GUF / Rennes

Groupes des Utilisateurs Francophones des standards CDISC

Introduction to

Clinical Trial Registry XML (CTR-XML)

V 1.0

by Xavier GOBERT

4th October 2016

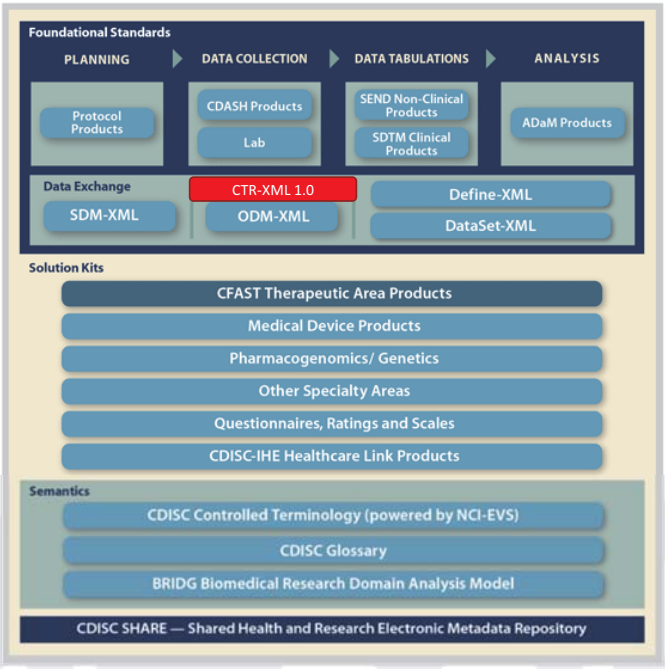
Agenda

MOVISIT

INTRODUCTION 1/2

- CTR-XML is one of the most recent CDISC standards
  - Release in March 2016
  - Kick off of CTR2 planned 2016 Q3/4.
- ODM extension for Clinical Trial Registration to
  - Health Organization (WHO)
  - European Medicines Agency (EMA) EudraCT Registry
  - United States ClinicalTrials.gov
- Provisionally approved / still under public review
  - remaining provisional until the CDISC Controlled Terminology is finalized
- Project lead by Paul Houston: phouston@cdisc.org

INTRODUCTION 2/2

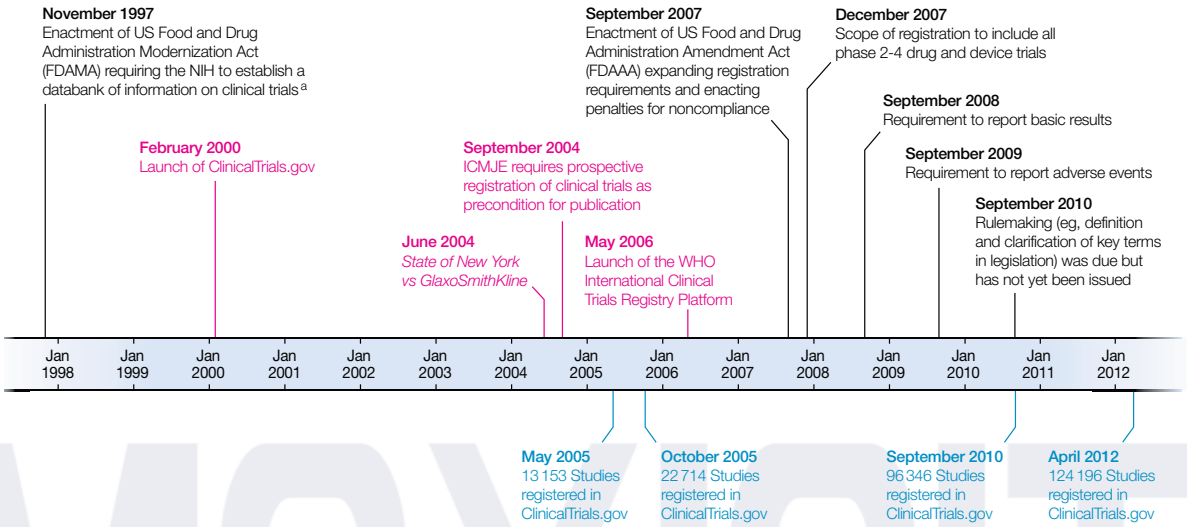


- Foundational Standards
- Data Exchange
- Based on ODM

REGULATORY REQUIREMENTS

- ❖Clinical Trials Registry (CTR) = platform and catalog for registering a clinical trial
- ❖General purpose of CTR is reveal the existence of all trials, published or not, to investigators and systematic reviewers
  - ❖ Avoid unpublished because results were unfavorable
  - ❖ Transparency and trust needed to protect patients (2005, New York's attorney general vs GSK, paroxetine in adolescents)
  - ❖ Inform potential subjects
- ❖International Committee of Medical Journal Editors (ICMJE) announced that their journals would not publish reports of trials if not registered (2005)
- ⚠Food and Drug Administration Amendments Act of 2007 (FDAAA),Final Rule for FDAAA 801 Issued (2016) > "civil money penalties"
- ⚠EU Directive 2001/20/EC (2014) > no penalties

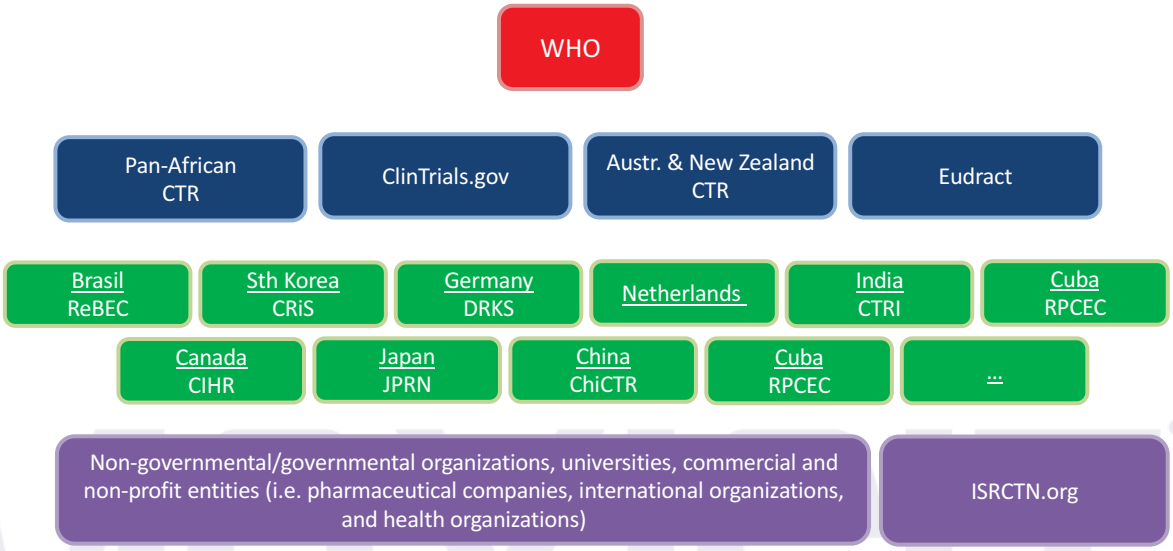
REGULATORY REQUIREMENTS



*Dickersin, K; Rennie, D (2009). "Registering clinical trials". JAMA. **290** (4): 516–523. doi:10.1001/jama.290.4.516. PMID 12876095.*

REGULATORY REQUIREMENTS

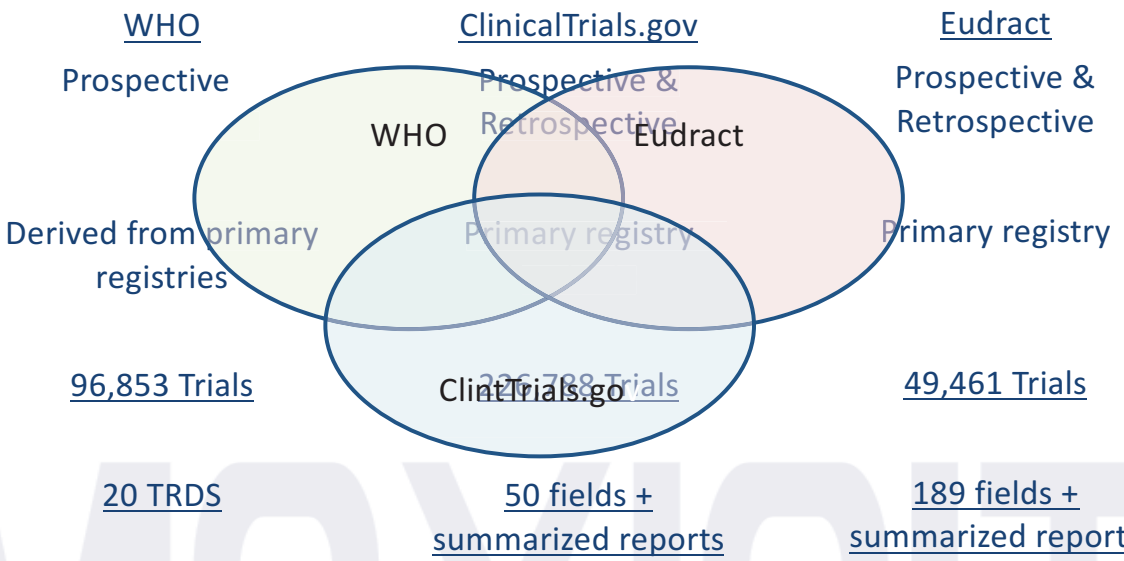
The landscape of Clinical Trial Registries



REGULATORY REQUIREMENTS

- Different groups of CTR:
  - Coverage: Global, Regional, National and Local
  - Prospective Vs Retrospective : results not registered Vs with registration summaries of safety results (WHO is Prospective / Eudract and ClinTrials.gov are Retrospective)
- Trial must be registered before participant enrollment.
- 6 to 12 Mths to register the study results
- Quality issues : incomplete information, results not registered in time
  - the primary purpose not reported : 6.8% of trials;
  - the number enrolled missing : 3.9%;
  - information about randomization and blinding missing in 4.2% and 2.7%, respectively.
  - 52% of trials registered after participant enrollment

REGULATORY REQUIREMENTS



REGULATORY REQUIREMENTS

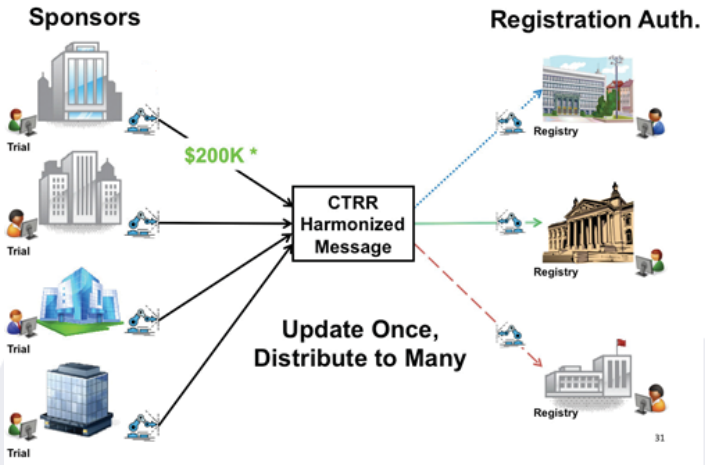
WHO
Primary Registry and Trial Identifying Number
Date of Registration in Primary Registry
Secondary Identifying Numbers

ClinicalTrials.gov
INFORMATION PROVIDED BY (RESPONSIBLE PARTY)
CLINICALTRIALS.GOV IDENTIFIER
FIRST RECEIVED
LAST UPDATED
LAST VERIFIED
HISTORY OF CHANGES
FIRST RECEIVED DATE
LAST UPDATED DATE
START DATE
PRIMARY COMPLETION DATE

Eudract
EudraCT Number
Title of the trial for lay people, in easily understood, i.e. non-technical, language
Name or abbreviated title of the trial where available
Full title of the trial
Sponsor's protocol code number
ISRCTN (International Standard Randomised Controlled Trial) Number
US NCT (ClinicalTrials.gov registry) number
WHO Universal Trial Reference Number (UTRN)
Other Identifier - Identifier
Other Identifier - Name
Trial is part of a Paediatric Investigation Plan
EMA Decision number of Paediatric Investigation Plan

CTR-XML Basics

❖Main goal is to provide a standard for representing the 20 TRDS requirements that can be re-used for submissions to ClinicalTrials.gov and to the EudraCT registry

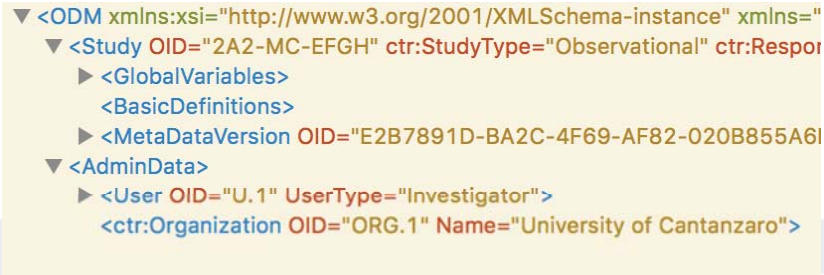


CTR-XML Basics

- CTR-XML is
  - founded on to the CDISC Operational Data Model (ODM) XML
  - upgraded with the Study Design Model SDM-XML for representing the structure, workflow, and timing of a study design.
  - harmonized vs CDISC Controlled Terminology
- Naming Convention
  - ODM are in the default namespace (i.e. no namespace prefix),
  - CTR-XML elements use the namespace prefix "ctr",
  - Elements defined in the EudraCT XML schemas use the namespace prefix "ct",
  - SDM-XML elements use the namespace prefix "sdm"
- XML structure with more than 113 nodes

CTR-XML Basics

- Root[0]: ODM
- Root[-1]: Study, AdminData
- Root[-2]: GlobalVariables, MetadataVersion

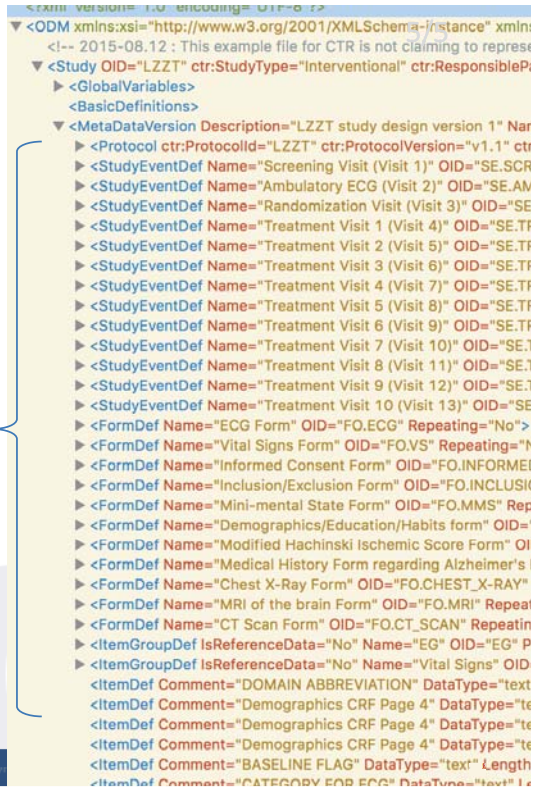


CTR-XML Basics

- Root[-2] GlobalVariables, MetadataVersion
- Root[-3]

CTR-XML Basics

- Root[-2] GlobalVariables, MetadataVersion
- Root[-3]



Use Cases

- Go though 4 use cases

- Programmed in R with "XML" package
  - Function "xmlParse" to parse XML file
  - Identify arm :

    xml_data$Study$GlobalVariables$FundingSupport

  - Calculate arms length : "xmlsize"
  - Read attributes:

    xml_data$Study$GlobalVariables$StudyName$StudyNameLocalizations[i]$TranslatedText$.attrs

  - Read values:

    xml_data$Study$GlobalVariables$StudyName$StudyNameLocalizations$TranslatedText

Use Cases

1)U.C.1: Date of First Enrollment

WHO	Anticipated or Actual date of enrollment of first participant.
EudraCT	Study Start Date, Study End Date
ClinicalTrials.gov	Study Start Date, Study End Date

- The ctr:StudyStartDate element and ctr:StudyEndDate elements are used to provide the Study Start Date and Study End Date information required for WHO, EudraCT and ClinicalTrials.gov.
- The Type attribute on the ctr:StudyStartDate element is used to indicate whether the date supplied is an "Actual" or "Anticipated" date.

```
136  xml_data$Study$StudyStartDate$.attrs
137
138  TRDS12 <- xml_data$Study$StudyStartDate$text
139  STUDYENDDATE <- xml_data$Study$StudyEndDate$text
```


Use Cases

2)U.C.1: Public Title

WHO	Public Title
EudraCT	Full Title, Lay Person Title, Abbreviated Title
ClinicalTrials.gov	Brief Title (protocol title intended for the lay public)

- The Public Title is the title for the general public. It is meant to be written in language that is easily understood.
- In consideration of the fact that this information is important and highly visible, the CTR-XML allows for translations.

```
<ctr:PublicTitle>
   <TranslatedText xml:lang="en">
      Vitamin D Plasma Level and Its Role in Headache
   </TranslatedText>
   <TranslatedText xml:lang="de">
      Vitamin D Plasma Niveau und ihre Rolle in Kopfschmerzen
   </TranslatedText>
</ctr:PublicTitle>
```

- WHO: only the English title is required.

Use Cases

- ❖ R code

1) Calculate the size of PublicTitle
2) Select Title if attribut = “en”

```
87  iSize <- xmlSize(xml_data$Study$GlobalVariables$PublicTitle$TranslatedText)
88  if (iSize == 1) {
89    TRDS9 <- xml_data$Study$GlobalVariables$PublicTitle$TranslatedText
90  } else if (xml_data$Study$GlobalVariables$PublicTitle$TranslatedText$.attrs == "en"){
91    TRDS9 <- xml_data$Study$GlobalVariables$PublicTitle$TranslatedText$text}
```

- ❖ Some Eudract non-mandatory fields are not available in CTR-XML 1.0

Use Cases

3)U.C.3: Contact for Public / Scientific Queries

WHO	Contact for Public Queries, contact for Scientific Queries
EudraCT	Sponsor Contact (Section B of Protocol Spreadsheet).
ClinicalTrials.gov	Recruitment Information/Contacts/Contact

- ❖ In CTR-XML the ctr:Contacts and ctr:Contact elements record contact information for the primary contact, the contact for scientific queries (WHO), and the contact for public queries (WHO).
- ❖ The UserOID attribute in the ctr:Contact element references a User element within the AdminData and the ContactRoleCodeListOID references a Codelist within the MetaDataVersion element.
- ❖ An ODM Codelist must be provided within the CTR-XML file to provide the list of Contact Roles.

Use Cases

```
<GlobalVariables>
   …
   <ctr:Contacts>
      <ctr:Contact UserOID="U.1" ContactRole="PRIMARY CONTACT"
           ContactRoleCodeListOID="CL.CONTACTROLES"/>
      <ctr:Contact UserOID="U.1" ContactRole="CONTACT FOR SCIENTIFIC QUERIES"
           ContactRoleCodeListOID="CL.CONTACTROLES"/>
      <ctr:Contact UserOID="U.1" ContactRole="CONTACT FOR PUBLIC QUERIES"
           ContactRoleCodeListOID="CL.CONTACTROLES"/>
   </ctr:Contacts>
</GlobalVariables>
```

```
<AdminData>
        <User OID="U.1" UserType="Investigator">
                <FullName>Luca Gallelli, MD</FullName>
                <Email>Gallelli@unicz.it</Email>
                <ctr:Role Context="ClinicalTrials.Gov">Primary Investigator</ctr:Role>
        </User>
        <ctr:Organization OID="ORG.1" Name="University of Cantanzaro"/>
</AdminData>
```


Use Cases

- ❖ R code

1) Calculate the nber of contacts
2) Check the role & select
3) (Parse admin data & select User details)

```
74  iSize <-xmlSize(xml_data$Study$GlobalVariables$Contacts)
75  i <-1
76  while (i < iSize + 1) {
77    Input1 <-xml_data$Study$GlobalVariables$Contacts[i]$Contact["ContactRole"]
78    if (Input1 == "CONTACT FOR SCIENTIFIC QUERIES"){TRDS8<- xml_data$Study$GlobalVariables$Contacts[i]$Contact["UserOID"]}
79    else if (Input1 == "CONTACT FOR PUBLIC QUERIES"){TRDS7 <- xml_data$Study$GlobalVariables$Contacts[i]$Contact["UserOID"]}
80    i <- i+1
81  }
```

Use Cases

Term	Explanation / Remarks
PRIMARY CONTACT	
CONTACT FOR PUBLIC QUERIES	
CONTACT FOR SCIENTIFIC QUERIES	
CA APPLICANT	Required by EudraCT
LEGAL REPRESENTATIVE	Required by EudraCT in case the sponsor is not established in the European Economic Area (EEA)
IEC APPLICANT	Optional field in EudraCT
PRINCIPAL INVESTIGATOR	
INVESTIGATOR	
FACILITY CONTACT	EudraCT
FACILITY CONTACT BACKUP	EudraCT
NETWORK CONTACT	EudraCT
SUBCONTRACTOR CONTACT	EudraCT
FURTHER CONTACT INFORMATION	EudraCT
CENTRAL CONTACT	ClinicalTrials.gov
CENTRAL CONTACT BACKUP	ClinicalTrials.gov
STUDY CHAIR	ClinicalTrials.gov
STUDY DIRECTOR	ClinicalTrials.gov

Use Cases

4. U.C.4: Health Condition(s) or Problem(s) Studied

WHO	Health condition(s) or problem(s) studied
EudraCT	Medical conditions
ClinicalTrials.gov	Conditions or Keywords (using NLM Medical Subject Heading (MeSH) terms)

- The CDISC Controlled Terminology for the SDTM Trial Summary dataset includes the term INDIC to refer to trial indication so the WHO Health Condition(s) study information uses the SDM-XML sdm:Parameter with the ShortName="INDIC" to provide the information needed for the Health Condition(s) field in the WHO registry.
- Possible to use controlled terminology or not
- External ODM codes list must be used

Use Cases

```
<Protocol>
   …
   <sdm:Summary>
      <sdm:Parameter OID="PAR.INDIC" ShortName="INDIC" Term="Trial Indication">
         <sdm:Value>Headache</sdm:Value>
      </sdm:Parameter>
   </sdm:Summary>
   …
</Protocol>
```

```
<sdm:Parameter OID="PAR.INDIC" ShortName="INDIC" Term="Trial Indication">
   <sdm:Value ctr:CodeListOID="CL.NLMESH">Headache</Value>
</sdm:Parameter>
…
<CodeList OID="CL.MeSH" Name="MeSH CT">
   <ExternalCodeList Dictionary="National Library of Medicine MeSH"
         Version="July 2015 International Version"
         href="http://www.nlm.nih.gov/mesh/MBrowser.html"/>
</CodeList>
```


Use Cases

- If the medical condition needs to be provided in several languages, the child element TranslatedText may be used

```
<sdm:Summary>
   <sdm:Parameter OID="PAR.INDIC" ShortName="INDIC" Term="Trial Indication">
      <sdm:Value>
         <TranslatedText xml:lang="en">Headache</TranslatedText>
      </sdm:Value>
      <sdm:Value>
         <TranslatedText xml:lang="de">Kopfschmerzen</TranslatedText>
      </sdm:Value>
      …
   </sdm:Parameter>
</sdm:Summary>
```

Use Cases

- ❖ R code

1) Loop 1 : select Parameter = “INDIC”
2) Loop 2 : select Language = “en”

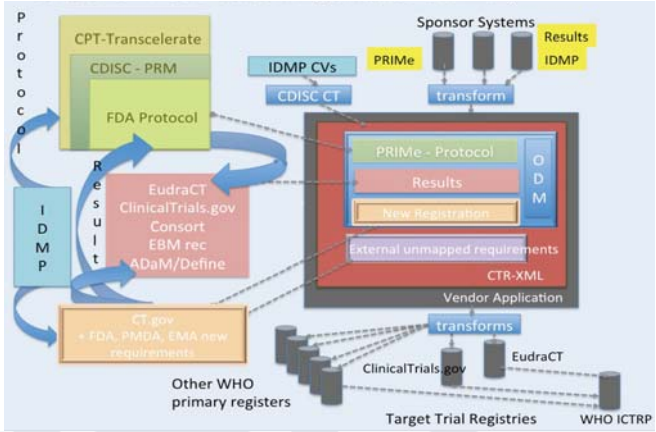
```
iSize <- xmlSize(xml_data$Study$MetaDataVersion$Protocol$Summary)
i <- 1
while (i < iSize+1){
  if(is.null(xml_data$Study$MetaDataVersion$Protocol$Summary[i]$Parameter$.attrs["OID"]) == FALSE &&
     xml_data$Study$MetaDataVersion$Protocol$Summary[i]$Parameter$.attrs["OID"]== "PAR.INDIC"){
    jSize <- xmlSize(xml_data$Study$MetaDataVersion$Protocol$Summary[i]$Parameter)
    j <- 1
    while (j < jSize+1){
      if (is.null (xml_data$Study$MetaDataVersion$Protocol$Summary[i]$Parameter[j]$Value$TranslatedText$.attrs) == FALSE &&
          xml_data$Study$MetaDataVersion$Protocol$Summary[i]$Parameter[j]$Value$TranslatedText$.attrs == "en") {
         TRDS12 <- xml_data$Study$MetaDataVersion$Protocol$Summary[i]$Parameter[j]$Value$TranslatedText$text
         j <- jSize
         }
      j <- j+1
    }
    i <-iSize
  }
  i <- i+1
}
```


Use Cases

```
▼<MetaDataVersion Description="LZZT study design version 1" Name="LZZT study design version 1" OID="LZZT_1">
  ▼<Protocol ctr:ProtocolId="LZZT" ctr:ProtocolVersion="v1.1" ctr:ProtocolVersionDate="2015-03-31" ctr:ProtocolVersio
    ▶<Description>
▼<sdm:Parameter OID="PAR.AGEMIN" ShortName="AGEMIN" Term="Planned minimum age of subjects">
  ▼<sdm:Value>
      50 years
▼<sdm:Parameter OID="PAR.AGESPAN" ShortName="AGESPAN" Term="Age span">
  ▼<sdm:Value>
      ADULT (18-65)
  ▼<sdm:Value>
      ELDERLY (> 65)
▼<sdm:Parameter OID="PAR.BLIND" ShortName="BLIND" Term="Trial blinding scheme">
  ▼<sdm:Value>
      DOUBLE BLIND
▼<sdm:Parameter OID="PAR.COMPTRT" ShortName="COMPTRT" Term="Comparative Treatment Name">
  ▼<sdm:Value>
      Placebo
▼<sdm:Parameter OID="PAR.CONTROL" ShortName="CONTROL" Term="Type of control">
  ▼<sdm:Value>
      PLACEBO
▶<sdm:Parameter OID="PAR.DIAGGRP" ShortName="DIAGGRP" Term="Diagnosis group">
▶<sdm:Parameter OID="PAR.DOSE" ShortName="DOSE" Term="Test product dose per administration">
▶<sdm:Parameter OID="PAR.DOSFRQ" ShortName="DOSFRQ" Term="Test product dosing frequency">
▼<sdm:Parameter OID="PAR.DOSU" ShortName="DOSU" Term="Test product dose units">
  ▼<sdm:Value>
      mg
▶<sdm:Parameter OID="PAR.TCNTRL" ShortName="TCNTRL" Term="Control Type">
▶<sdm:Parameter OID="PAR.HLTSUBJI" ShortName="HLTSUBJI" Term="Healthy Subject Indicator">
▶<sdm:Parameter OID="PAR.INTTYPE" ShortName="INTTYPE" Term="Intervention Type">
```

Future Developments

- CTR_2 launched Q3/2016
  - ISO IDMP (Identification of Medicinal Products Standards) -CDISC Gap Analysis and Alignment
  - Protocol extensions and a structured protocol standard (PRIMe – Protocol Representation Implementation Model)
  - Summary Results Integration



Conclusions

✓CTR-XML constitutes the only common source for registries data mapping

✓Parse XML to directly access values > mapping process

✓Comprehensive trial description with full description of study process > full data mapping

✓Flexible XML structure > covering all study cases

▪To be efficient: registries should be harmonized

✖Flexible XML structure > complex implementation

✖CTR-XML doesn't completely fulfill Eudract and ClinTrials.gov

✖CTR-XML is derived from SDM-XML, ODM-XML > versioning

✖ CTR-XML not addressing other local registries

✖ No results summary > mix between CTR-XML & AdaM

MAXISIT®

USA :
203, Main Street,
Metuchen
New Jersey 08840, USA
Phone: 732 – 494 – 2005

INDIA :
ClinAsia Labs Pvt. Ltd.
PHONIX IT Park, Gachibowli,
Hyderabad 500032 (AP) India.
Tel: +91-40-67234615

