EudraCT Project

Simon Bond 30th April 2019

Elevator Pitch

- All CTIMP studies are required to enter results into EudraCT within 1 year of completion
- Detailed safety results could take 1000s of hours to enter by hand
- Or upload an XML with the data in seconds.

Overview

- Update on Safety data project
- Worked Example
- Where to find resources
- Opportunities to contribute
- Discussion on Future extensions

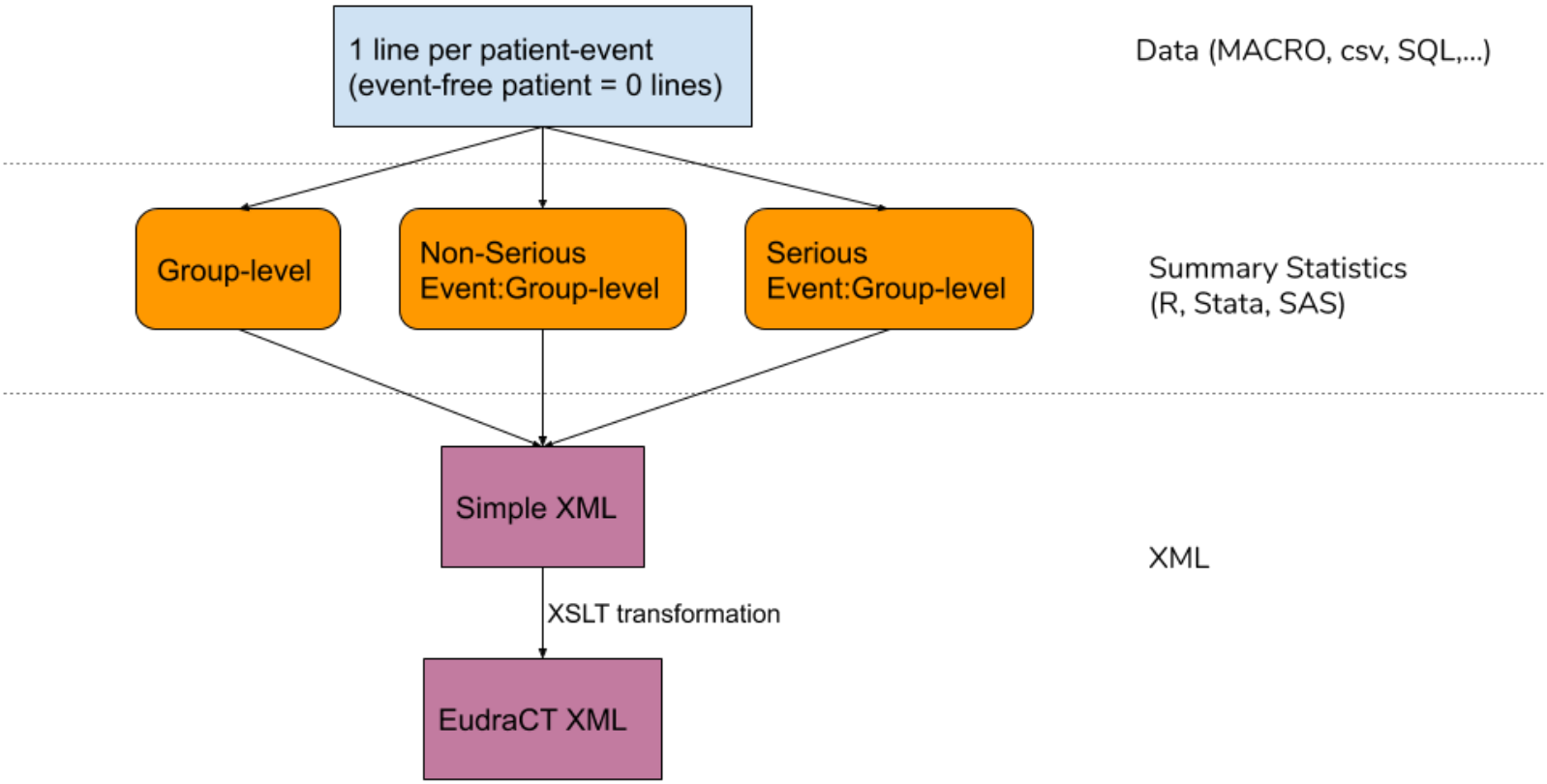
Project Timelines: End date is October 19

- ✓ Survey
- ✓ Specification Document
- ~ Website
- ~ Github code sharing and collaboration
- ~ Draft versions of code
- » Testing
- » Documentation

Doing one thing well (to start with)

- Produce summary safety stats
  - Advisory code not tested, or use your own
  - Versions for R, Stata, SAS
  - Data provided to link to EudraCT codes for SOCs
- Standardise column names and save in “simple” XML
  - R package function - tested
  - SAS Proc Datasets (but limited by variable name length)
  - Stata code
- XSLT script to convert from “Simple” to EudraCT xml.

Flow Chart of process



Input Data

RStudio Source Editor

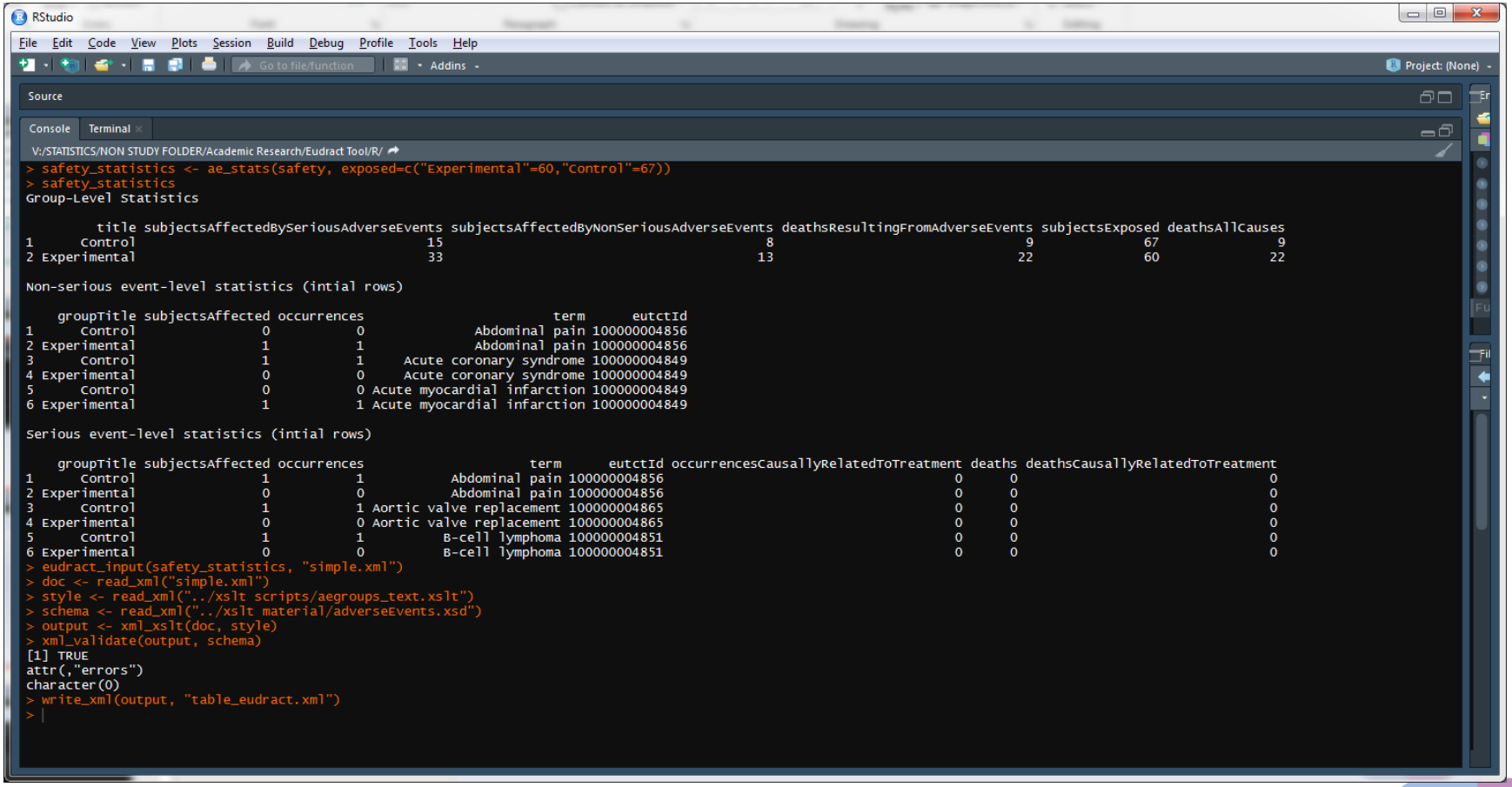
safety

Filter

	pt	subjid	related	soc	fatal	serious	group	term
1	10000081	US6-006	FALSE	10017947	0	1	Control	Abdominal pain
2	10000081	N04-006	FALSE	10017947	0	0	Experimental	Abdominal pain
3	10000891	US3-002	TRUE	10007541	0	0	Experimental	Acute myocardial infarction
4	10002383	US6-012	FALSE	10007541	0	0	Experimental	Angina pectoris
5	10002895	US5-001	FALSE	10047065	0	0	Experimental	Aortic dissection
6	10002916	US8-006	FALSE	10042613	0	1	Control	Aortic valve replacement
7	10003658	N01-008	FALSE	10007541	0	0	Experimental	Atrial fibrillation
8	10003673	N01-018	FALSE	10007541	0	0	Experimental	Atrioventricular block complete
9	10003899	US7-006	FALSE	10005329	0	1	Control	B-cell lymphoma
10	10005064	CN1-006	FALSE	10029104	0	1	Experimental	Bladder papilloma
11	10006482	US6-009	FALSE	10038738	0	0	Experimental	Bronchospasm
12	10007515	AS1-006	FALSE	10007541	1	1	Control	Cardiac arrest

Showing 1 to 12 of 116 entries

R Code


RStudio
File Edit Code View Plots Session Build Debug Profile Tools Help
Source
Console Terminal
V:/STATISTICS/NON STUDY FOLDER/Academic Research/Eudract Tool/R/
> safety_statistics <- ae_stats(safety, exposed=c("Experimental"=60,"Control"=67))
> safety_statistics
Group-Level Statistics
title subjectsAffectedBySeriousAdverseEvents subjectsAffectedByNonSeriousAdverseEvents deathsResultingFromAdverseEvents subjectsExposed deathsAllCauses
1 Control 15 8 9 67 9
2 Experimental 33 13 22 60 22
Non-serious event-level statistics (intial rows)
groupTitle subjectsAffected occurrences term eutctId
1 Control 0 0 Abdominal pain 100000004856
2 Experimental 1 1 Abdominal pain 100000004856
3 Control 1 1 Acute coronary syndrome 100000004849
4 Experimental 0 0 Acute coronary syndrome 100000004849
5 Control 0 0 Acute myocardial infarction 100000004849
6 Experimental 1 1 Acute myocardial infarction 100000004849
Serious event-level statistics (intial rows)
groupTitle subjectsAffected occurrences term eutctId occurrencesCausallyRelatedToTreatment deaths deathsCausallyRelatedToTreatment
1 Control 1 1 Abdominal pain 100000004856 0 0 0
2 Experimental 0 0 Abdominal pain 100000004856 0 0 0
3 Control 1 1 Aortic valve replacement 100000004865 0 0 0
4 Experimental 0 0 Aortic valve replacement 100000004865 0 0 0
5 Control 1 1 B-cell lymphoma 100000004851 0 0 0
6 Experimental 0 0 B-cell lymphoma 100000004851 0 0 0
> eudract_input(safety_statistics, "simple.xml")
> doc <- read_xml("simple.xml")
> style <- read_xml("../xslt scripts/aegroups_text.xslt")
> schema <- read_xml("../xslt material/adverseEvents.xsd")
> output <- xml_xslt(doc, style)
> xml_validate(output, schema)
[1] TRUE
attr(,"errors")
character(0)
> write_xml(output, "table_eudract.xml")

Activities RStudio Thu 09:46

RStudio

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Source

Console **Terminal**

~/EudraCT/eudraCT/R/R example/

```
> safety_statistics <- ae_stats(safety, exposed=c("Experimental"=60,"Control"=67))
> safety_statistics
Group-Level Statistics

         title subjectsAffectedBySeriousAdverseEvents subjectsAffectedByNonSeriousAdverseEvents
1      Control                                    15                                        8
2 Experimental                                    33                                       13
  deathsResultingFromAdverseEvents subjectsExposed deathsAllCauses
1                                9              67               9
2                               22              60              22

Non-serious event-level statistics (intial rows)

    groupTitle subjectsAffected occurrences                      term      eutctId
1      Control                0           0              Abdominal pain 100000004856
2 Experimental                1           1              Abdominal pain 100000004856
3      Control                1           1     Acute coronary syndrome 100000004849
4 Experimental                0           0     Acute coronary syndrome 100000004849
5      Control                0           0 Acute myocardial infarction 100000004849
6 Experimental                1           1 Acute myocardial infarction 100000004849
```

RStudio

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Go to file/functior | Addins | Project: (None)

Source

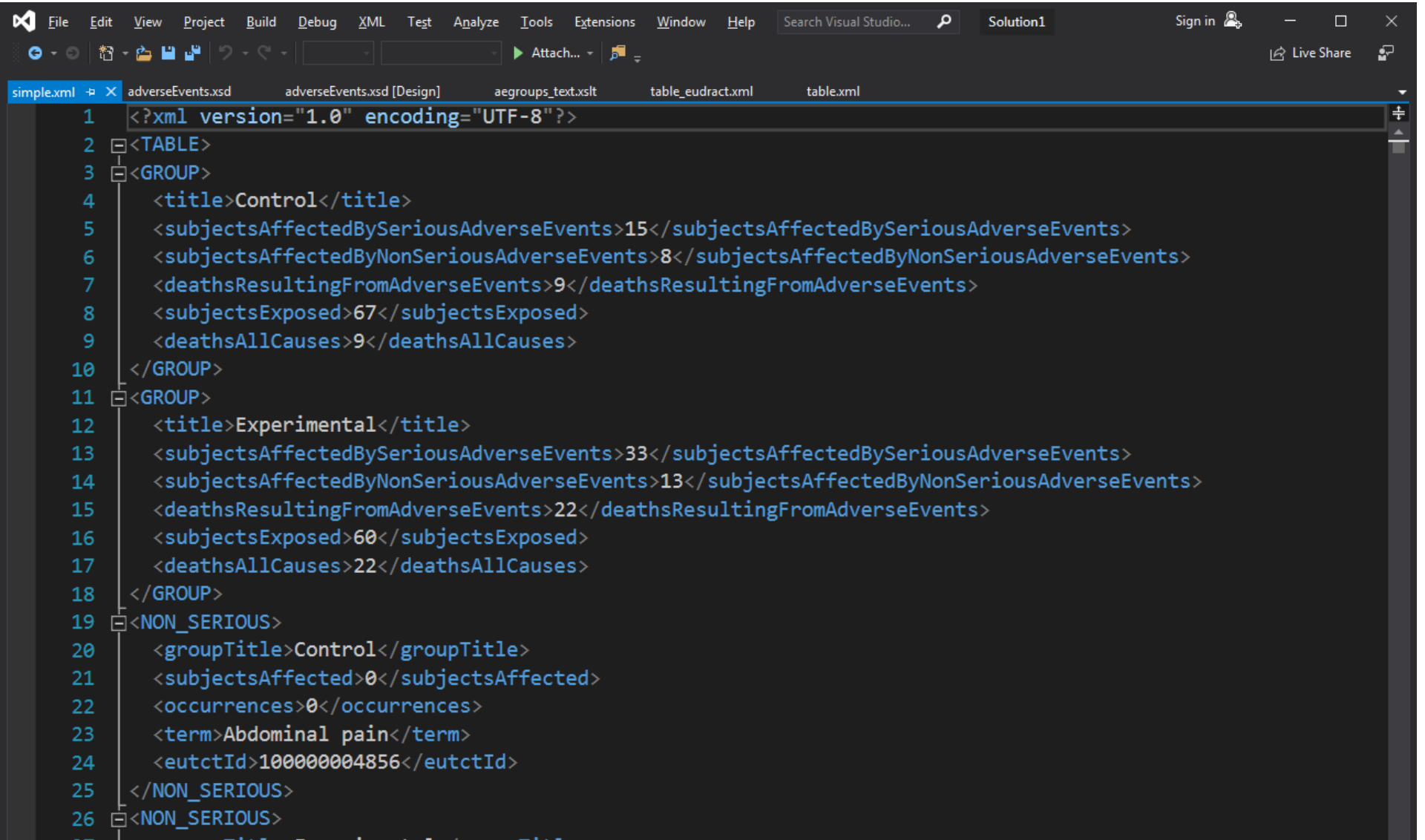
Console **Terminal**

~/EudraCT/eudraCT/R/R example/

```
> eudract_input(safety_statistics, "simple.xml")
> eudract_convert(input="simple.xml", output="table_eudract.xml",
+                 xslt="simpleToEudraCT.xslt", schema_output="adverseEvents.xsd"
+                 )
table_eudract.xml is created or modified
Validation Status:
[1] TRUE
attr(,"errors")
character(0)
>
```

CCTU

Save in Simple xml with standard names




```
<?xml version="1.0" encoding="UTF-8"?>
<TABLE>
<GROUP>
  <title>Control</title>
  <subjectsAffectedBySeriousAdverseEvents>15</subjectsAffectedBySeriousAdverseEvents>
  <subjectsAffectedByNonSeriousAdverseEvents>8</subjectsAffectedByNonSeriousAdverseEvents>
  <deathsResultingFromAdverseEvents>9</deathsResultingFromAdverseEvents>
  <subjectsExposed>67</subjectsExposed>
  <deathsAllCauses>9</deathsAllCauses>
</GROUP>
<GROUP>
  <title>Experimental</title>
  <subjectsAffectedBySeriousAdverseEvents>33</subjectsAffectedBySeriousAdverseEvents>
  <subjectsAffectedByNonSeriousAdverseEvents>13</subjectsAffectedByNonSeriousAdverseEvents>
  <deathsResultingFromAdverseEvents>22</deathsResultingFromAdverseEvents>
  <subjectsExposed>60</subjectsExposed>
  <deathsAllCauses>22</deathsAllCauses>
</GROUP>
<NON_SERIOUS>
  <groupTitle>Control</groupTitle>
  <subjectsAffected>0</subjectsAffected>
  <occurrences>0</occurrences>
  <term>Abdominal pain</term>
  <eutctId>100000004856</eutctId>
</NON_SERIOUS>
<NON_SERIOUS>
```

Transformation code: 108 lines

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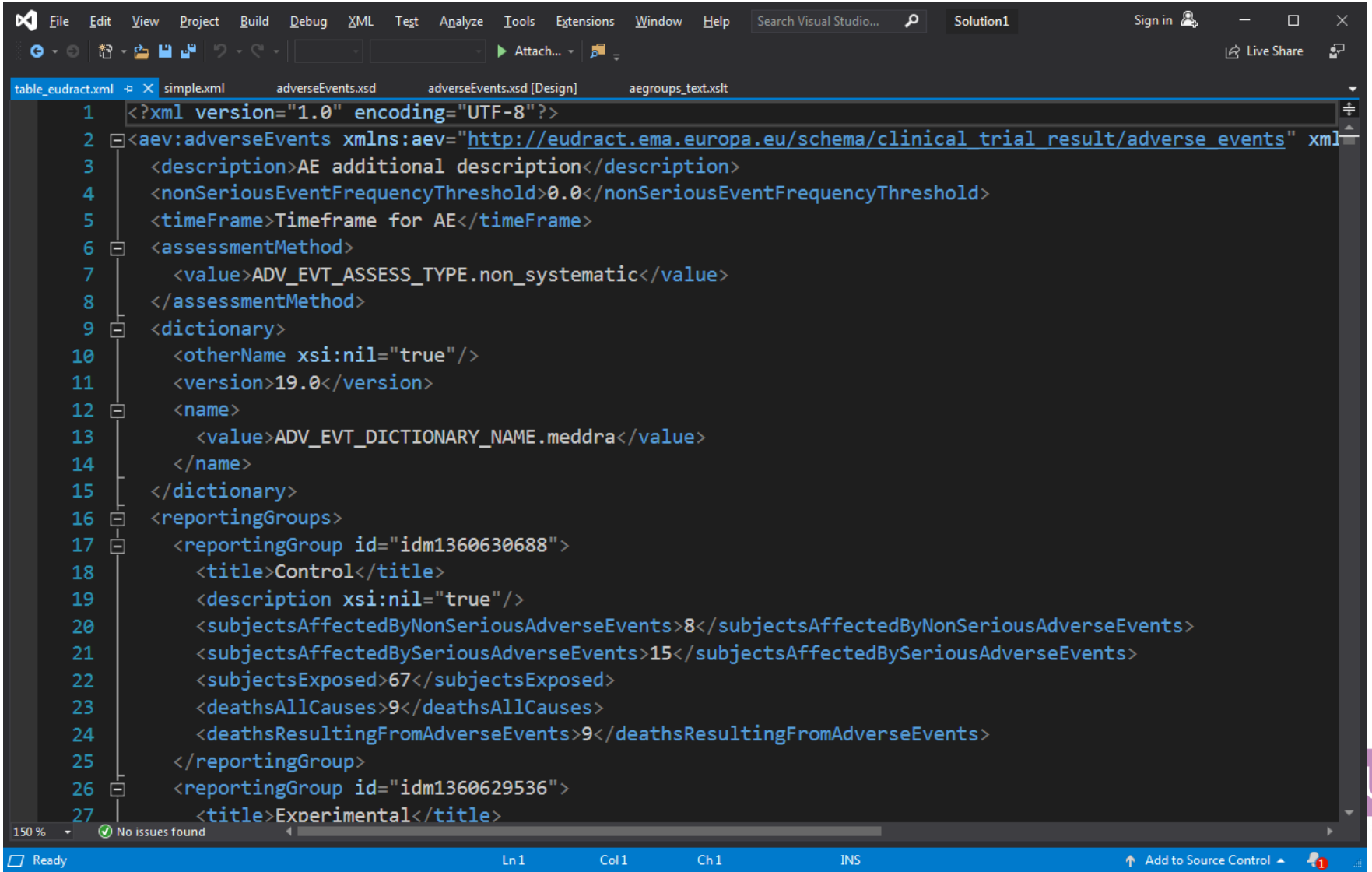
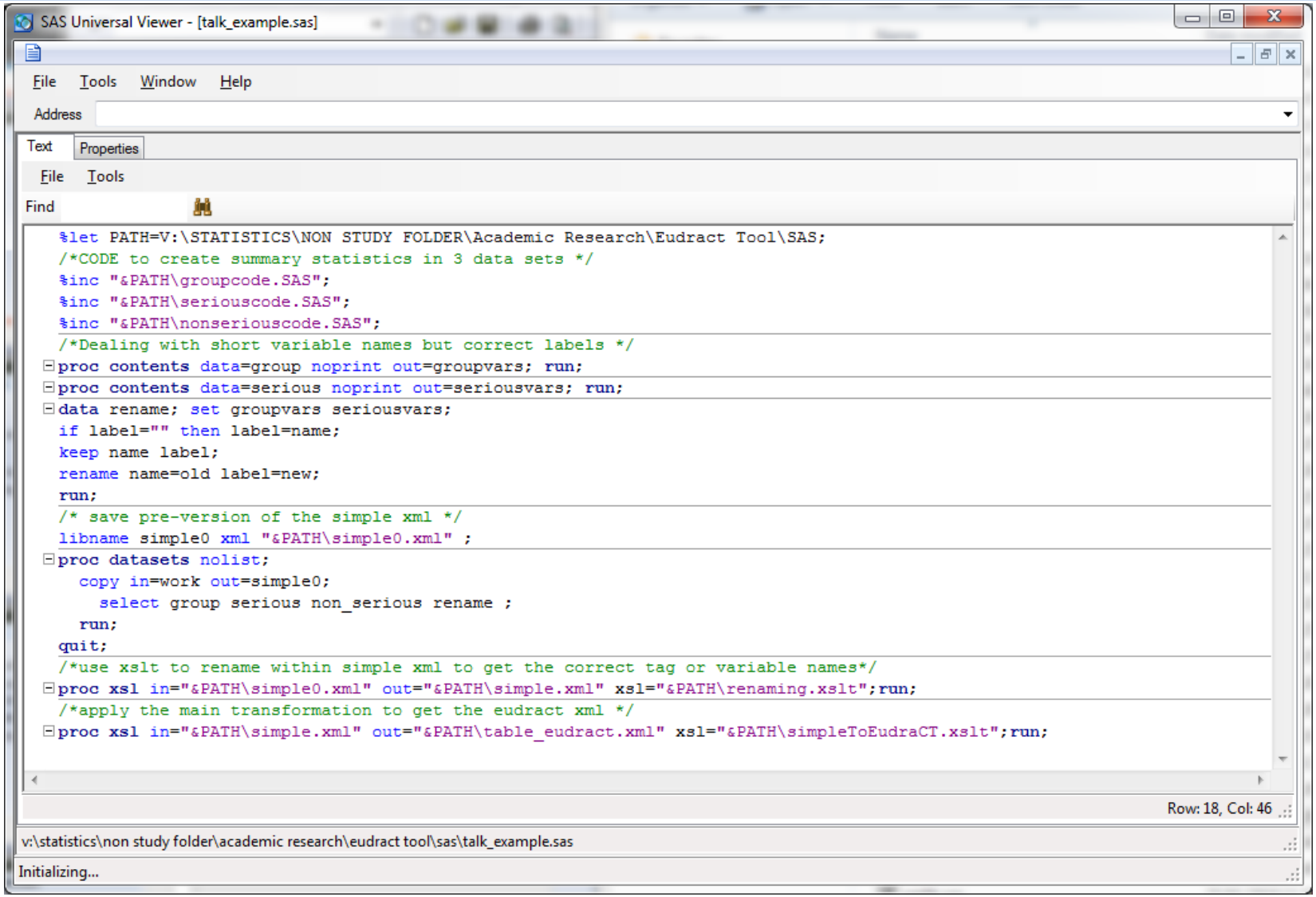
simple.xml adverseEvents.xsd adverseEvents.xsd [Design] aegroups_text.xslt

```
<?xml version="1.0" encoding="UTF-8"?>
<xsl:stylesheet version="1.0"
xmlns:xsl="http://www.w3.org/1999/XSL/Transform">
<xsl:output method="xml" indent="yes"/>

<xsl:key name="group_id" match="GROUP/title" use="."/>
<xsl:key name="term" match="SERIOUS | NON_SERIOUS" use="concat(term, eutctId, name())"/>


<xsl:template match="/">
<aev:adverseEvents xmlns:aev="http://eudract.ema.europa.eu/schema/clinical_trial_result/adverse_events" xml
  <description>AE additional description</description>
  <nonSeriousEventFrequencyThreshold>0.0</nonSeriousEventFrequencyThreshold>
  <timeFrame>Timeframe for AE</timeFrame>
  <assessmentMethod>
    <value>ADV_EVT_ASSESS_TYPE.non_systematic</value>
  </assessmentMethod>
  <dictionary>
    <otherName xsi:nil="true"/>
    <version>19.0</version>
    <name>
      <value>ADV_EVT_DICTIONARY_NAME.meddra</value>
    </name>
  </dictionary>


```

Final Output

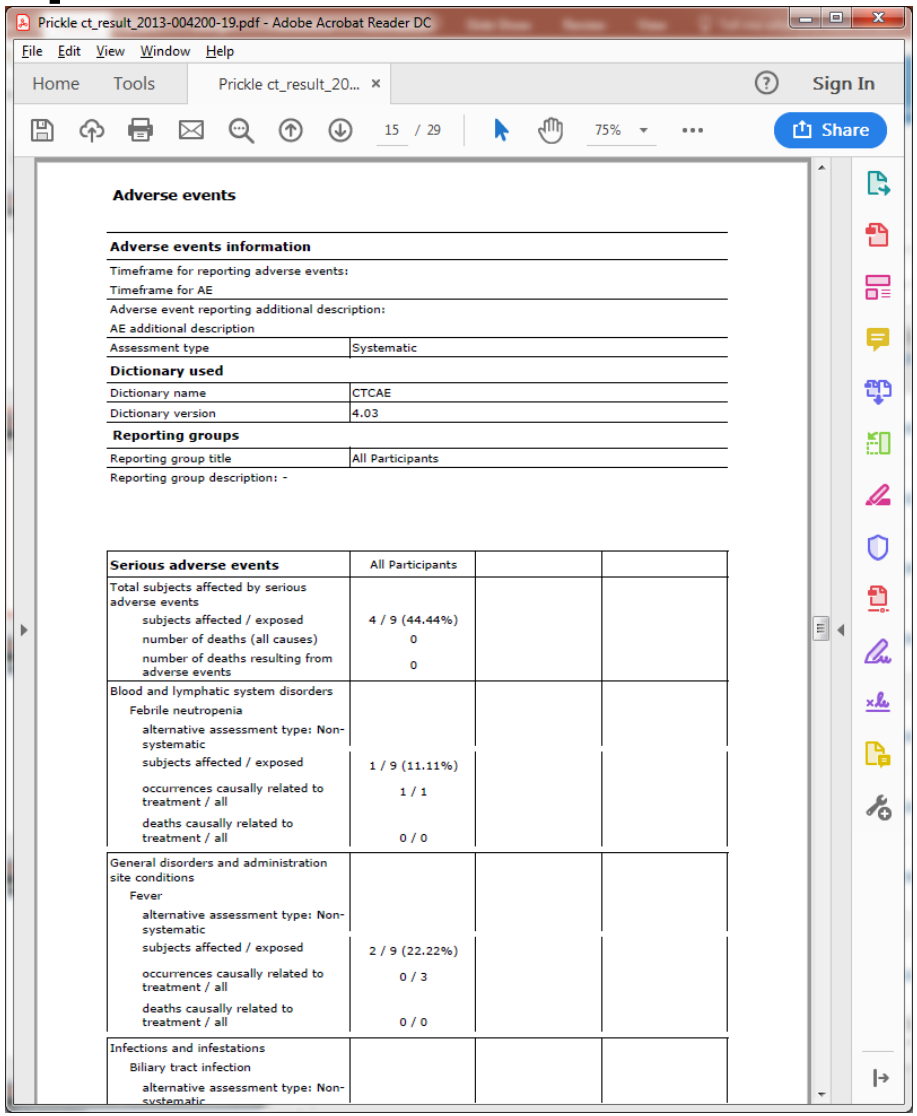


SAS Equivalent



CCTU

Final Report from EudraCT


Prickle ct_result_2013-004200-19.pdf - Adobe Acrobat Reader DC

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15 / 29 75% Share

Adverse events

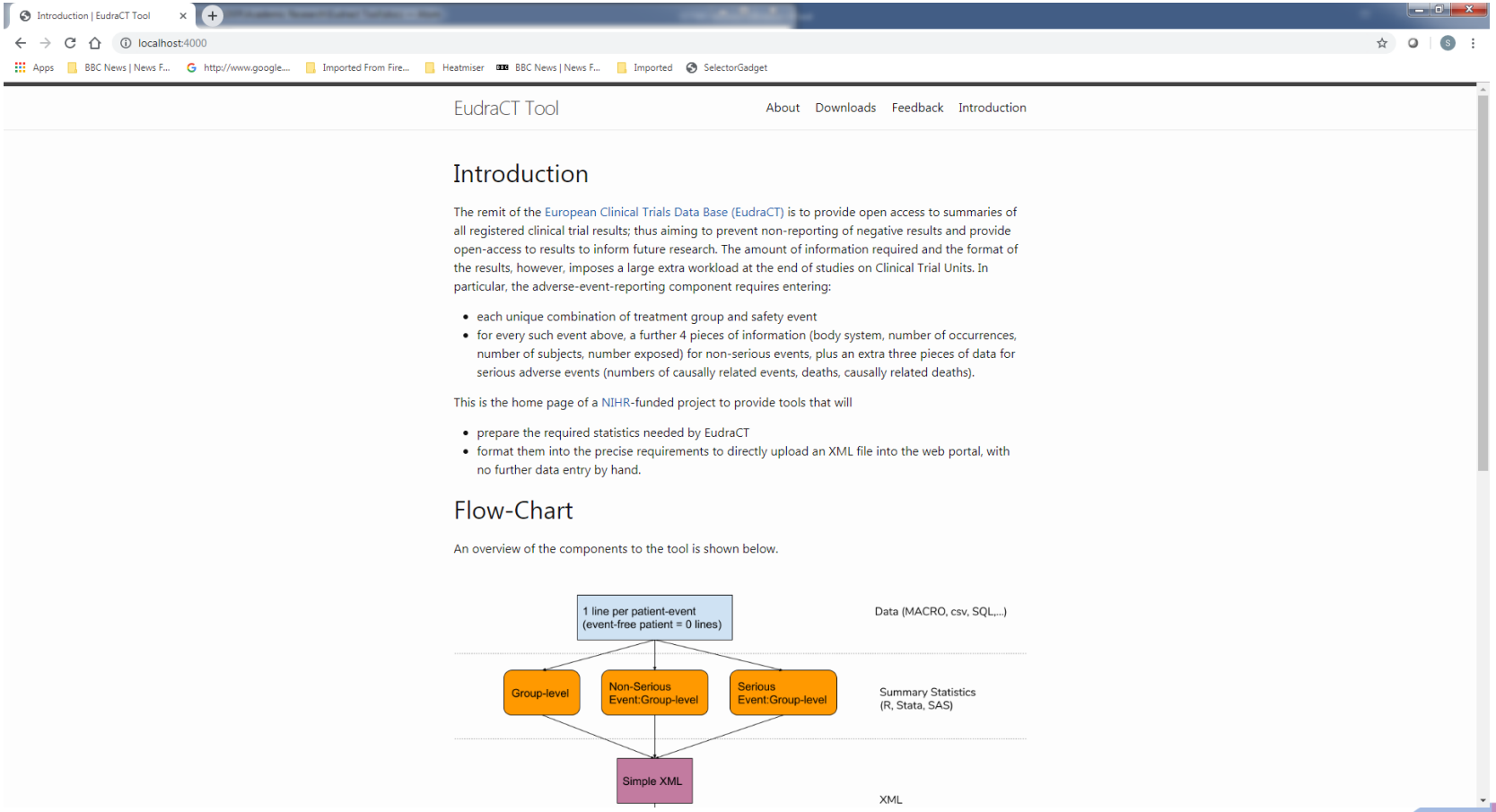
Adverse events information	
Timeframe for reporting adverse events:	
Timeframe for AE	
Adverse event reporting additional description:	
AE additional description	
Assessment type	Systematic
Dictionary used	
Dictionary name	CTCAE
Dictionary version	4.03
Reporting groups	
Reporting group title	All Participants
Reporting group description: -	

Serious adverse events	All Participants		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 9 (44.44%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Blood and lymphatic system disorders			
Febrile neutropenia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Fever			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Biliary tract infection			
alternative assessment type: Non-systematic			

Unification across R/SAS/Stata

- *Could* export directly writing output mixing text and data
  - Print (“<blah>”, count[i,j], “</blah>”)
- *But*: one unified XSLT stage for the details
  - Easy to amend for future changes
  - Open-source code on GitHub for anyone to propose amendments
  - Leaves the statisticians to do statistics
  - Need to export into “Simple” XML from Stata

https://eudract-tool.medschl.cam.ac.uk



Where can you get this

- R Code -> package via the github link
- SAS code equivalent..
- Stata code equivalent?
- Documentation
- Training

Test overview

- Use the training version of EudraCT
- Take a past trial already uploaded to EudraCT from another CTU, and compare output
- Unit testing within R, Stata,SAS.
- Feedback from other units welcome

Acknowledgements

- Birmingham
- Leeds
- Glasgow
- All who participated in the Survey and spec feedback

- NIHR funding

Future Direction: Discussion

- Extensions:
  - Baseline
  - Efficacy
  - Meta Data
- Beyond EudraCT
  - ClinicalTrials.gov
  - CDISC

Extra Slides

Schema downloaded from EudraCT

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simple.xml | adverseEvents.xsd | adverseEvents.xsd [Design] | aegroups_text.xslt

```
1  <?xml version="1.0" encoding="UTF-8"?>
2  <xs:schema elementFormDefault="unqualified"
3      targetNamespace="http://eudract.ema.europa.eu/schema/clinical_trial_result/adverse_events"
4      version="1.1"
5      xmlns:tns="http://eudract.ema.europa.eu/schema/clinical_trial_result/adverse_events" xmlns:xs="http://w
6
7      <xs:element name="adverseEvents" type="tns:AdverseEvents"/>
8      <xs:complexType name="AdverseEvents">
9          <xs:sequence>
10             <xs:element minOccurs="0" name="description">
11               <xs:simpleType>
12                 <xs:restriction base="xs:string">
13                   <xs:maxLength value="350"/>
14                 </xs:restriction>
15               </xs:simpleType>
16             </xs:element>
17             <xs:element minOccurs="0" name="nonSeriousEventFrequencyThreshold">
18               <xs:simpleType>
19                 <xs:restriction base="xs:decimal">
20                   <xs:minInclusive value="0.00"/>
21                   <xs:maxInclusive value="5.00"/>
22                 </xs:restriction>
23               </xs:simpleType>
24             </xs:element>
25             <xs:element minOccurs="0" name="timeFrame">
26               <xs:simpleType>
27                 <xs:restriction base="xs:string">
```