious Adverse Events
3. Treatment-Emergent, Other (Non-Serious) Adverse Events, and
4. Treatment-Emergent, Serious, Related Adverse Events.

We have sourced the information required for the list above from our CSR outputs. Each of the four Adverse Events tables that need to be created will be very similar, so the ***%ctgovxls*** macro is an ideal tool for producing consistent outputs. As mentioned above, part of our standard process for table creation includes producing a dataset, so that any values can be validated by dual programming. We use these datasets to create the files for upload to the clinical registries, but it would also be possible to read in the values from an RTF file in an analogous process.

UTILIZING THE MACRO AND FORMATTING THE OUTPUT FILE

The PHOENIX Treatment-Emergent, Serious Adverse Events that we just explained contains a small number of records and seems as though it could be manually entered easily enough. However, each of these tables has potential to contain many more records than would be reasonable to enter in that manner, hence we elect to automate.

There are some notes to consider when creating the files for automation. They must be in XLSX format, as shown above. Additionally, the headers for the counts must not begin until line 15 of the excel file. We

have included text from the template on lines 1-14, which describes that changes to the column headers (names or placement) will cause an upload to fail.

Adverse Event Type (column A) should designate the record as 'Serious' or 'Other' and should always be populated. Assessment Type (Column B) can contain 'Systematic Assessment', 'Non-systematic Assessment', or can be left blank. Additional Description (Column C) can also be left blank, and there is no suggested text for this field. Organ System Name (Column D) must be comprised of the high-level categories provided on ClinicalTrials.gov, which are listed on the ClinicalTrials website. Source Vocabulary (Column E) may be blank, but we have elected to populate it with the MedDRA dictionary version used. Term (Column F) should never be blank and contain each of the individual AE terms that occurred over the study.

Besides the restrictions on how the text should be entered for columns A through F, the counts are expected to be displayed in a certain format as well. This is where it is advantageous that we have a standard format for CSR-table outputs, because we can write a macro that will reformat the dataset into this three-column format, and output an XLSX file. Therefore we gain the functionality of automation as a post-processing step.

The data displayed on our CSR table is already split into columns by treatment group. While records of no adverse events have been simplified to just '0' for a cleaner looking output, any adverse events that did occur are presented in the form of x:y (p%) where x refers to the number of treatment-emergent adverse events, y refers to the number of subjects experiencing treatment-emergent adverse events, and p is the percent of subjects for the given treatment.

Based on the information that has been laid out above, we create a conversion macro:

```
%macro ctgovxls(AEType= ,
                DictVer= ,
                Fname= ,
                AType= "Systematic Assessment",
                Desc= "",
                intab=other2,
                outxls=other2);
```

Taking a study we have completed these registry files for, PRIMROSE, as an example, we will illustrate how to populate the macro call based on the structurally pre-defined dataset in Figure 17. (For readability purposes we have only included two treatment groups from this example.)

	TABLEORD	IDORD	AE System Organ Class	CAT1	N=64	N=62
1	1	1		*TOTAL	9:4 (6.3%)*	3:3 (4.8%)*
2	2	2	Cardiac disorders	Cardiac disorders	1:1 (1.6%)	0
3	2	2	Cardiac disorders	Cardiac disorders	1:1 (1.6%)	0
4	2	2	General disorders and administration site conditions	General disorders and administration site conditions	0	1:1 (1.6%)
5	2	2	Infections and infestations	Infections and infestations	1:1 (1.6%)	0
6	2	2	Injury, poisoning and procedural complications	Injury, poisoning and procedural complications	0	1:1 (1.6%)
7	2	2	Injury, poisoning and procedural complications	Injury, poisoning and procedural complications	0	1:1 (1.6%)
8	2	2	Investigations	Investigations	1:1 (1.6%)	0
9	2	2	Metabolism and nutrition disorders	Metabolism and nutrition disorders	1:1 (1.6%)	0
10	2	2	Metabolism and nutrition disorders	Metabolism and nutrition disorders	1:1 (1.6%)	0
11	2	2	Psychiatric disorders	Psychiatric disorders	1:1 (1.6%)	0
12	2	2	Respiratory, thoracic and mediastinal disorders	Respiratory, thoracic and mediastinal disorders	1:1 (1.6%)	0
13	2	2	Vascular disorders	Vascular disorders	1:1 (1.6%)	0

Figure 17. Treatment-Emergent, Serious Adverse Event table data for PRIMROSE study

The macro will need to read in the Adverse Event dataset output with the associated table, in Figure 17, and output an appropriately formatted excel file in the format of Figure 18.

AEType is the first parameter and the user is intended to enter free text into this field to be displayed in column A of the excel file, AdverseEventType. Since the example we are using is 'Treatment-Emergent, Serious Adverse Events', this input parameter should be set to 'Serious'.

DictVer is the next parameter and the user is intended to enter the corresponding MedDRA dictionary version that was used for coding. By checking study documentation we can confirm that version 17 of MedDRA is used, and thus this parameter should be set to 'MedDRA (17.0)'. It is displayed in column E, SourceVocabulary, of the excel file.

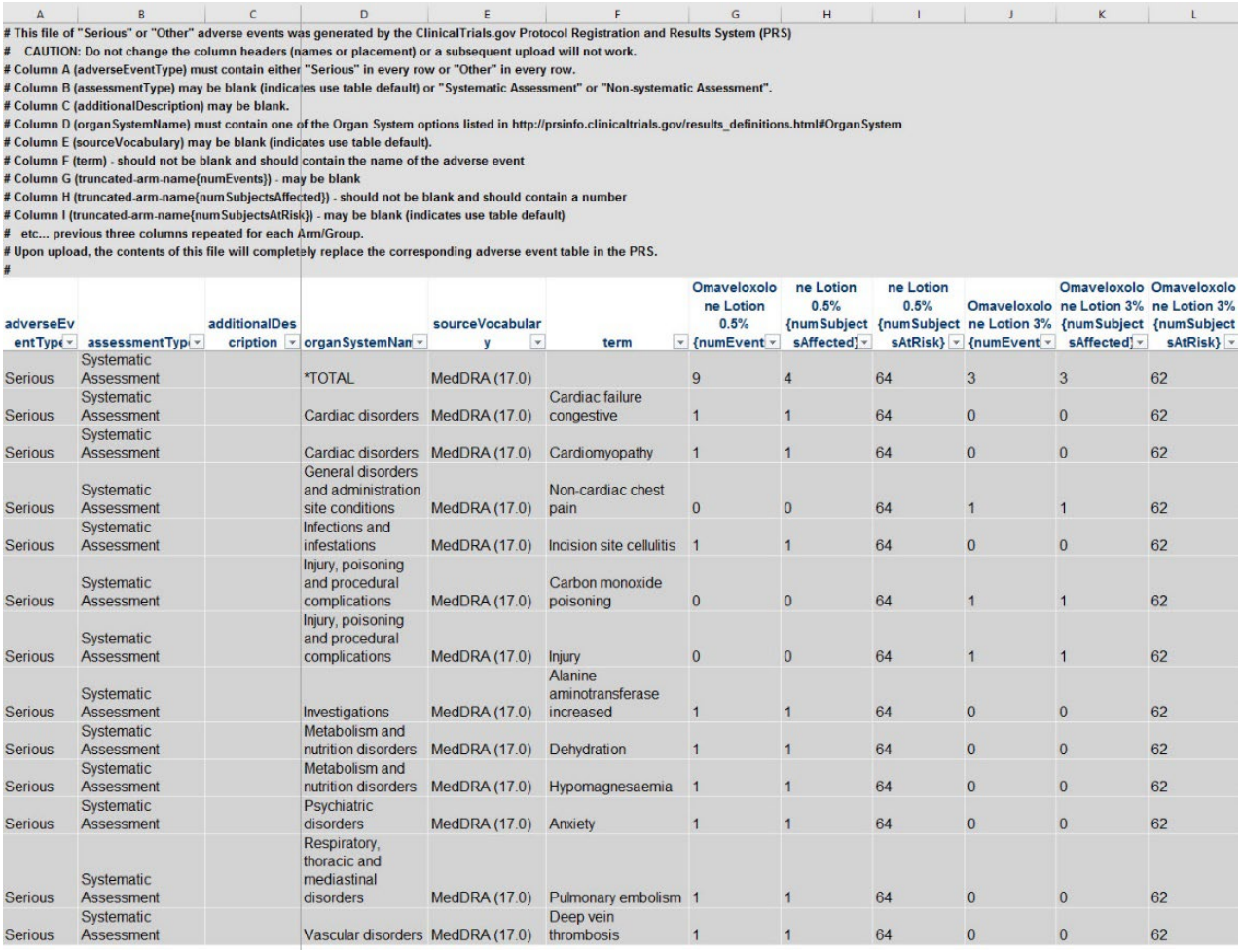
Fname refers to the input dataset being called on. We must differentiate this from the analysis study data, since our goal is to use the values that we displayed on our outputs for the CSR, rather than completely rederive these values. In our case, we must direct the macro to the name of our output dataset – 'serious_adverse_events'. This will not be displayed anywhere in the output excel file.

AType is a free-text parameter that will be used to populate column B, AssessmentType, in the excel file. The recommended text for this field is "Systematic Assessment" so we have set this as a default value.

Desc is a free-text parameter that can be used to provide additional description regarding the subset of study data. It is populated in column C of the excel file, AdditionalDescription. While we generally elect to leave this blank, and example of how you may populate this is to set it to "Related" when AdverseEventType is "Serious" and you intend to produce the Treatment-Emergent, Serious, Related Adverse Events. In our case we are not creating an output for related events, so we will leave this blank.

Intab and **OutxIs** are not displayed in the resulting excel file but are used to provide libraries for the incoming and outgoing data and files. In the example macro call above, both values are set to 'Other2', which is indicating that we are pulling the adverse event dataset from the same location that we are outputting the excel file for the registry to.

Once the parameters described above are input to the macro, all information needed for creating this output has been provided. The macro will pick the appropriate information from the corresponding fields of the dataset and output them into an excel file that we can upload. It will additionally include the standard, required text on the first 14 lines of the excel file, and begin the headings on line 15. Once the validator has dual programmed and verified the values in the resulting, associated dataset, the document is ready for upload to the clinical registry.



This file of "Serious" or "Other" adverse events was generated by the ClinicalTrials.gov Protocol Registration and Results System (PRS)
CAUTION: Do not change the column headers (names or placement) or a subsequent upload will not work.
Column A (adverseEventType) must contain either "Serious" in every row or "Other" in every row.
Column B (assessmentType) may be blank (indicates use table default) or "Systematic Assessment" or "Non-systematic Assessment".
Column C (additionalDescription) may be blank.
Column D (organSystemName) must contain one of the Organ System options listed in http://prsinfo.clinicaltrials.gov/results_definitions.html#OrganSystem
Column E (sourceVocabulary) may be blank (indicates use table default).
Column F (term) - should not be blank and should contain the name of the adverse event
Column G (truncated-arm-name{numEvents}) - may be blank
Column H (truncated-arm-name{numSubjectsAffected}) - should not be blank and should contain a number
Column I (truncated-arm-name{numSubjectsAtRisk}) - may be blank (indicates use table default)
etc... previous three columns repeated for each Arm/Group.
Upon upload, the contents of this file will completely replace the corresponding adverse event table in the PRS.
#

adverseEventType	assessmentType	additionalDescription	organSystemName	sourceVocabulary	term	Omaveloxolone Lotion 0.5% {numEvents}	ne Lotion 0.5% {numSubjectsAffected}	ne Lotion 0.5% {numSubjectsAtRisk}	Omaveloxolone Lotion 3% {numEvents}	Omaveloxolone Lotion 3% {numSubjectsAffected}	Omaveloxolone Lotion 3% {numSubjectsAtRisk}
Serious	Systematic Assessment		*TOTAL	MedDRA (17.0)		9	4	64	3	3	62
Serious	Systematic Assessment		Cardiac disorders	MedDRA (17.0)	Cardiac failure congestive	1	1	64	0	0	62
Serious	Systematic Assessment		Cardiac disorders	MedDRA (17.0)	Cardiomyopathy	1	1	64	0	0	62
Serious	Systematic Assessment		General disorders and administration site conditions	MedDRA (17.0)	Non-cardiac chest pain	0	0	64	1	1	62
Serious	Systematic Assessment		Infections and infestations	MedDRA (17.0)	Incision site cellulitis	1	1	64	0	0	62
Serious	Systematic Assessment		Injury, poisoning and procedural complications	MedDRA (17.0)	Carbon monoxide poisoning	0	0	64	1	1	62
Serious	Systematic Assessment		Injury, poisoning and procedural complications	MedDRA (17.0)	Injury	0	0	64	1	1	62
Serious	Systematic Assessment		Investigations	MedDRA (17.0)	Alanine aminotransferase increased	1	1	64	0	0	62
Serious	Systematic Assessment		Metabolism and nutrition disorders	MedDRA (17.0)	Dehydration	1	1	64	0	0	62
Serious	Systematic Assessment		Metabolism and nutrition disorders	MedDRA (17.0)	Hypomagnesaemia	1	1	64	0	0	62
Serious	Systematic Assessment		Psychiatric disorders	MedDRA (17.0)	Anxiety	1	1	64	0	0	62
Serious	Systematic Assessment		Respiratory, thoracic and mediastinal disorders	MedDRA (17.0)	Pulmonary embolism	1	1	64	0	0	62
Serious	Systematic Assessment		Vascular disorders	MedDRA (17.0)	Deep vein thrombosis	1	1	64	0	0	62

Figure 18. Treatment-Emergent, Serious Adverse Event file for upload to clinical registry, for PRIMROSE study

UPLOADING RESULTS TO CLINICALTRIALS.GOV

ClinicalTrials.gov relies on a data entry system called the Protocol Registration and Results System, or PRS. You must have a PRS account in order to register a trial or enter/upload study results to the registry. Before applying for a PRS account, you should consider if that is necessary. To avoid duplication of any registry information, only the Responsible Party should register and submit information. Therefore, be sure that you should, in fact, be registering for this account before you do.

Once you have an account, you will need to log into PRS, and follow the instructions to enter (or upload) information. The system is accompanied by both a Quick Start Guide, and a more detailed PRS User's Guide that should be able to answer any of your questions. After entering or uploading information, you will need to review it to make sure it's accurate, and (then and only then) submit. The general process is very similar whether you are registering a study or posting the results. There are also instructions included in the accompanying guides that explain how to edit a record, so if ever you upload errant information that needs to be changed for any reason it can be updated.

CONCLUSION

While setting up the macro and getting the process implemented for the first study did require some effort, it was easy to repeat this process for additional studies. There is admittedly more of an advantage to creating a macro for this process when multiple studies need to be uploaded in a repeatable process, as was our case. However, even if only one study needs to be logged in the registry, it is still a reasonable

way to ensure that no mistakes are made in data-entry. We have found that utilizing this process leads to a more efficient upload of accurate results.

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RECOMMENDED READING

- *ClinicalTrials.gov (http://clinicaltrials.gov/ct2/info/about)*
- *HL7 Clinical Trial Registration and Results (http://www.hl7.org/special/Committees/projman/searchableProjectIndex.cfm?action=edit&ProjectNumber=372)*
- *U.S. Public Law 110-85 (Food and Drug Administration Amendments Act of 2007), Title VIII, Section 801 (https://register.clinicaltrials.gov/prs/html/fdaaa-info.html)*
- *Final Rule for FDAAA 801 and NIH Policy on Clinical Trial Reporting (https://clinicaltrials.gov/ct2/manage-recs/fdaaa#)*
- *Clinical Trials Regulation EU No 536/2014 (https://ec.europa.eu/health/medicinal-products/clinical-trials_en)*
- *Code of Federal Regulations, Title 42, Part 11 (https://www.ecfr.gov/current/title-42/chapter-I/subchapter-A/part-11?toc=1)*

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