The Compliance and Implementation of Clinical Trial Outcome Disclosure on ClinicalTrials.gov

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ABSTRACT

Section 801 of the Food and Drug Administration Amendments Act (FDAAA) mandates the following information be loaded into ClinicalTrials.gov effective from 27SEP2009 for all trials for Drugs, Biologics and Devices:

- The basic results information described in the law.
- Information about serious and frequent adverse events (AE) observed.

To comply with the Law, the trial sponsor must register Phase I trials in patients and Phase II to IV trials as early as first regulatory approval and at the latest 21 days after first enrollment. To accommodate these additional requirements SOPs were established and cross functional teams were involved in the implementation collaboratively.

In this paper, the following points are discussed.
- the brief background and the drive of FDAAA Section 801
- the reaction and formation of a team at sanofi-aventis for analysis and solutions
- the experience learned in stages (e.g. data consolidation, loading, QC and official release)
- the critical points in developing automated programs and understanding the concept and design of partial loading

INTRODUCTION

As per FDA Amendment Act of 2007 legislation – Title VIII, disclosure of basic results on the ClinicalTrials.gov site managed by the National Institutes of Health (NIH), has become mandatory for studies performed on approved drugs. The compliance and implementation of new legislative requirements at the company level are always starts with an understanding of the spirit of the law as determined by related initiatives, history, laws / regulations and case law. Once this interpretations by internal departments is formulated then the actions needed to meet the requirements are transformed into serial plans that each stakeholder and owner utilizes to work together per trial submission schedules and posting deadline.

What the paper resented here are (1) digested and condensed pieces of various FDAAA Section 801 related publications that affect the contribution of the content definitions of Protocol Registration System (PRS) data elements; (2) study trial data collection and conversion through identified element owners of involved departments; and (3) the experience summary of implementation that includes the creation and integration of Extensible Markup Language (XML) deliverables, outcome quality assurance, verification and automations especially for the AE posting in the study results section.

The Clinical Services Center Team was assigned to explore a systematical approach to convert AE reports generated by the Biostatistics Department into XML database structure defined by the result XML schema before uploading to PRS, a manual data entry and batch loading system. The teams key objectives:
- Reduce data entry efforts and minimize human error
- Step by step development starting from AEs moving to all other tables defined in the result section
- Make this toolkit sharable with other departments such as Medical Affairs and Biologics

A real case study is provided on the AE posting to ClinicalTrials.gov according to the definition in the result XML schema via a SAS macro plus the experiences on PRS partial uploading. The Utility macro is designed to run under Unix (HPUX, SUN/Solaris) and Windows (2000, XP) with both SAS® V8.2 (32-bit) and V9.13 (32 and 64-bit).

DISCLOSURE SCOPE

For those involved in Trial Disclosure, it is helpful to read through two introductory documents for a better understanding on required data elements and descriptions of their contents and purposes for the two major trial disclosure categories in PRS and ClinicalTrials.gov: Protocol Overview and Study Results.
1. ClinicalTrials.gov Protocol Data Element Definitions (DRAFT)*
2. ClinicalTrials.gov “Basic Result” Data Element Definitions (DRAFT)*
Though the law took effect more than half a year ago, these documents are still evolving and some criteria listed in the documents conflict with what has been required to be loaded to the ClinicalTrials.gov. Before sharing some examples of these conflicts, let us get a high level understanding of these data elements based on these drafts that was updated in February 2010.

The legend in (Figure 1) at the beginning of these two documents can be of interest for people involved in the data collection/preparation.

![Figure 1: Legend from ClinicalTrials.gov Protocol Data Element Definitions (DRAFT) and ClinicalTrials.gov “Basic Result” Data Element Definitions (DRAFT).](image)

To provide better linkages between the detail elements from this document and the standard sections organized and presented in the PRS and ClinicalTrials.gov, we bolded the sections from the PRS and listed the items mentioned in the Data Element Definitions document for readers’ better understanding and efficient cross referencing.

<Category I: Protocol Overview >

![Figure 2: Screen shot from the ClinicalTrials.gov website for study efc5555.](image)

- **PURPOSE**
  Descriptions of the purpose of the clinical trail. The numbers (e.g. 1.) are referenced in the DRAFT documents.
  1. **Titles and Background Information:** Protocol ID, Brief and Official titles, Study type,
  2. **US Food and Drug Administration (FDA) Information:** Protocol number & type (e.g. IND or IDE), Grantor
  4. **Sponsors:** Sponsor’s and/or Collaborator’s information
  5. **Study Description:** Brief summary,
  6. **Status:** Overall enrollment, Record validation date, Overall recruitment status, Study start/completion dates
  7. **Study Design:** Primary purpose, Observational study model, Study phase, Number of arms, Masking & Allocation (open or blinded etc), Study classification, Primary / secondary outcome measurements
  8. **Arms, Groups and Interventions:** The label/type/description of Arm and Intervention

- **ELIGIBILITY**
  Descriptions of subject qualifications to participate in the clinical trial.
  10. **Eligibility:** Study population description, sampling method, eligibility criteria (inclusion, exclusion), gender, age limits (minimum, maximum)
• CONTACTS AND LOCATIONS
Multiple locations conducting the clinical trial shall be specified.
11. Protocol Location, Contact and Investigator Information: Facility (Name, city, state, country etc.), recruitment status, facility contact (names, phone, email etc.) and backup, central contact, overall study officials

• MORE INFORMATION
The contents can be Results or Other Publications.
3. Human Subjects Review: Reviewing board approval, name, contact and oversight authorities
12. Related information: References and links

<Category II: Study Results>

To view the NIH's position of the current definition of Study Results see the "The "basic results" data element definitions and requirements currently included in ClinicalTrials.gov represent the NIH’s current thinking on this topic, and were developed in response to the provision contained within FDAAA that required the Agency to develop a "basic results" databank within one year of enactment." quoted from the doc ClinicalTrials.gov "Basic Result" Data Element Definitions (DRAFT).

There are many data entries or batch loading in strict defined tabulation style for statistical presentation and some calculations about sum and percentage performed by the data schema and programs within the PRS – not per sponsor’s stat reports. The data elements those are included in the Study Results from the PRS and the final face on ClinicalTrials.gov (Figure 3).

- Participant Flow
- Baseline Characteristics
- Outcome Measures
- Serious Adverse Events
- Other Adverse Events
- More Information

Figure 3: Snapshot of the study results tab from ClinicalTrials.gov

• PARTICIPANT FLOW
3. Participant Flow: Talking about the FLOW the PRS adapted the CONSORT flow diagram (Figure 4) as the outline for descriptions of data elements needed in each trial stage, such as:
   - Recruitment details: to provide summary of enrollment, date, site information
   - Pre-assignment details: for significant events & approaches happened in enrollment but before group assignment
   - Arm/Group: for Reporting Groups tabulation,
   - Period(s): for Overall Study subject count per milestones/arm like Start, Complete and Reason not complete (subject dispositions) per defined items in the guide
Figure 4: CONSORT flow diagram.

- **BASELINE CHARACTERISTICS**

  4. Baseline Characteristics: Besides the reporting group displayed with the same information as in the participant flow, the baseline measures table shall display the head count of age, race and gender of each arm for categorical variable and measure of central tendency (mean, median etc) for a continuous variable.

- **OUTCOME MEASURES**

  5. Outcome Measures: The outcome measure type can be one of the following.
  
  - Primary (from protocol section)
  - Secondary (from protocol section)
  - Other pre-specified
  - Post-hoc

  The data cell for this measurement summary table, depends on the study design, can accommodate these three types: categorical, continuous or time to event by treatment group.

  Various statistical options and methods shall be carefully entered with all necessary supplemental descriptions.

  Note: Primary and secondary outcomes are required for interventional studies, optional for observational studies.

- **SERIOUS ADVERSE EVENTS**

  7. Adverse Events: Serious Adverse Events: A table of all anticipated and unanticipated serious adverse events, grouped by organ system, with number and frequency of such events in each arm of the clinical trial.

- **OTHER ADVERSE EVENTS**

  7. Adverse Events: Other Adverse Events: A table of anticipated and unanticipated events (not included in the serious adverse event table) that exceed a frequency threshold (normally 5%) within any arm of the clinical trial, grouped by organ system, with number and frequency of such events in each arm of the clinical trial.

- **MORE INFORMATION**

  1. Results Point of Contact: Name of official title, organization name, phone, email
  2. Certain Agreements: Information on whether there exists an agreement between the sponsor or its agent and the principal investigators
  3. Overall Limitations and Caveats: If appropriate, it is used to describe significant limitations of the trial.
BEFORE SUBMISSION

Checking results is another labour intensive activity due to the large volume of requested data integrated from many departments/sources. The correct conversion from various data format into XML if not done in a systematic, automatic and validated procedure will be completed by an visual inspection.

The PRS provided a pre-submission checklist (still in draft 04SEP2009, Figure 5 below) that provides not necessary detailed but at least fundamental check points from PRS’s point of view plus some links to supporting documents.

Figure 5: Snapshot of the PRS pre-submission checklist. [http://prsinfo.clinicaltrials.gov/pre-submission-checklist.pdf](http://prsinfo.clinicaltrials.gov/pre-submission-checklist.pdf)

Referencing the checklist above, the study Owner/administrator shall use the administrative functions (Figure 6) provided in the PRS to check and validate working copies. It is from this experience that the contents are validated and ready to release to the public on ClinicalTrials.gov, the study owner/administrator shall open the target study in edit mode (Figure 6) by clicking the “Check all records” option.

Note: NOT to use the “Release all records”, it is almost not possible in that situation and too dangerous to do so in the reality that many studies/records are still ongoing.

Figure 6: Administrative functions from the PRS
The owner/administrator will have the ability to select the study that needs to be edited (Figure 7).

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Title</th>
<th>Status</th>
<th>Registry ID</th>
<th>Update Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>EFC49121</td>
<td>Atrial Fibrillation: Clopidogrel Trial With Ibuprofen for Prevention of Vascular Events (ACTIVE II)</td>
<td>Completed</td>
<td>2009-10</td>
<td>Public Registry ICD</td>
</tr>
<tr>
<td>EFC5555</td>
<td>A Trial With Dronedarone to Prevent Hospitalization or Death in Patients With Atrial Fibrillation (ATHENA)</td>
<td>Completed</td>
<td>2009-07</td>
<td>Public Registry ICD</td>
</tr>
</tbody>
</table>

Figure 7: A snapshot of the check all records from the PRS.

And then change the study status through 4 steps (arrow pointed in figure 8 below) toward the final release to ClinicalTrials.gov.

Figure 8: A snapshot of the Edit Protocol Record.

CHALLENGES

There are some challenges expected or unexpected that naturally happen after the full implementation. Here are the findings experienced thus far:

DATA COLLECTION AND INPUT

PRS’s fundamental design is to allow the trial sponsor to upload the required data online. The trial sponsor has to log into the PRS and manually enter the trial information for overall head count and subject at risk, (Figure 9) the individual event entry, (Figure 10) and statistical entry for primary or secondary outcome, (Figure 11)

Figure 9: A snapshot of the PRS for overall head count and subject at risk.
EVOLVING PRS REQUIREMENTS

Two years of preparation before September 27, 2009 release of the Section 801 of the FDAAA, the implementation of PRS is the beginning of graduate enhancements of the quality and statistical presentation of content that meets the changing needs of the clinical trial outcome disclosure. These changes shall constantly be monitored, and correctly interpreted by the designated person(s) for proper reaction and implementation.

For example, On December 7, 2009 the National Institutes of Health (NIH) proposed to issue new regulations that will recommend procedures for registering and reporting the results, including adverse events, of clinical trials in ClinicalTrials.gov, in accordance with section 801 of the Food and Drug Administration Amendments Act of 2007, (FDAAA, Pub. L. 110-85). Rather than proceed with separate regulations for registration and results reporting as previously announced, the agency intends to proceed with a single rulemaking to implement the expanded registry, results, and adverse event information reporting requirements of the statute. This is expected to be released around September, 2010 - RIN: 0925-AA55(1)
Also like the “What’s New” in the PRS main page (Figure 12) – Help section may post many trivial updates on e.g. new data point definitions, improvement on data entry screens or the quick reference of major regulation announcement such as the statement “Adverse Events now required September 28, 2009”.

Figure 12: Screen shot from the PRS main page.

IMPLEMENTATION

The laws, regulations and guidelines for clinical trial disclosure though may be evolving with more complexities but the enforcement of compliance remains simple and straight. However the implementations from trial sponsors are definitely varied. To share how the data element stakeholders at sanofi-aventis comply with the requirements with stage-approaches and integration efforts on XML generation and loading. Sanofi-aventis will also share the design concept of the in-house developed SAS® Macro that generates the Serious and Other AE XML files for partial loading specifically designed for the “Study Results” portion.

Systematic approaches were completed in line with the two major disclosure categories below with the computer system CRYSTAL and a SAS®/Macro based Utility RUBY-STAR, corresponding SOP, procedures created to ensure the completeness and quality of data collection, transformation and posting.

<PROTOCOL OVERVIEW> with CRYSTAL<sup>2</sup>

CRYSTAL is a sanofi-aventis R&D cross-functional system

- ensure the consistency and the traceability of the information disclosed on the public registries of clinical studies such as ClinicalTrials.gov or to the regulatory authorities
- manage and track all clinical trial information disclosed, from the early development stage to post-marketing

Its primary information sources include Corporate Regulatory Affairs, Global/Local Medical Affairs and International Clinical Development and the secondary sources from Global Pharmacovigilance and Epidemiology, Global Pre-Clinical Development.

With the backend database connectivity, the CRYSTAL centralized the trial disclosure procedures and operations for involved departments and key players, Editor and Final Approver, who walk through disclosure stages – Creation, Approval and Publishing. All ClinicalTrials.gov needed data points are either extracted automatically or transformed into GUI based selections from the databases or manually entered into the system as screenshots demonstrated in Figure 13.

Creating a Study Disclosure

Figure 13: Snapshot from CRYSTAL for input selections of Central Contacts
All the data fields related publishing in the system are designed with attributes (Purpose, length) per PRS’s guidelines and its entry specifications (Figure 14)

![Table](image)

**Figure 14:** Snapshot from CRYSTAL for Trial Title (Brief/Official) input

Most of the Protocol Overview elements like Trial Identification, Oversight authority, Sponsor Info, Primary/Secondary Outcome Measures’ info (general description, time frame, and safety issue), Eligibility and Contacts and locations are collected or auto populated in the system then later converted into two XML files:

- Master Trial Disclosure file which is 100% compatible for uploading to PRS
- Contacts and locations file good for “Partial Upload” due to its size expansion and participated site data accumulation through the time being

From the loading, quality check and release to public the system also enforce the internal approval procedure and post publishing tracking for the completeness of a disclosure task.

**<STUDY RESULTS> with Ruby-Star³**

By design, data has to be entered manually in the NIH’s PRS. Besides being time consuming, it demands careful quality checks to insure there are no data entry errors. In particular, adverse events reports consist of a large amount of MedDRA terms and figures that have to be carefully maintained after data entry for quality.

**Markup Language**

Mark-up language is a language that “marks-up” the text of a document by putting tags around content to describe what that content is.

**SAS XML Mapper**

SAS XML Mapper is an XMLMap support tool for the SAS XML LIBNAME engine. SAS XML Mapper is a Java-based, stand-alone application that creates an XMLMap. The XMLMap displays in the XMLMap primary pane and on the **XMLMap** tab of the information pane as seen in Figure 15.

![Image](image)

**Figure 15:** Snapshot of the XMLMap from SAS.
Incorporating SAS XML Mapper

The first step is to use the SAS XML Mapper to “Map” the XML master file provided with each study. This mapping of the Master XML file only has to occur once. The XML map file can then be stored and used with any future studies XML master files.

However, the PRS also offers, the possibility to upload the results directly in the protocol record by XML file. Specifications of the XML schema file for the results portion is available on the PRS site (Figure 16). XML is a meta-language part of the web standard specification defined by the W3C (World Wide Web Consortium). It allows exchanging structured data files through the web independently of the system it comes from. For example, SAS® Software commonly used by statisticians to produce statistical reports may be utilized to produce XML-structured data files per PRS defined result schema template.

The SAS system enables the SAS user the ability to use markup language to create an XML file that can then be used to upload the FAE and SAE finding to RUBY-STAR. The project also incorporates the SAS XML Mapper to read the XML master file and create a SAS dataset that is read in to create the XML uploaded header.

Creating Tagset Template

Define the Tagset by using the Proc Template procedure and starting with the Tagset.Custom template.

```
proc template;
  define tagset tagsets.custom ;
  notes "SAS XML Engine output event model(interface)";
Define Tagset
```

The tagset template allows a user to use macro variables into the tagset template. Incorporate macro variables into the tagset template.

```
%do i = 1 %to &number_of_arms;
  mvar ReportingGroupId&i numSubjectsAffected&i;
%end;
  mvar event;
The macro variables created in the program are defined in the Tagset
```

Create the XML header in the tagset template.

```
define event EmitMeta;
  start:
    indent;
    put "<study_collection>" / if cmp(event, "sae");
    put "<clinical_study>" CR / if cmp(event, "sae");
    put "<id_info>" CR / if cmp(event, "sae");
    indent;
Create the XML header using the tagset template IF statement and macro variables.
```

Write out the column values.

```
set $name  "organSystemName";   trigger EmitCol;
set $name  "sourceVocabulary";  trigger EmitCol;
set $name  "term";              trigger EmitCol;
Column values are written out.
```

End the XML file.

```
finish:
  xdent;
  put "</seriousAdverseEvents>" CR / if cmp(event, "sae");
  put "</frequentAdverseEvents>" CR / if cmp(event, "fae");
  put "</reportedEvents>" CR / if cmp(event, "fae");
  put "</result>" CR / if cmp(event, "fae");
  put "</clinical_study>" CR / if cmp(event, "fae");
  put "</study_collection>" / if cmp(event, "fae");
  xdent;
  break;
end;
The xml file is completed.
```
**SAS® Macro code and Parameters**

The tagset template is then incorporated into SAS macro language. The macro parameters gather user input that is passed to the tagset template to create the final XML file.

```
data _null_;  
do i=1 to &number_of_arms;  
call symput("reportinggroupid"||compress(i),'<reportingGroupId>ReportedEvents-InterventionGroup.'||compress(i)||'</reportingGroupId>');  
call symput("numSubjectsAffected"||compress(i),"numSubjectsAffected"||compress(i));  
end;  
run;  
```

<table>
<thead>
<tr>
<th>Macro variables created in SAS macro and passed to tagset template.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macro parameters inputted by the user. The order of these parameters is very important due to the difference between the order of treatments in the tables for a normal FDA submission vs. the ClinicalTrials.gov website.</td>
</tr>
<tr>
<td><strong>Xmlin:</strong> The xml master file.</td>
</tr>
<tr>
<td><strong>Xmlmap:</strong> The mapping program that gives SAS the ability to read in the xml master file. This file is created by SAS mapper one time and assumes the xml master file will not change. If it does then SAS mapper code will have to be created.</td>
</tr>
<tr>
<td><strong>Faedataset:</strong> SAS AE dataset.</td>
</tr>
<tr>
<td><strong>Saedataset:</strong> SAS SAE dataset.</td>
</tr>
<tr>
<td><strong>Xmlout:</strong> The location and file name of the output XML file.</td>
</tr>
<tr>
<td><strong>Numfreqa:</strong> The variable(s) found in the AE dataset and used in the numSubjectsFrequentEvents output XML header.</td>
</tr>
<tr>
<td><strong>Riskfreqa:</strong> The variable(s) found in the AE dataset and used in the partAtRiskFrequentEvents output XML header.</td>
</tr>
<tr>
<td><strong>Numfreqs:</strong> The variable(s) found in the SAE dataset and used in the numSubjectsSeriousEvents output XML header.</td>
</tr>
<tr>
<td><strong>Riskfreqs:</strong> The variable(s) found in the SAE dataset and used in the partAtRiskSeriousEvents output XML header.</td>
</tr>
<tr>
<td><strong>Dslocation:</strong> The location of the SAS AE and SAE datasets. The libname.</td>
</tr>
<tr>
<td><strong>Case:</strong> The ability to turn Uppercased AE terms into sentence case.</td>
</tr>
</tbody>
</table>

```
%xml(xmlin=U:\xml\protocol_record_EFC4912I_03_03.xml  
,xlmap=U:\xml\xml.map  
,faedataset=efc4912_nsaes  
,saedataset=efc4912_saes  
,numfreqa=__val1_1 __val1_2  
,riskfreqa=__den_1 __den_2  
,numfreqs=__val1_1 __val1_2  
,riskfreqs=__den_1 __den_2  
dslocation=&REPORT\DATA  
,case=Y);
```

The user inputted parameters.

The SAS macro now creates the xml file for serious adverse events and frequent adverse events.

```
filename xmlout "&xmlout";  
libname xmlout xml xmltype=GENERIC tagset=tagsets.custom;  
data xmlout.class;  
set class;  
run;  
```

The final XML file is created for SAE and FAE by appending SAE and FAE data.
XML Schema for Study Results

The schema (Figure 16) defined, periodically updated and provided by the PRS is a critical document for uploading especially Partial uploading that is channel opened for automation

Each element however are qualified for PARTIAL upload as long as the Boolean switch turned on in the full tag hierarchy like left (Figure 17) using AE Reported Events as an example.

Figure 16: Snapshot for the XML schema from the PRS dated 12/02/2009

In the ‘dashed box 1’ it defined all the element names that are required to post. The ‘Complex Type’ of each Element has strictly defined data points and their names in the XML tag structure.

Figure 17 code example for Results partial upload

- For any partial upload of including the Result session, the <clinical_study> tag shall be replaced with <clinical_study partial_upload="true"/>

- In the corresponding <result> tag in Master (complete study download) XML file, the partialUpload="true" shall be added and reloaded back to the PRS to allow upcoming partial uploads happen.

2 Keys for a successful RESULT upload:

1. Each element however are qualified for PARTIAL upload as long as the Boolean switch turned on in the full tag hierarchy like left (Figure 17) using AE Reported Events as an example.
2. For any partial upload of including the Result session, the <clinical_study> tag shall be replaced with <clinical_study partial_upload="true"/>

In the ‘dashed box 2’ it defined the ‘Complex Type’ of each Element has strictly defined data points and their names in the XML tag structure.
GET ON TRACK

For people intensively involved in the PRS account management or a trial disclosure supervisor you want to receive occasional email announcements with information about US Public Law 110-85 by registering yourselves at NIH FDAAA Update LISTSERV. Follow the instructions and pick the subscription options that fit your needs. (Figure 18) You’ll never miss any changes and updates of the US Public Law 110-85 any more.

Join or Leave FDAAA-UPDATE-L, or Change Options

This screen allows you to join or leave the FDAAA-UPDATE-L list. To confirm your identity and prevent third parties from subscribing you to the list against your will, an e-mail message with a confirmation code will be sent to the address you specify in the form. Simply wait for this message to arrive, then follow the instructions to confirm the operation.

Alternatively, you can [login with your LISTSERV password] (if you have one) and update your subscription interactively, without e-mail confirmation.

Your e-mail address: 
Your FULL name: 

Subscription type:  
- Regular 
- Digest (traditional) 
- Digest (HTML format) 
- Index (traditional) 
- Index (HTML format)


CONCLUSION

We sincerely wish this paper will bring you the quality information and the usefulness of
- understanding the FDAAA801, related regulations and needs for publishing to ClinicalTrials.gov
- sharing a practical model has been developed and operated at sanofi-aventis and key points to watch that may ease the preparation of the XML deliverables for whom involved in the trial disclosure tasks

REFERENCES

* See sub-links in official webpage of PRS and U.S. Public Law 110-85 at [http://prsinfo.clinicaltrials.gov/fdaaa.html](http://prsinfo.clinicaltrials.gov/fdaaa.html)

(1) December 7, 2009 DHHS Unified Agenda (pp. 101-102) (pdf) page 98
(2) Crystal User Guide - GMA-CO (s-a internal document)
(3) RubyStar-PC-T-WW-EN-V1 (s-a internal document)

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