

Streamlining the Results Reporting for ClinicalTrials.gov and EudraCT

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Summary – Q&A

Introduction: ClinicalTrials.gov/EudraCT Background



Reasons To Register Clinical Trials and Report Results

- ✓ Human Subject Protections
- ✓ Research Integrity
- ✓ Evidence-Based Medicine
- ✓ Allocation of Resources

Introduction: ClinicalTrials.gov/EudraCT Background



What is ClinicalTrials.gov

- A registry and results database of publicly and privately supported research studies conducted in the United States and around the world.
- Information on ClinicalTrials.gov is provided and updated by the sponsor or principal investigator of the clinical study.
- Studies are generally registered to the Web site when they begin, and the information on the site is updated throughout the study and results of the study are submitted after the study ends.

What is EudraCT (European Clinical Trials Database)

Like ClinicalTrials.gov in the US, EudraCT is a database of all clinical trials with at least one site in the European Union (EU).

Introduction: ClinicalTrials.gov Background



What is the Results Database

- Results database was launched in September 2008 to implement Section 801 of the Food and Drug Administration Amendments Act of 2007 (FDAAA)
- FDAAA requires submission of "basic results" for certain clinical trials, generally no later than 1 year after their Primary Completion Date (PCD).
- 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 Final Rule:



Final Rule (42 CFR Part 11) Information

- Clarifies and expands the regulatory requirements and procedures for submitting registration and results information for certain trials to ClinicalTrials.gov, in accordance with FDAAA 801.
- Intended to make it clear to sponsors, investigators, and the public which trials must be reported, when they must be reported, and whether compliance with requirements has been achieved.
- The effective date for the Final Rule is January 18, 2017 and the compliance date is April 18, 2017.
- Failure to comply with these requirements can result in civil penalties up to \$10,000 per day if required results are not submitted, withholding of grant funds for trials supported by federal agencies.

Results Disclosure requirements :



What constitutes clinical trial results information?

Basic Results scientific information is submitted as four separate modules:

- (1) Participant Flow
- (2) Demographic and baseline characteristics
- (3) Outcomes and statistical analyses
- (4) Adverse event information

Other Information:

- “Certain Agreements” related to restrictions on results disclosure
- Overall Limitations and Caveats
- Results Point of Contact

Results Disclosure requirements:



Participant Flow:

Reporting Groups

	Description
Drug A	10mg Drug A administered twice daily
Drug B	20mg Drug B administered twice daily
Placebo	Participants were given a single pill, twice daily.

Participant Flow: Overall Study

	Drug A	Drug B	Placebo
STARTED	50	50	50
COMPLETED	48	49	47
NOT COMPLETED	2	1	3
Lost to Follow-up	1	0	2
Adverse Event	1	1	1

Results Disclosure requirements :



Demographic and baseline characteristics:

Baseline Measures

	Drug A	Drug B	Placebo	Total
Number of Participants [units: participants]	50	50	50	150
Age [units: participants]				
<=18 years	0	0	0	0
Between 18 and 65 years	50	50	50	150
>=65 years	0	0	0	0
Age [units: years] Mean $\pm$ Standard Deviation	41 $\pm$ 12	42 $\pm$ 11	41 $\pm$ 11	41 $\pm$ 11
Gender [units: participants]				
Female	25	23	28	76
Male	25	27	22	74

Results Disclosure requirements :



Outcomes and statistical analyses:

1. Primary Outcome Measure: Time to Disease Progression

Measure Type	Primary
Measure Name	Time to Disease Progression
Measure Description	Disease progression was defined as >25% loss in hearing compared to baseline.
Time Frame	24 months
Safety Issue	No

Measured Values

	Drug A	Drug B	Placebo
Number of Participants Analyzed [units: Participants]	50	50	50
Time to Disease Progression [units: Days] Log Mean $\pm$ Standard Deviation	4.94 $\pm$ 1.32	5.52 $\pm$ 1.28	4.78 $\pm$ 1.11

Statistical Analysis 2 for Time to Disease Progression

Groups ^[1]	Drug A vs. Drug B
Method ^[2]	t-test, 2 sided
P Value ^[3]	0.017
Mean Difference (Net) ^[4]	-0.672
95% Confidence Interval	(-1.224 to -0.119)

Results Disclosure requirements :



Adverse Event Information:

All-Cause Mortality: A table of *all* deaths due to any cause, with the number and frequency of such events by arm/comparison group.

Serious Adverse Events: A table of *all* serious adverse events, grouped by organ system, with the number and frequency of such events by arm/comparison group.

Frequent Adverse Events : A table of AEs (not included in the serious adverse event table) that exceed a frequency threshold (Maximum 5%) within any arm of the clinical study, grouped by organ system, with the number and frequency of such events by arm/ comparison group.

Results Disclosure requirements :



Adverse Events Results Example:

All-Cause Mortality			
	Drug A	Drug B	Placebo
	Affected / at Risk (%)	Affected / at Risk (%)	Affected / at Risk (%)
Total	0/50 (0.00%)	0/50 (0.00%)	0/50 (0.00%)
▼ Serious Adverse Events			
	Drug A	Drug B	Placebo
	Affected / at Risk (%)	Affected / at Risk (%)	Affected / at Risk (%)
Total	0/50 (0.00%)	0/50 (0.00%)	0/50 (0.00%)
▼ Other (Not Including Serious) Adverse Events			
Frequency Threshold for Reporting Other Adverse Events	5%		
	Drug A	Drug B	Placebo
	Affected / at Risk (%)	Affected / at Risk (%)	Affected / at Risk (%)
Total	16/50 (32.00%)	4/50 (8.00%)	13/50 (26.00%)
Ear and labyrinth disorders			
Ear pain ^{††}	4/50 (8.00%)	2/50 (4.00%)	2/50 (4.00%)
Gastrointestinal disorders			
Abdominal distension ^{††}	3/50 (6.00%)	2/50 (4.00%)	6/50 (12.00%)
Abdominal pain ^{††}	10/50 (20.00%)	1/50 (2.00%)	11/50 (22.00%)
Abdominal pain upper ^{††}	2/50 (4.00%)	1/50 (2.00%)	4/50 (8.00%)

Manual Entry (via interactive Web-based Protocol Registration and Results System (PRS))

- Usually handled by Regulatory Affairs/Clinical Trial Disclosure Lead
- time consuming and error-prone
- many review cycles among different functional groups.
- only feasible for a very small number of trials with a reasonable number of necessary entries.

Current methods in Results Reporting



XML upload (per PRS XML schemas)

- Facilitates the transfer of data into ClinicalTrials.gov from sponsor's computer system.
- Results are not readily available in a format that can be converted into XML
- Requires significant technical expertise to structure the data according to the PRS XML schemas

Streamlining the process:



Proposed Method :

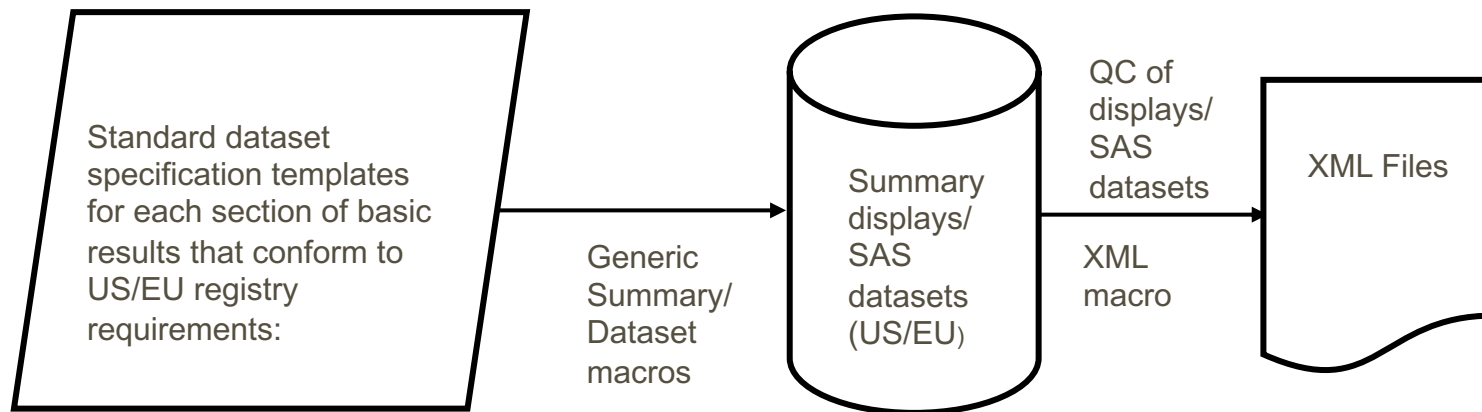
- SAS® will be used to gather the required information from existing databases and generate an XML file to be uploaded directly to ClinicalTrials.gov/EudraCT
- Requires planning at the study start up although this being an end of study deliverable.
- Required data displays (tables/datasets) will be part of study analysis plans in the format that conform to regulatory standards.
- The information needed for the registries will be produced during the clinical trial reporting, at which these data elements are produced anyway.

Streamlining the process:



Flow Chart of Proposed Method:

Flow of data in the proposed method where XML files are created that are ready to be uploaded onto the registries



Streamlining the process::



Sample Adverse Events Results Dataset Specification:

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: AEBODSYS 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)

Streamlining the process::

Sample Adverse Events Results Dataset:



TRT TRTORD MEDDRA AEBODSYS AEDECOD AETYPE N_AE N_ARM RATIO

TRT	TRTORD	MEDDRA	AEBODSYS	AEDECOD	AETYPE	N_AE	N_ARM	RATIO
Drug A	1	MedDRA 20.0	Ear and labyrinth disorders	Ear pain	NONSAE	4	50	8
Drug B	2	MedDRA 20.0	Ear and labyrinth disorders	Ear pain	NONSAE	2	50	4
Placebo	3	MedDRA 20.0	Ear and labyrinth disorders	Ear pain	NONSAE	2	50	4
Drug A	1	MedDRA 20.0	Gastrointestinal disorders	Abdominal distension	NONSAE	3	50	6
Drug B	2	MedDRA 20.0	Gastrointestinal disorders	Abdominal distension	NONSAE	2	50	4
Placebo	3	MedDRA 20.0	Gastrointestinal disorders	Abdominal distension	NONSAE	6	50	12
Drug A	1	MedDRA 20.0	Gastrointestinal disorders	Abdominal pain	NONSAE	10	50	20
Drug B	2	MedDRA 20.0	Gastrointestinal disorders	Abdominal pain	NONSAE	1	50	2
Placebo	3	MedDRA 20.0	Gastrointestinal disorders	Abdominal pain	NONSAE	11	50	22
Drug A	1	MedDRA 20.0	Gastrointestinal disorders	Abdominal pain upper	NONSAE	2	50	4
Drug B	2	MedDRA 20.0	Gastrointestinal disorders	Abdominal pain upper	NONSAE	1	50	2
Placebo	3	MedDRA 20.0	Gastrointestinal disorders	Abdominal pain upper	NONSAE	4	50	8
Drug A	1	MedDRA 20.0	Total # participants affected		NONSAE	16	50	32
Drug B	2	MedDRA 20.0	Total # participants affected		NONSAE	4	50	8
Placebo	3	MedDRA 20.0	Total # participants affected		NONSAE	13	50	26
Drug A	1	MedDRA 20.0	Total # participants affected		SAE	0	50	0
Drug B	2	MedDRA 20.0	Total # participants affected		SAE	0	50	0
Placebo	3	MedDRA 20.0	Total # participants affected		SAE	0	50	0
Drug A	1				MORT	0	50	
Drug B	2				MORT	0	50	
Placebo	3				MORT	0	50	

Streamlining the process:



Sample Annotated Adverse Event Results with XML tags:

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

Frequency Threshold for Reporting Other Adverse Events	5%		
	reportingGroupID (TRT)		
	Drug A	Drug B	Placebo
	Affected / at Risk (%)	Affected / at Risk (%)	Affected / at Risk (%)
Total	16/50 (32.00%)	4/50 (8.00%)	13/50 (26.00%)
Ear and labyrinth disorders	organSystemName (AEBODSYS)		
Ear pain ††	4/50 (8.00%)	2/50 (4.00%)	2/50 (4.00%)
Gastrointestinal disorders	term (AEDECOD)		
Abdominal distension ††	3/50 (6.00%)	2/50 (4.00%)	6/50 (12.00%)
Abdominal pain ††	10/50 (20.00%)	1/50 (2.00%)	11/50 (22.00%)
Abdominal pain upper ††	2/50 (4.00%)	1/50 (2.00%)	4/50 (8.00%)

numSubjectsFrequentEvents (N_AE) **partAtRiskfrequentEvents (N_ARM)**

-
- 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.
 - Eliminates the need to manually transcribe summary results there by improving the accuracy, efficiency and consistency of the result posting.
 - Eliminates the potential transcription errors.
 - Simplifies study team review of summary results process before they are released in the public domain.
 - Requires upfront investment of resources to develop standard templates and macro tools, but saves significant time and resources in the long run.

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
- ClinicalTrials.gov Training Materials <https://clinicaltrials.gov/ct2/manage-recs/present>
- [ClinicalTrials.gov PRS Results Schema](#): Describes the XML format suitable for uploading the results data elements