ClinicalTrials.gov Results Entry Automation

PhUSE 2010 Single Day Event Brussel

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J&J PRD

Agenda

- ClinicalTrials.gov
  - Background
  - Protocol Registry System (PRS)
- ClinicalTrials.gov Results
  - Requirements/documentation
  - Schema/DTD file
- Results Automation
  - Generation of “flat” XML files
  - Mapping of “flat” files into required XML structure
  - XML validation according to schema
  - Display : XSL style sheet
- Q & A

ClinicalTrials.gov Background

- Levels of transparency
  - Register clinical trial
    - ✓ Summary of protocol details
    - ✓ Within 21 days of first subject enrollment
  - Post results
    - ✓ Summary results for completed trial
    - ✓ Within 1 year of “primary completion date”
- Primary Completion Date
  - The date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome.
    - ✓ May or may not be the same as last subject last visit date

FDA Amendments Act

- Public Law 110-85 (Sep. 2007)
- Requires trial registration (Dec. 2007)
  - Phase 2-4 trials
- Requires results reporting (Sep. 2008)
  - Clinical trials of FDA-approved compounds
  - Basic results reporting
    - ✓ Baseline characteristics
    - ✓ Primary and secondary outcomes (efficacy)
- Adverse events (Sep. 2009)
- "Expanded" results (Sep. 2010)
- System to register results into is PRS (Protocol Registry System)

ClinicalTrials.gov website

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ClinicalTrials.gov website

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Results Reporting : in a standard tabular format

- Participant Flow
  - Subjects completed and discontinued trial + discontinuation reasons
- Baseline and Demographic Characteristics
  - Age, gender, etc.
- Outcome Measures and statistical analyses
  - Primary and secondary efficacy
- Adverse Events
  - Serious adverse events
  - Frequent adverse events : non-serious, frequency threshold
- Administrative Information

Results Reporting : Participant Flow

Participant Flow

Hide Participant Flow

Recruitment Details

Key information relevant to the recruitment process for the overall study, such as dates of the recruitment period and locations
The recruitment period for this out-patient, multicenter study occurred between 14 November 2006 and 25 July 2008.

Pre-Assignment Details

Significant events and approaches for the overall study following participant enrollment, but prior to group assignment
The study consisted of a screening period (duration up to 14 days), a washout period (duration 3 to 7 days), and an open label active treatment phase with titration and maintenance (total duration of 52 weeks).

Reporting Groups

	Description
Tapentadol (CG5503)	Tapentadol (CG5503) extended release (ER) 100 to 250mg twice daily (BID) for up to one year
Oxycodone	oxycodone controlled release (CR) 20 to 50mg twice daily (BID) for up to one year.

Participant Flow: Overall Study

	Tapentadol (CG5503)	Oxycodone
STARTED	894	223
COMPLETED	413	78
NOT COMPLETED	481	145
Withdrawal by Subject	94	31
Lost to Follow-up	40	7
Adverse Event	203	82
Lack of Efficacy	72	7
Resolution of Pain	2	0
Study medication non compliant	42	15
All other	28	3

Results Reporting : Baseline Results

Baseline Characteristics

Hide Baseline Characteristics

Reporting Groups

	Description
Tapentadol (CG5503)	Tapentadol (CG5503) extended release (ER) 100 to 250mg twice daily (BID) for up to one year
Oxycodone	oxycodone controlled release (CR) 20 to 50mg twice daily (BID) for up to one year.

Baseline Measures

	Tapentadol (CG5503)	Oxycodone	Total
Number of Participants [units: participants]	894	223	1117
Age [units: participants]			
<=18 years	0	0	0
Between 18 and 65 years	649	156	805
>=65 years	245	67	312
Age [units: years] Mean ± Standard Deviation	56.8 ± 12.51	58.1 ± 11.83	57.0 ± 12.38
Gender [units: participants]			
Female	515	125	640
Male	379	98	477
Region of Enrollment [units: participants]			
North America	684	170	854
Europe	210	53	263

Results Reporting : Adverse Events

Serious Adverse Events

Hide Serious Adverse Events

Time Frame	No text entered.
Additional Description	No text entered.

Reporting Groups

	Description
Tapentadol (CG5503)	Tapentadol (CG5503) extended release (ER) 100 to 250mg twice daily (BID) for up to one year
Oxycodone	oxycodone controlled release (CR) 20 to 50mg twice daily (BID) for up to one year.

Serious Adverse Events

	Tapentadol (CG5503)	Oxycodone
Total, serious adverse events		
# participants affected	49	9
Cardiac disorders		
Atrial Fibrillation *		
# participants affected / at risk	3/894 (0.34%)	0/223 (0.00%)
Acute myocardial infarction *		
# participants affected / at risk	1/894 (0.11%)	0/223 (0.00%)
Angina Pectoris *		
# participants affected / at risk	1/894 (0.11%)	0/223 (0.00%)
Cardiac Failure Congestive *		
# participants affected / at risk	1/894 (0.11%)	0/223 (0.00%)
Coronary Artery Disease *		
# participants affected / at risk	1/894 (0.11%)	0/223 (0.00%)
Myocardial Infarction *		
# participants affected / at risk	1/894 (0.11%)	0/223 (0.00%)
Ventricular Fibrillation *		
# participants affected / at risk	1/894 (0.11%)	0/223 (0.00%)
Congenital, familial and genetic disorders		
Hydrocele *		
# participants affected / at risk	1/894 (0.11%)	0/223 (0.00%)
Ear and labyrinth disorders		

Results Reporting : Outcome I

1. Primary: Number of Participants Who Had a Mood Relapse. [Time Frame: 24 months]

Hide Outcome Measure 1

Measure Type	Primary
Measure Title	Number of Participants Who Had a Mood Relapse.
Measure Description	Mood Relapse was defined as: The subject met DSM-IV criteria for a manic, hypomanic, mixed, or depressive episode; or, the subject needed treatment intervention with any mood stabilizer, antipsychotic medication (other than study drug), benzodiazepine (beyond the dosage allowed), or antidepressant medication; or the subject required hospitalization for any bipolar mood episode; or the subject had a YMRS or MADRS score >12 or a CGI-S score >4; or a dose increase, or supplementation with oral risperidone or another antipsychotic or mood stabilizer, was needed in the opinion of the investigator.
Time Frame	24 months
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
Intention to treat. 28 subjects from a Good Clinical Practice noncompliant site and 1 site with alleged research misconduct were excluded from efficacy analyses. The median (interquartile range) for time to relapse (d): Risperdal Consta: NA (173, NA) & Placebo: 219 (82, NA) [NA = not available; Risperdal Consta relapse percent < 50% & Placebo <75%]

Reporting Groups

	Description
RISPERDAL CONSTA	risperidone long acting injectable (RIS LAI) 12.5, 25, 37.5 or 50 mg IM injection every 2 weeks
Placebo	IM injection every 2 weeks

Measured Values

	RISPERDAL CONSTA	**Placebo**
Number of Participants Analyzed [units: participants]	**140**	**135**
Number of Participants Who Had a Mood Relapse. [units: Participants]		
Relapsed	**42**	**76**
Not Relapsed	**98**	**59**

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Results Reporting : Outcome II

Measured Values

	RISPERDAL CONSTA	Placebo
Number of Participants Analyzed [units: participants]	140	135
Number of Participants Who Had a Mood Relapse. [units: Participants]		
Relapsed	42	76
Not Relapsed	98	59

Statistical Analysis 1 for Number of Participants Who Had a Mood Relapse.

Groups [1]	All groups
Method [2]	Log Rank
P Value [3]	<0.001
Hazard Ratio (HR) [4]	0.40
95% Confidence Interval	(0.27 to 0.59)

[1] Additional details about the analysis, such as null hypothesis and power calculation:

No text entered.

[2] Other relevant information, such as adjustments or degrees of freedom:

Adjusting for country

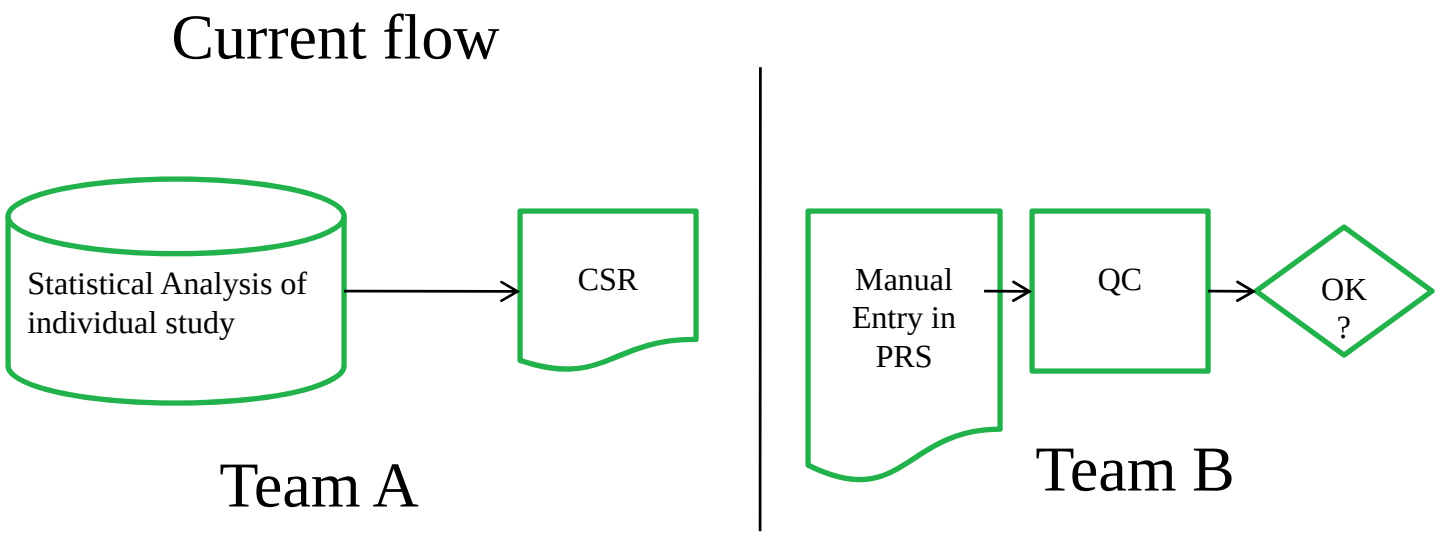
[3] Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:

No text entered.

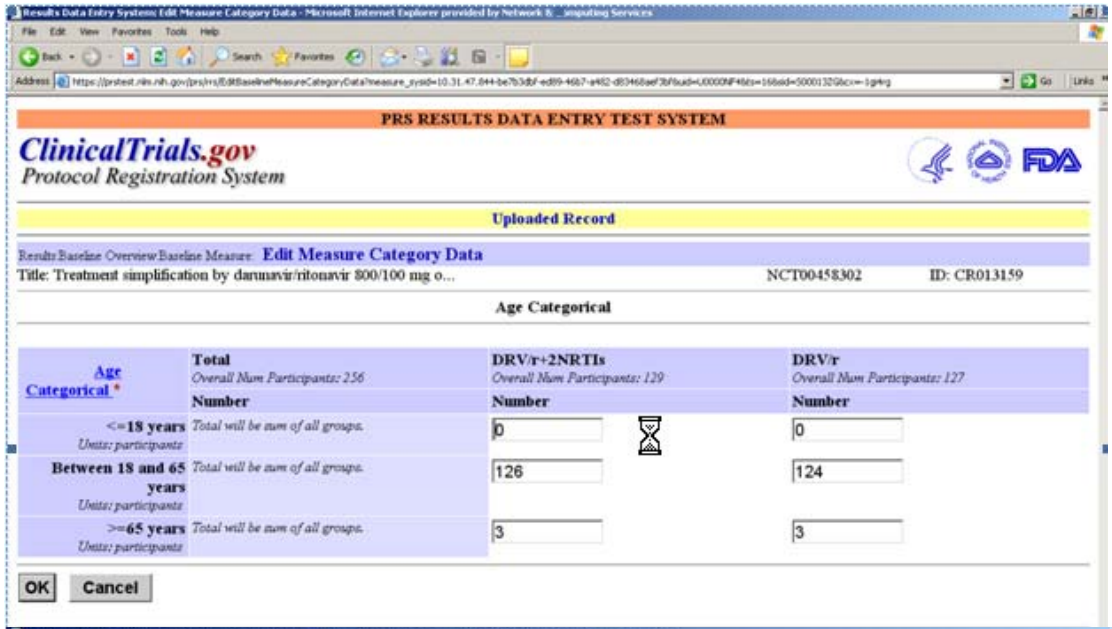
[4] Other relevant estimation information:

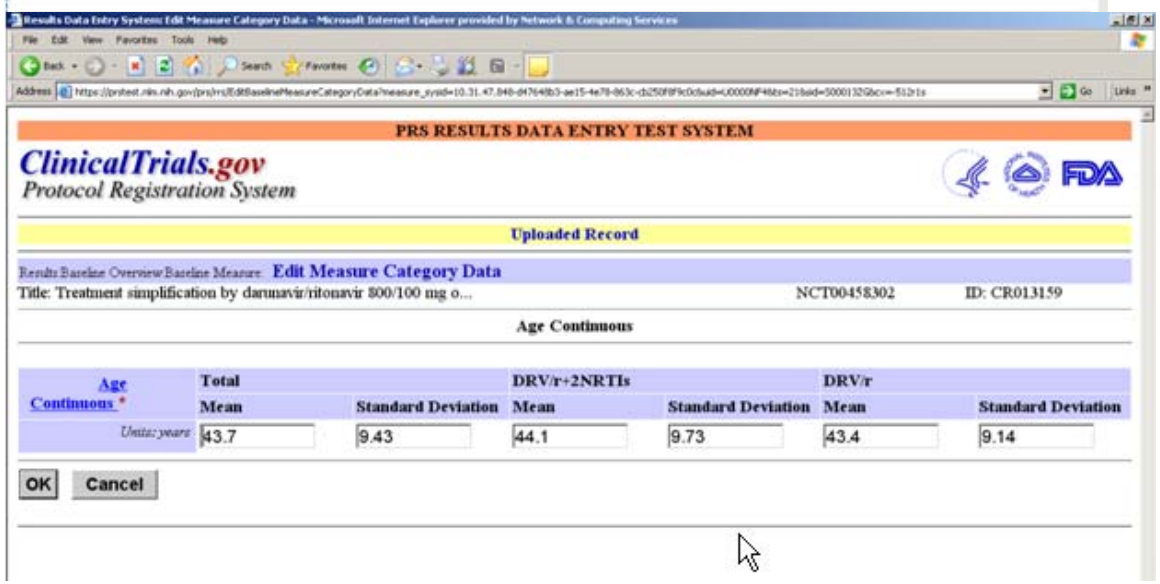
RISPERDAL CONSTA hazard in numerator, placebo hazard in denominator.

Flow


Current flow
Statistical Analysis of individual study
CSR
Team A
Manual Entry in PRS
QC
OK ?
Team B

Flow : Manual Entry into PRS





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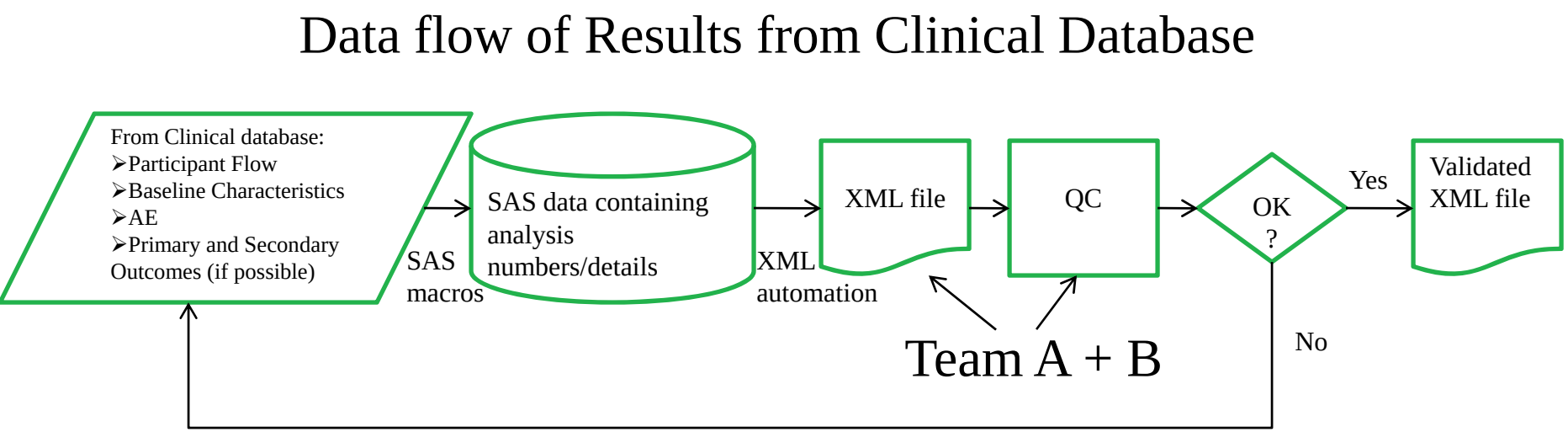
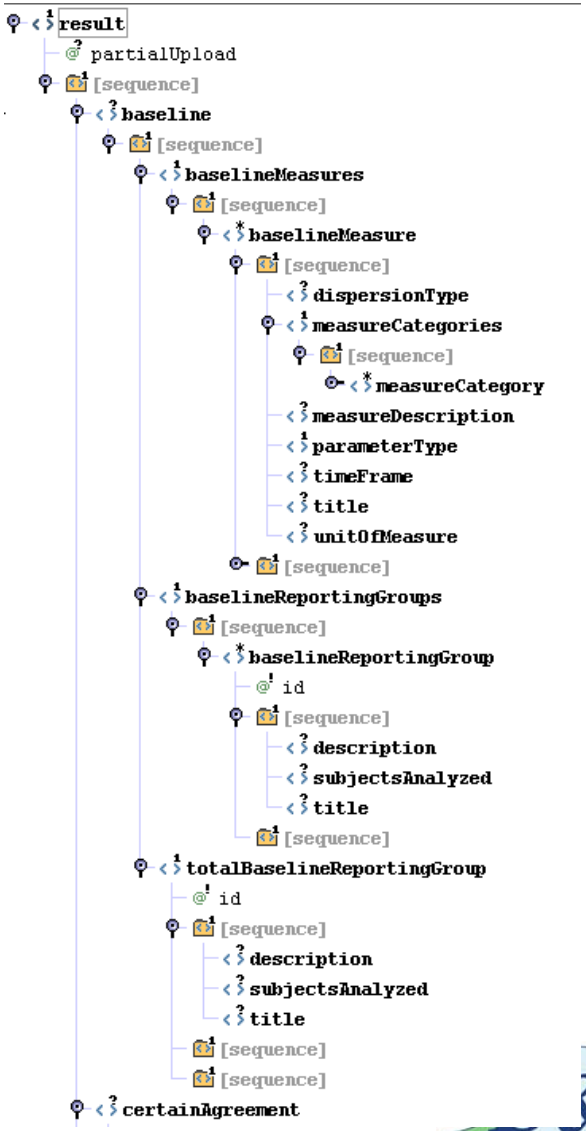
Flow

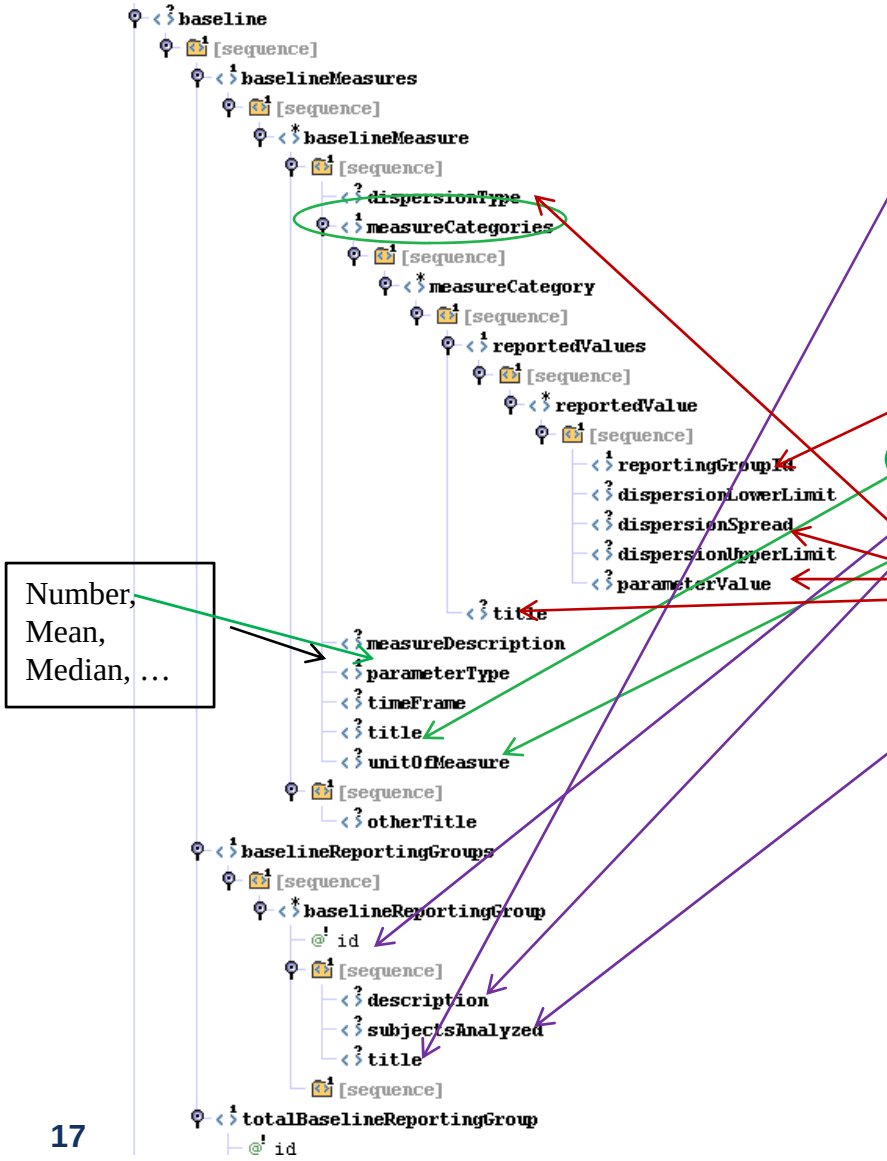

Data flow of Results from Clinical Database
From Clinical database:
➢Participant Flow
➢Baseline Characteristics
➢AE
➢Primary and Secondary Outcomes (if possible)
SAS macros
SAS data containing analysis numbers/details
XML automation
XML file
QC
OK ?
Yes
Validated XML file
No
Team A + B

Result Requirement Specifications

- "what" to present :
  - PRS instruction details "Basic Results" Data Element Definitions (DRAFT) (open file)
- "how" to present :
  - XML schema file for results section RRSUploadSchema.xsd
- Combine "what" and "how" guidance, a sample XML file and the corresponding displayed results on ClinicalTrials.gov website



Result Requirement Specifications



Number,
Mean,
Median, …

Reporting Groups

	Description
Tapentadol (CG5503)	Tapentadol (CG5503) extended release (ER) 100 to 250mg twice daily (BID) for up to one year
Oxycodone	oxycodone controlled release (CR) 20 to 50mg twice daily (BID) for up to one year.

Baseline Measures

Group.1 Group.2

	Tapentadol (CG5503)	Oxycodone	Total
Number of Participants [units: participants]	894	223	1117
Age [units: participants]			
<=18 years	0	0	0
Between 18 and 65 years	649	156	805
>=65 years	245	67	312
Age [units: years] Mean ± Standard Deviation	56.8 ± 12.51	58.1 ± 11.83	57.0 ± 12.38
Gender [units: participants]			
Female	515	125	640
Male	379	98	477
Region of Enrollment [units: participants]			
North America	684	170	854
Europe	210	53	263

Result Requirement : XML File

```
<result>
  <baseline>
    <baselineMeasures>
      <baselineMeasure>
        <dispersionType>Not Applicable</dispersionType>
        <measureCategories>
          <measureCategory>
          <measureCategory>
            <reportedValues>
              <reportedValue>
                <reportingGroupId>BaselineGroup.01</reportingGroupId>
                <parameterValue>649</parameterValue>
              </reportedValue>
              <reportedValue>
                <reportingGroupId>BaselineGroup.02</reportingGroupId>
                <parameterValue>156</parameterValue>
              </reportedValue>
            </reportedValues>
            <title>Between 18 and 65 Years</title>
          </measureCategory>
          <measureCategory>
        </measureCategories>
        <parameterType>Number</parameterType>
        <title>Age Groups</title>
        <unitOfMeasure>participants</unitOfMeasure>
      </baselineMeasure>
      <baselineMeasure>
    </baselineMeasures>
    <baselineReportingGroups>
      <baselineReportingGroup id="BaselineGroup.01">
        <description>Tapentadol (CG5503) extended release (ER) 100 to 250mg twice daily (BID) for up to one year</descr
        <subjectsAnalyzed>894</subjectsAnalyzed>
        <title>Tapentadol ER</title>
      </baselineReportingGroup>
      <baselineReportingGroup id="BaselineGroup.02">
        <description>oxycodone controlled release (CR) 20 to 50mg twice daily (BID) for up to one year.</description>
        <subjectsAnalyzed>223</subjectsAnalyzed>
        <title>Oxycodone CR</title>
      </baselineReportingGroup>
    </baselineReportingGroups>
```

Automation of Results Proposal

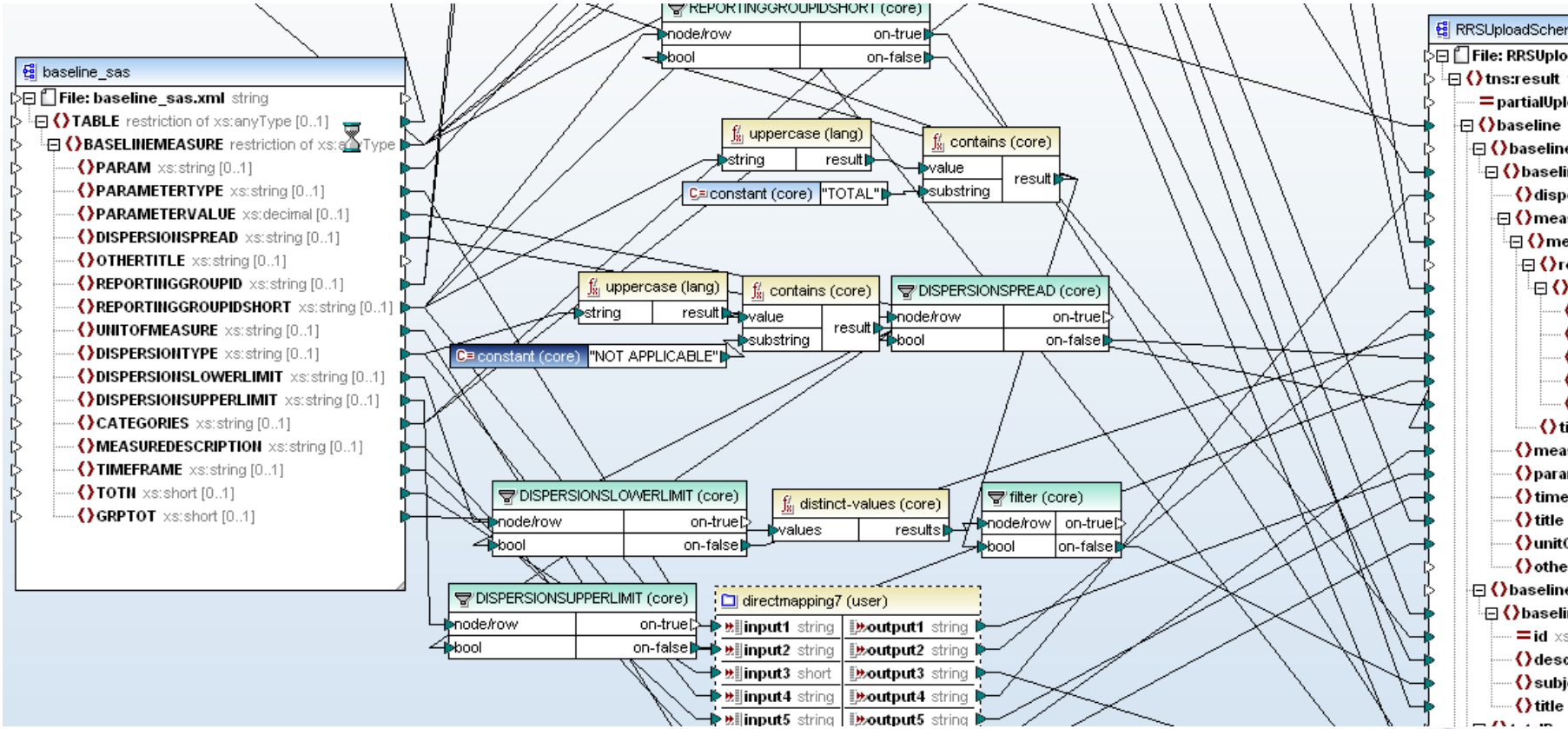
- Analysis database (SAS data sets)
  - All information for CSR tables
  - Most information for ClinicalTrials.gov results
    - ✓ Require some descriptive information from protocol registry

XML automation

- Not just one single approach possible
- Limited SAS based + outside SAS XML Mapping
  - Dataset containing analysis content
  - Conversion of SAS dataset into XML is handled by other application (Mapping from ‘flat XML file’ to required XML file)
- Full SAS based approach
  - Dataset containing analysis content
  - Dataset is split up into pieces for the construction of XML file : SAS macro’s
  - Used data _null_ approach to gradually construct XML file

XML Mapping – baseline section

- Used Altova MapForce
- Graphical data mapping between flat source file and target XML file



- C code was generated by Altova MapForce application

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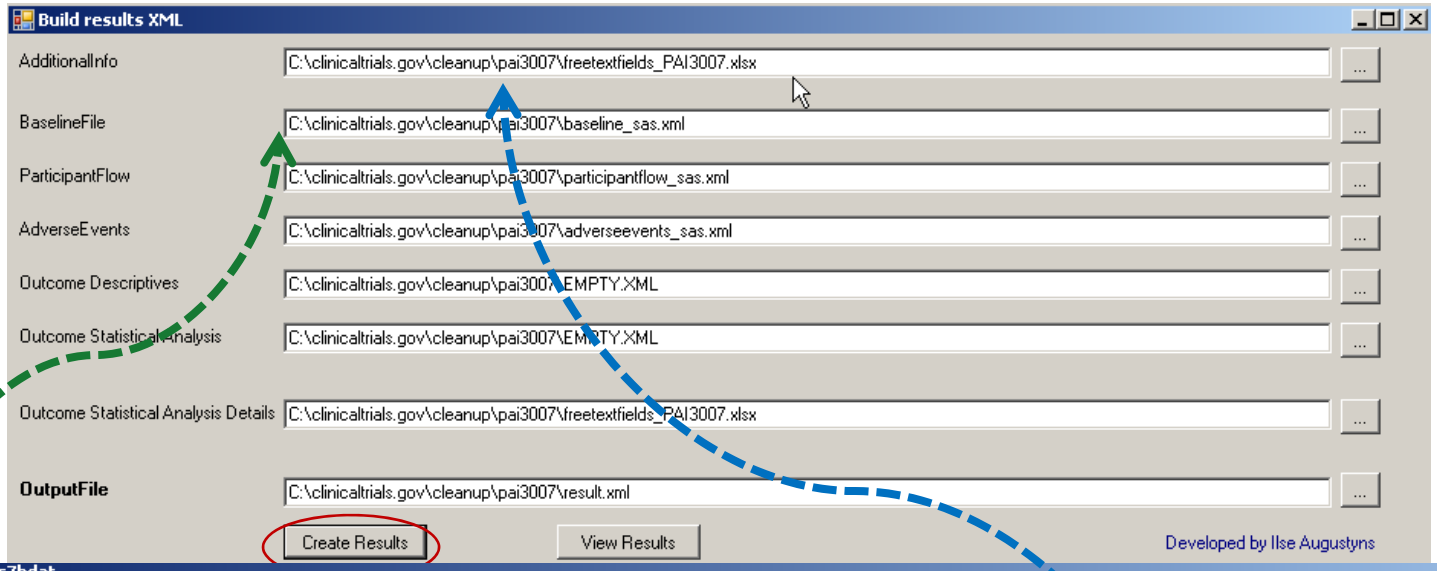
XML Mapping – resulting application

- A “Form”-application was built around the Mapforce’s generated C-code for ease of usage
- This application has as input :
  - 5 flat xml files : baseline, participant flow, AE file and 2 files for outcomes analysis: containing numerical details
  - 2 excel files : to deal with “verbatim” text details from the various sections. Verbatim fields are likely to change after team’s review.
- Output : 2 XML files
  - One version for uploading into PRS system
  - One version further used for XML validation and displaying results.

XML Mapping – resulting application



baseline.sas7bdat

	PARAM	PARAMETER TYPE	PARAMETER VALUE	DISPERSIONSPREAD	OTHERTITLE	REPORTINGGROUPID	REPORTING GROUPIDSHORT	UNITOFMEASURE	DISPERSIONTYPE	CATEGORIES	GRPTOT	STUDYID	TOTN
1	Age (years)	Mean	56.8	12.51	Age (years)	Tapentadol ER	BaselineG	Age (year	Standard	Not Appli	894	R331333-P	1117
2	Age Groups	Number	0		Age Groups	Tapentadol ER	BaselineG	participa	Not Appli	<= 18 yea	894	R331333-P	1117
3	Age Groups	Number	649		Age Groups	Tapentadol ER	BaselineG	participa	Not Appli	Between 1	894	R331333-P	1117
4	Age Groups	Number	245		Age Groups	Tapentadol ER	BaselineG	participa	Not Appli	>=65 year	894	R331333-P	1117
5	Age (years)	Mean	58.1	11.83	Age (years)	Oxycodone CR	BaselineG	Age (year	Standard	Not Appli	223	R331333-P	1117
6	Age Groups	Number	0		Age Groups	Oxycodone CR	BaselineG	participa	Not Appli	<= 18 yea	223	R331333-P	1117
7	Age Groups	Number	156		Age Groups	Oxycodone CR	BaselineG	participa	Not Appli	Between 1	223	R331333-P	1117
8	Age Groups	Number	67		Age Groups	Oxycodone CR	BaselineG	participa	Not Appli	>=65 year	223	R331333-P	1117
9	Age (years)	Mean	57.0	12.38	Age (years)	Total	Baseline-	Age (year	Standard	Not Appli	1117	R331333-P	1117

	A	B	C	D
1	section	description	group	text_field
3	baseline	description	Tapentadol ER	Tapentadol (CG5503) extended release (ER) 100 to 250mg twice daily (BID) for up to one year
4	baseline	description	Oxycodone CR	oxycodone controlled release (CR) 20 to 50mg twice daily (BID) for up to one year.
5	baseline	description	Total	Total

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XML file for uploading

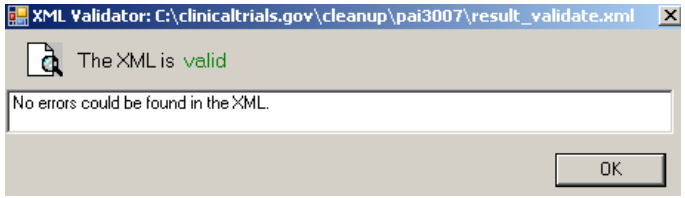
- Output : 2 XML files
  - One version for uploading into PRS system

```
<study_collection>
  <clinical_study partial_upload="true">
    <id_info>
      <org_name>JNJ</org_name>
      <org_study_id>CR011074</org_study_id>
    </id_info>
    <result>
      <baseline>
      <certainAgreement>
      <limitationsAndCaveats>
      <participantFlow>
      <pointOfContact>
      <reportedEvents>
    </result>
  </clinical_study>
</study_collection>
```

XML file for validation and display

- Output :
  - One version further used for XML validation and displaying results.
  - Only root element reference is different.
  - Reference to XML schema file for validation : To checks adherence to specific rules.

```
<?xml version="1.0" encoding="UTF-8" standalone="yes"?>
<?xml-stylesheet type='text/xsl' href='viewresult.xsl'?>
<JNJ:study_collection d1p1:schemaLocation="http://clinicaltrials.gov/rrs images\clinical_study_limited.xsd"
                      xmlns:d1p1="http://www.w3.org/2001/XMLSchema-instance"
                      xmlns:JNJ="http://clinicaltrials.gov/rrs">
  <clinical_study partial_upload="true">
    <id_info>
    <result>
```



  - Reference to XML style sheet file for instructions to browser.

Displaying XML file to facilitate content validation

Content

```
<?xml version="1.0" ?>
- <my:study_collection
    xmlns:my="http://clinicaltrials.gov/rrs"
    xmlns:xsi="http://www.w3.org/2001/XMLSchema-
    instance"
    xsi:schemaLocation="http://clinicaltrials.gov/rrs
    clinical_study_limited.xsd">
  - <clinical_study>
    - <id_info>
        <org_name>JNJ</org_name>
        <org_study_id>CR011074</org_study_id>
      </id_info>
    - <result>
      - <baseline>
        - <baselineMeasures>
          - <baselineMeasure>
              <dispersionType>Standard
                Deviation</dispersionType>
            - <measureCategories>
              - <measureCategory>
                - <reportedValues>
                  - <reportedValue>
```

(Without stylesheet)

Content + Style

Summary of Results for Study CR011074

Only for internal purpose to facilitate the validation of the content of the xml file

Participant Flow

Recruitment Details

Key information relevant to the recruitment process for the overall study, such as dates of the recruitment period and locations
The recruitment period for this out-patient, multicenter study occurred between 14 November 2006 and 25 July 2008.

Pre-Assignment Details

Significant events and approaches for the overall study following participant enrollment, but prior to group assignment
The study consisted of a screening period (duration up to 14 days), a washout period (duration 3 to 7 days), and an open label active treatment phase with titration and maintenance (total duration of 52 weeks).

(With stylesheet)

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Displaying XML file to facilitate content validation

- Current style sheet mimicked the presentation of ClinicalTrials.gov website
- It is used for internal validation of content of XML file, prior to uploading XML into PRS system
- Stylesheet is written in XSL-T Language (eXtensible Stylesheet Language for Transformations)
- It is a language for transforming XML documents into something else, such as an HTML document

Summary

- Automation tool successful
- Currently piloting tool for different studies (various design, various database structure)
- Teams are enthusiastic, as people can concentrate on validation rather than manual entry

References

- PRS and FDA Amendments Act of 2007
  - http://prsinfo.clinicaltrials.gov/fdaaa.html
    - ✓ US Public Law 110-85
- Protocol Registration System (PRS) Information Page
  - http://prsinfo.clinicaltrials.gov/index.html
- ClinicalTrials.gov
  - http://clinicaltrials.gov/
    - ✓ Searchable registry of clinical trials

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