

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

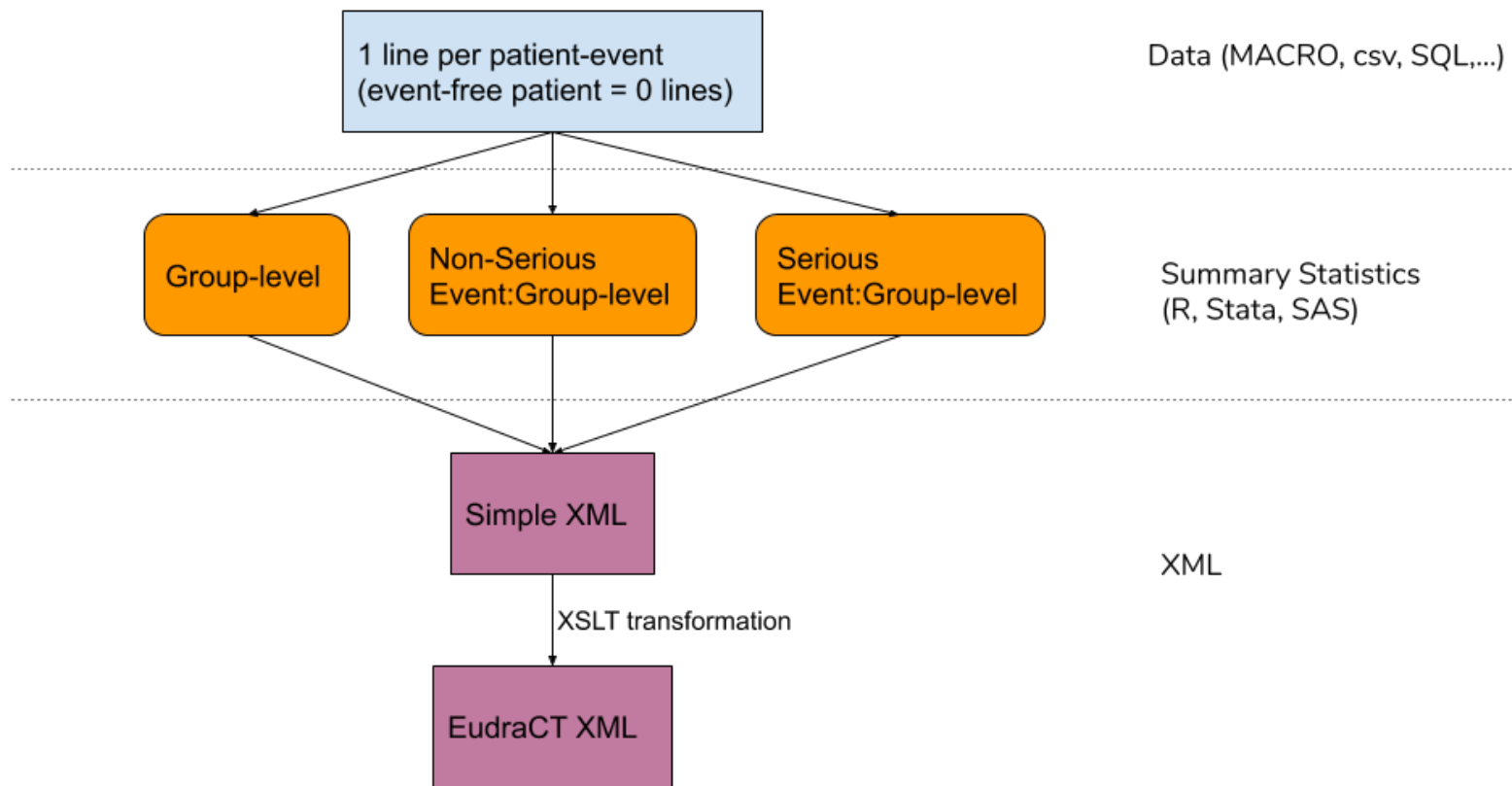
Project Timelines: End date is October 19

- ✓ 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 SOC_s
- 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 x

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
Go to file/function Addins
Project: (None)

Source
Console Terminal x
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

  1      title subjectsAffectedBySeriousAdverseEvents subjectsAffectedByNonSeriousAdverseEvents deathsResultingFromAdverseEvents subjectsExposed deathsAllCauses
  2 Experimental                33                    13                        22                60                22

Non-serious event-level statistics (initial rows)

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

Serious event-level statistics (initial rows)

  1 groupTitle subjectsAffected occurrences term eutctId occurrencesCausallyRelatedToTreatment deaths deathsCausallyRelatedToTreatment
  2 Control      1              1 Abdominal pain 100000004856 0 0 0
  3 Experimental 0              0 Abdominal pain 100000004856 0 0 0
  4 Control      1              1 Aortic valve replacement 100000004865 0 0 0
  5 Experimental 0              0 Aortic valve replacement 100000004865 0 0 0
  6 Control      1              1 B-cell lymphoma 100000004851 0 0 0
  7 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")
> |
```


Console

Terminal

	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

Source



Console Terminal ×

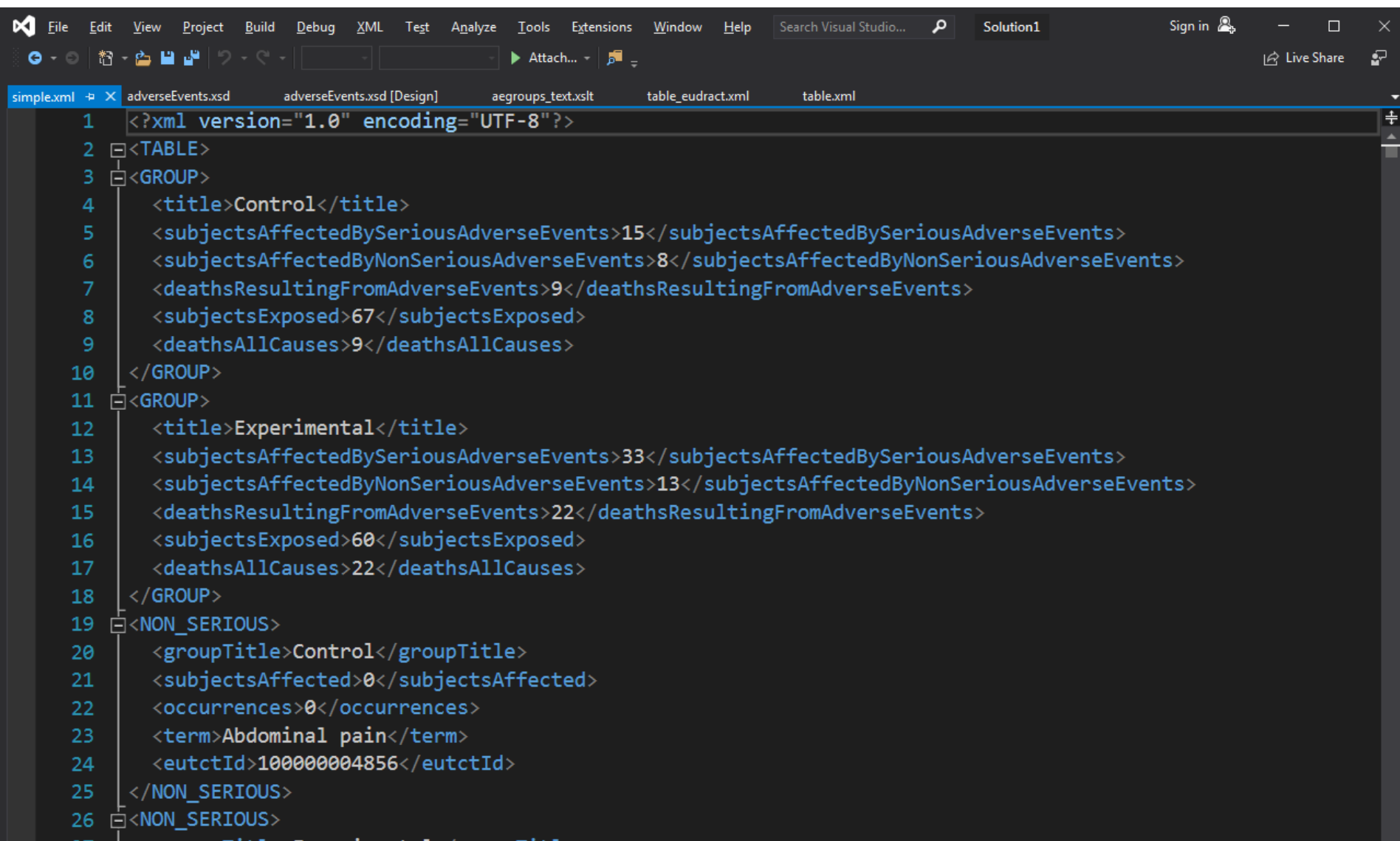


~/EudraCT/eudraCT/R/R example/ ➡️



```
> 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)
> |
```

Save in Simple xml with standard names

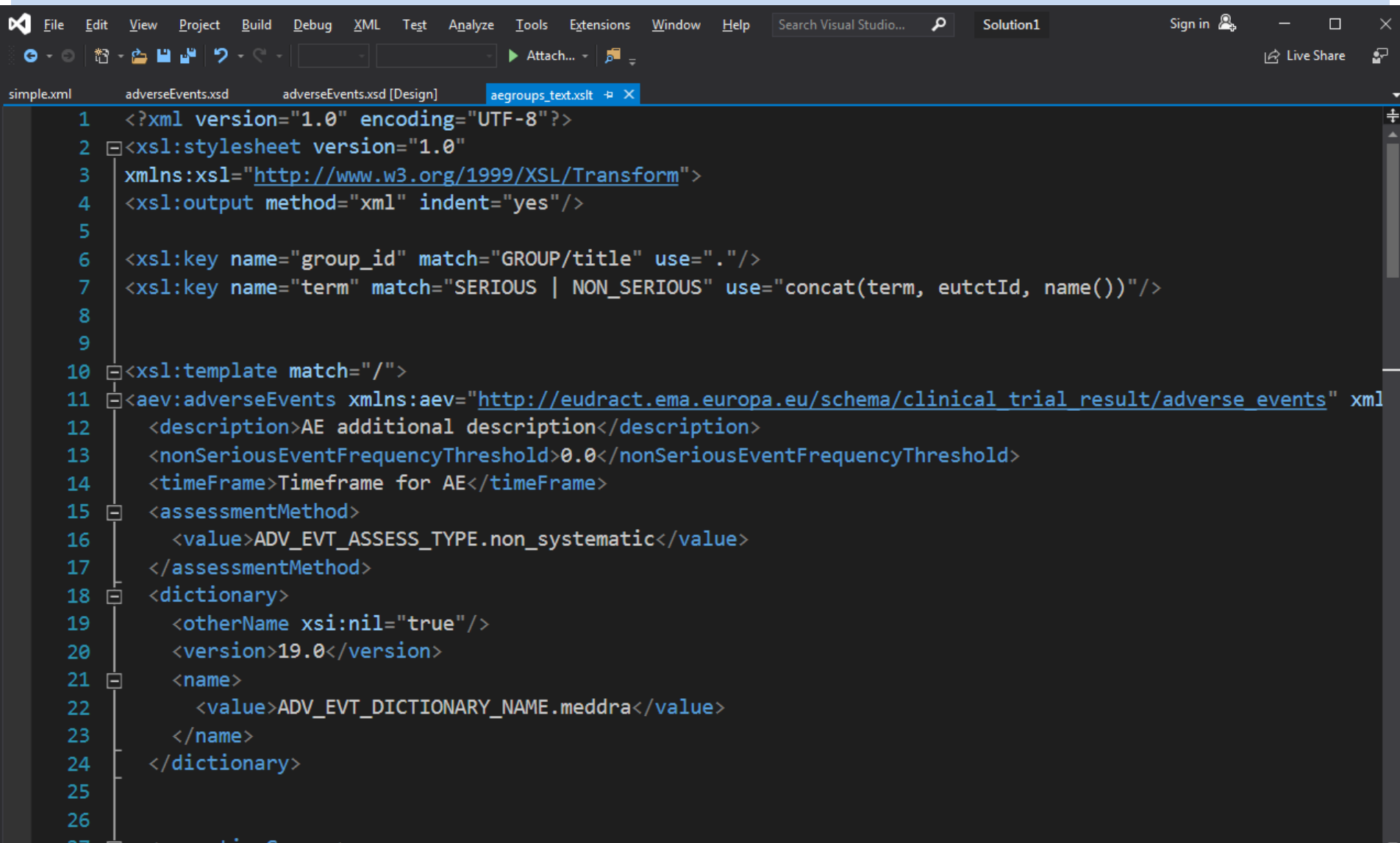


```

1  <?xml version="1.0" encoding="UTF-8"?>
2  <TABLE>
3    <GROUP>
4      <title>Control</title>
5      <subjectsAffectedBySeriousAdverseEvents>15</subjectsAffectedBySeriousAdverseEvents>
6      <subjectsAffectedByNonSeriousAdverseEvents>8</subjectsAffectedByNonSeriousAdverseEvents>
7      <deathsResultingFromAdverseEvents>9</deathsResultingFromAdverseEvents>
8      <subjectsExposed>67</subjectsExposed>
9      <deathsAllCauses>9</deathsAllCauses>
10   </GROUP>
11   <GROUP>
12     <title>Experimental</title>
13     <subjectsAffectedBySeriousAdverseEvents>33</subjectsAffectedBySeriousAdverseEvents>
14     <subjectsAffectedByNonSeriousAdverseEvents>13</subjectsAffectedByNonSeriousAdverseEvents>
15     <deathsResultingFromAdverseEvents>22</deathsResultingFromAdverseEvents>
16     <subjectsExposed>60</subjectsExposed>
17     <deathsAllCauses>22</deathsAllCauses>
18   </GROUP>
19   <NON_SERIOUS>
20     <groupTitle>Control</groupTitle>
21     <subjectsAffected>0</subjectsAffected>
22     <occurrences>0</occurrences>
23     <term>Abdominal pain</term>
24     <eutctId>100000004856</eutctId>
25   </NON_SERIOUS>
26   <NON_SERIOUS>

```

Transformation code: 108 lines

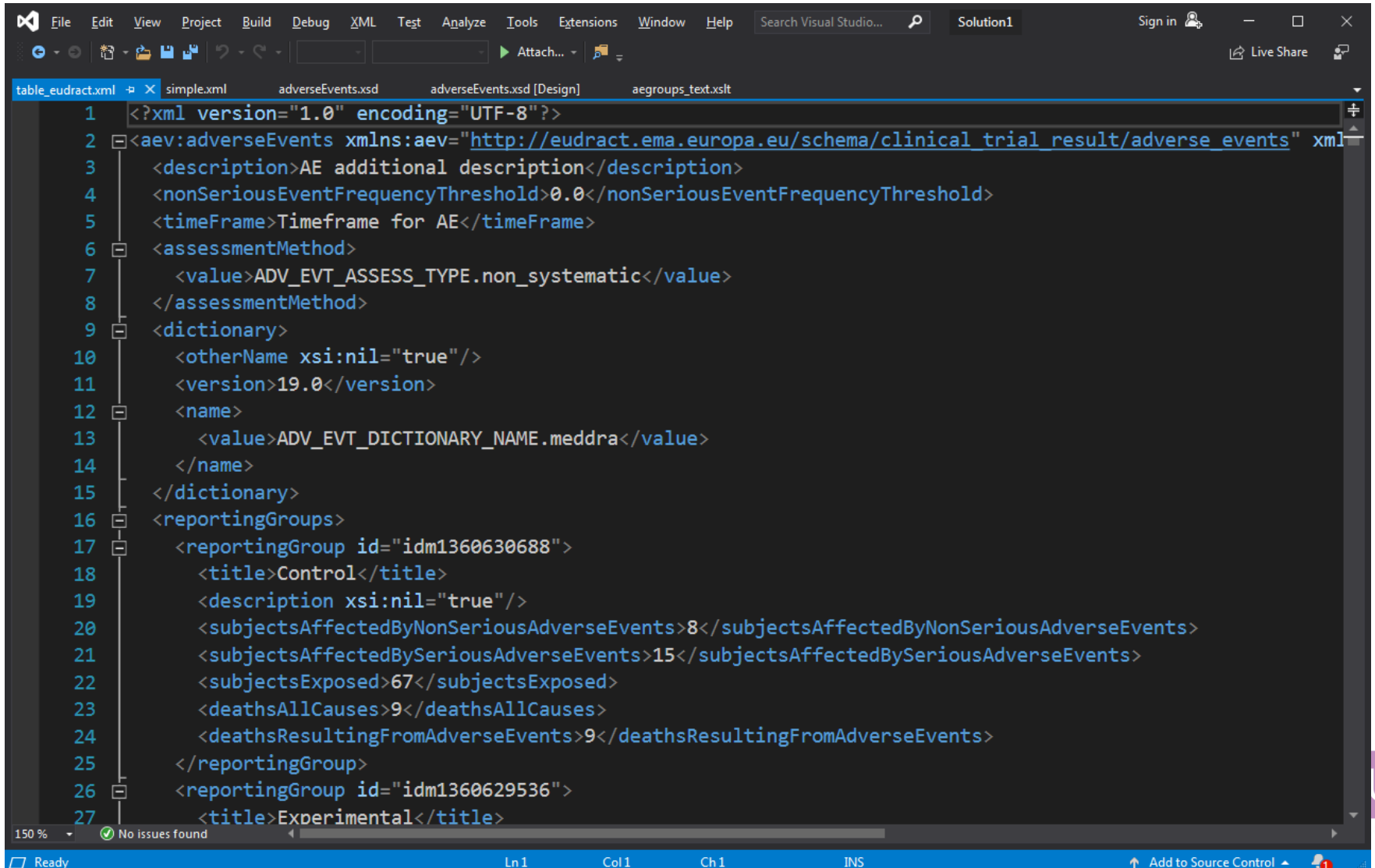


```

1  <?xml version="1.0" encoding="UTF-8"?>
2  <xsl:stylesheet version="1.0"
3    xmlns:xsl="http://www.w3.org/1999/XSL/Transform">
4    <xsl:output method="xml" indent="yes"/>
5
6    <xsl:key name="group_id" match="GROUP/title" use="."/>
7    <xsl:key name="term" match="SERIOUS | NON_SERIOUS" use="concat(term, eutctId, name())"/>
8
9
10 <xsl:template match="/">
11 <aev:adverseEvents xmlns:aev="http://eudract.ema.europa.eu/schema/clinical_trial_result/adverse_events" xml
12   <description>AE additional description</description>
13   <nonSeriousEventFrequencyThreshold>0.0</nonSeriousEventFrequencyThreshold>
14   <timeFrame>Timeframe for AE</timeFrame>
15   <assessmentMethod>
16     <value>ADV_EVT_ASSESS_TYPE.non_systematic</value>
17   </assessmentMethod>
18   <dictionary>
19     <otherName xsi:nil="true"/>
20     <version>19.0</version>
21     <name>
22       <value>ADV_EVT_DICTIONARY_NAME.meddra</value>
23     </name>
24   </dictionary>
25
26
27

```

Final Output

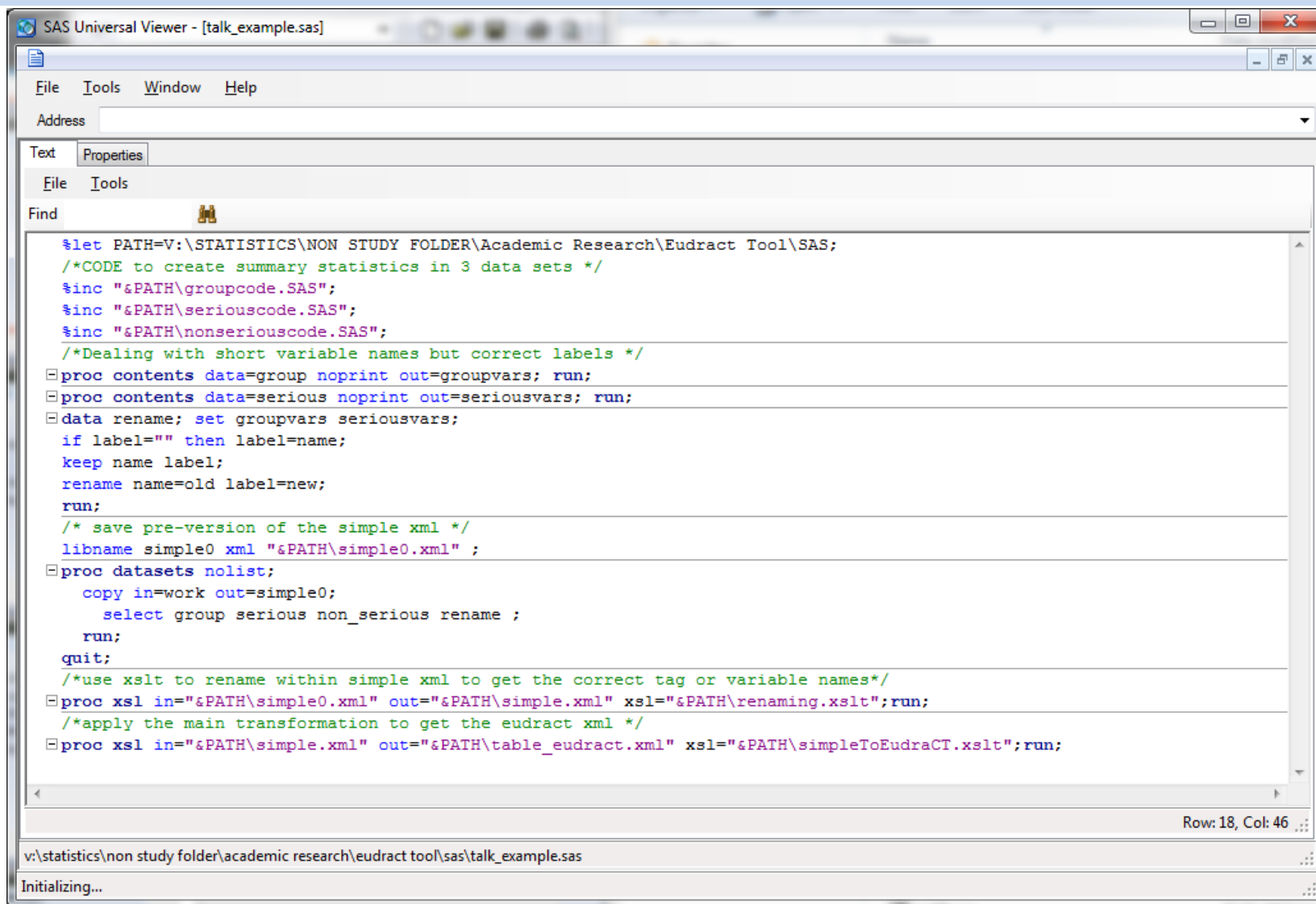


```

1 <?xml version="1.0" encoding="UTF-8"?>
2 <aev:adverseEvents xmlns:aev="http://eudract.ema.europa.eu/schema/clinical_trial_result/adverse_events" xml:lang="en">
3   <description>AE additional description</description>
4   <nonSeriousEventFrequencyThreshold>0.0</nonSeriousEventFrequencyThreshold>
5   <timeFrame>Timeframe for AE</timeFrame>
6   <assessmentMethod>
7     <value>ADV_EVT_ASSESS_TYPE.non_systematic</value>
8   </assessmentMethod>
9   <dictionary>
10    <otherName xsi:nil="true"/>
11    <version>19.0</version>
12    <name>
13      <value>ADV_EVT_DICTIONARY_NAME.meddra</value>
14    </name>
15  </dictionary>
16  <reportingGroups>
17    <reportingGroup id="idm1360630688">
18      <title>Control</title>
19      <description xsi:nil="true"/>
20      <subjectsAffectedByNonSeriousAdverseEvents>8</subjectsAffectedByNonSeriousAdverseEvents>
21      <subjectsAffectedBySeriousAdverseEvents>15</subjectsAffectedBySeriousAdverseEvents>
22      <subjectsExposed>67</subjectsExposed>
23      <deathsAllCauses>9</deathsAllCauses>
24      <deathsResultingFromAdverseEvents>9</deathsResultingFromAdverseEvents>
25    </reportingGroup>
26    <reportingGroup id="idm1360629536">
27      <title>Experimental</title>

```


SAS Equivalent



SAS Universal Viewer - [talk_example.sas]

File Tools Window Help

Address

Text Properties

File Tools

Find

```

%let PATH=V:\STATISTICS\NON STUDY FOLDER\Academic Research\Eudract Tool\SAS;
/*CODE to create summary statistics in 3 data sets */
%inc "&PATH\groupcode.SAS";
%inc "&PATH\seriouscode.SAS";
%inc "&PATH\nonseriouscode.SAS";
/*Dealing with short variable names but correct labels */
proc contents data=group noprint out=groupvars; run;
proc contents data=serious noprint out=seriousvars; run;
data rename; set groupvars seriousvars;
if label="" then label=name;
keep name label;
rename name=old label=new;
run;
/* save pre-version of the simple xml */
libname simple0 xml "&PATH\simple0.xml" ;
proc datasets nolist;
copy in=work out=simple0;
select group serious non_serious rename ;
run;
quit;
/*use xslt to rename within simple xml to get the correct tag or variable names*/
proc xsl in="&PATH\simple0.xml" out="&PATH\simple.xml" xsl="&PATH\renaming.xslt";run;
/*apply the main transformation to get the eudract xml */
proc xsl in="&PATH\simple.xml" out="&PATH\table_eudract.xml" xsl="&PATH\simpleToEudract.xslt";run;
  
```

Row: 18, Col: 46

v:\statistics\non study folder\academic research\eudract tool\sas\talk_example.sas

Initializing...

Final Report from EudraCT

Prickle_ct_result_2013-004200-19.pdf - Adobe Acrobat Reader DC

File Edit View Window Help

Home Tools Prickle_ct_result_20... x Sign In

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>

Introduction | EudraCT Tool

localhost:4000

Apps BBC News | News F... http://www.google... Imported From Fire... Heatmiser BBC News | News F... Imported SelectorGadget

EudraCT Tool About Downloads Feedback Introduction

Introduction

The remit of the [European Clinical Trials Data Base \(EudraCT\)](#) is to provide open access to summaries of all registered clinical trial results; thus aiming to prevent non-reporting of negative results and provide open-access to results to inform future research. The amount of information required and the format of the results, however, imposes a large extra workload at the end of studies on Clinical Trial Units. In particular, the adverse-event-reporting component requires entering:

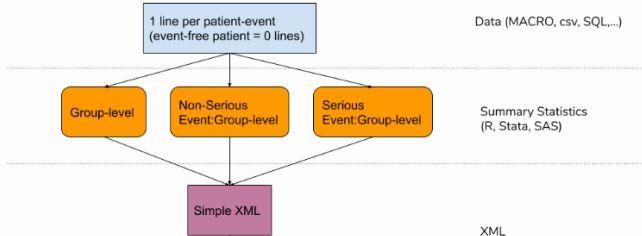
- each unique combination of treatment group and safety event
- for every such event above, a further 4 pieces of information (body system, number of occurrences, number of subjects, number exposed) for non-serious events, plus an extra three pieces of data for serious adverse events (numbers of causally related events, deaths, causally related deaths).

This is the home page of a NIHR-funded project to provide tools that will

- prepare the required statistics needed by EudraCT
- format them into the precise requirements to directly upload an XML file into the web portal, with no further data entry by hand.

Flow-Chart

An overview of the components to the tool is shown below.



```

graph TD
    A["1 line per patient-event  
(event-free patient = 0 lines)"] --> B["Group-level"]
    A --> C["Non-Serious  
Event:Group-level"]
    A --> D["Serious  
Event:Group-level"]
    B --> E["Simple XML"]
    C --> E
    D --> E
    
```

Data (MACRO, csv, SQL,...)

Summary Statistics
(R, Stata, SAS)

XML

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

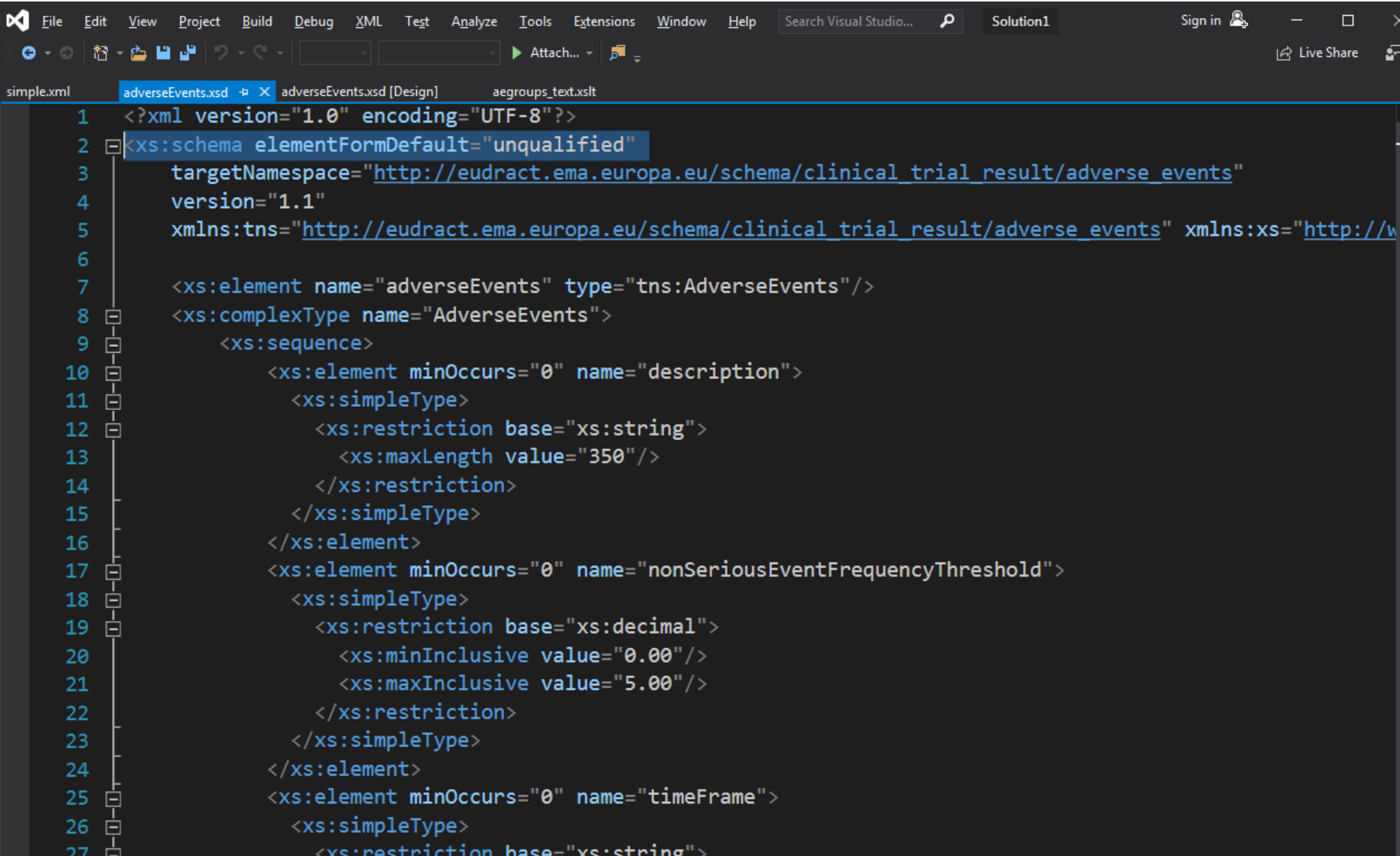
- Birmingham
- Leeds
- Glasgow
- All who participated in the Survey and spec feedback
- NIHR funding

Future Direction: Discussion

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

Extra Slides

Schema downloaded from EudraCT



```

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://www.w3.org/2001/XMLSchema"
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">

```