



**Production implementation of a CDISC
ODM- and SDTM-based Clinical Data Warehouse**

Dr. Philippe Verplancke
XClinical

CDISC Interchange, Bethesda, 27 September 2006

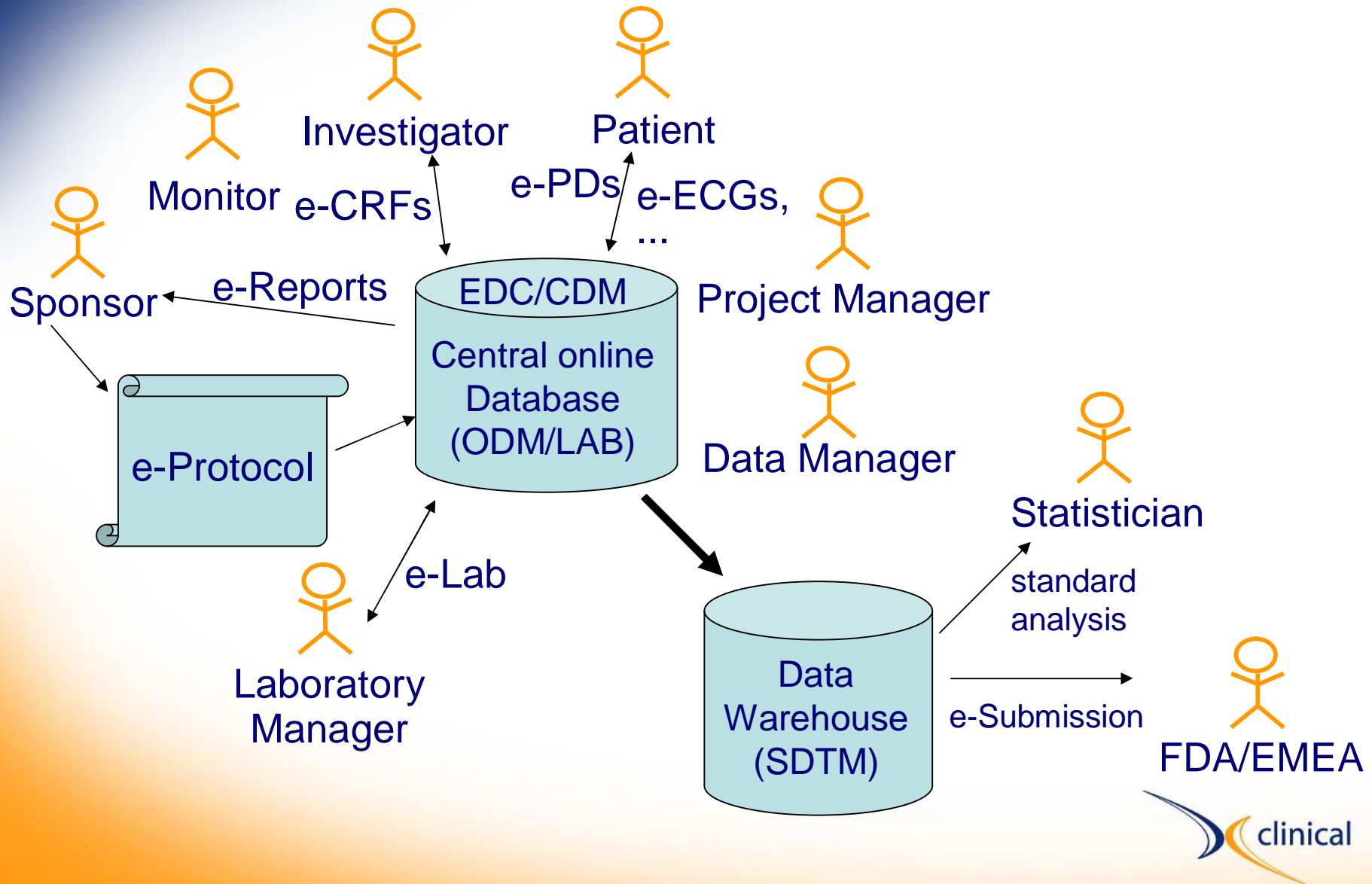
Company and References

- § EDC-CDM system vendor with offices in Munich, Paris and Bethesda
- § Integrated EDC-CDM system, MARVIN, featuring fast and automatic set-up and amendments of e-CRFs based on CDISC ODM metadata
- § Founded in 2002, fast and profitably growing without venture capital
- § Active member of the CDISC organization
- § Non-exclusive partnerships with the German Society of Cardiology and a number of international CRO's
- § 26+ trials (Phase II, III, IIIb, IV, Drugs & Medical Devices, Registries), 43.000+ patients
- § 21 CFR 11 compliant, GCP system validated, multiple external audits
- § From full service Hosting to full Technology Transfer
- § Experienced team, also working on pharma consulting projects (EDC change management)

- § XClinical / MARVIN were formerly named CRO24 / XTrial. Company and product brand names have been changed for strategic reasons.

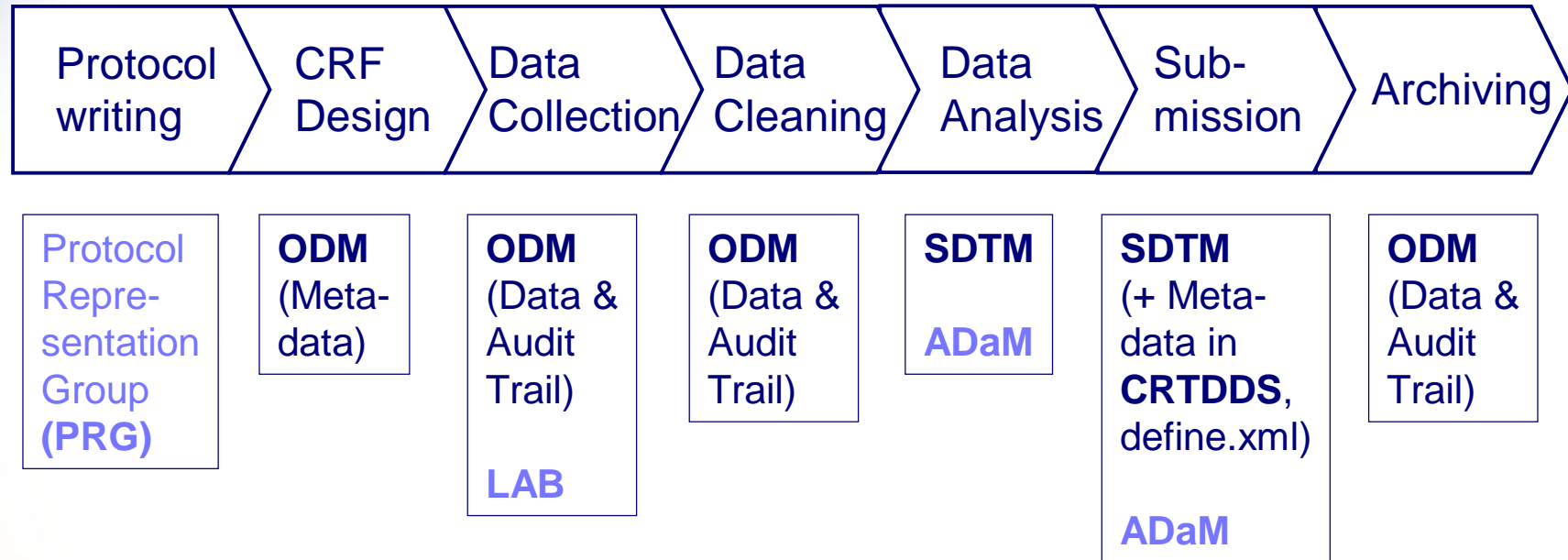


Our Vision: System Integration based on CDISC Standards

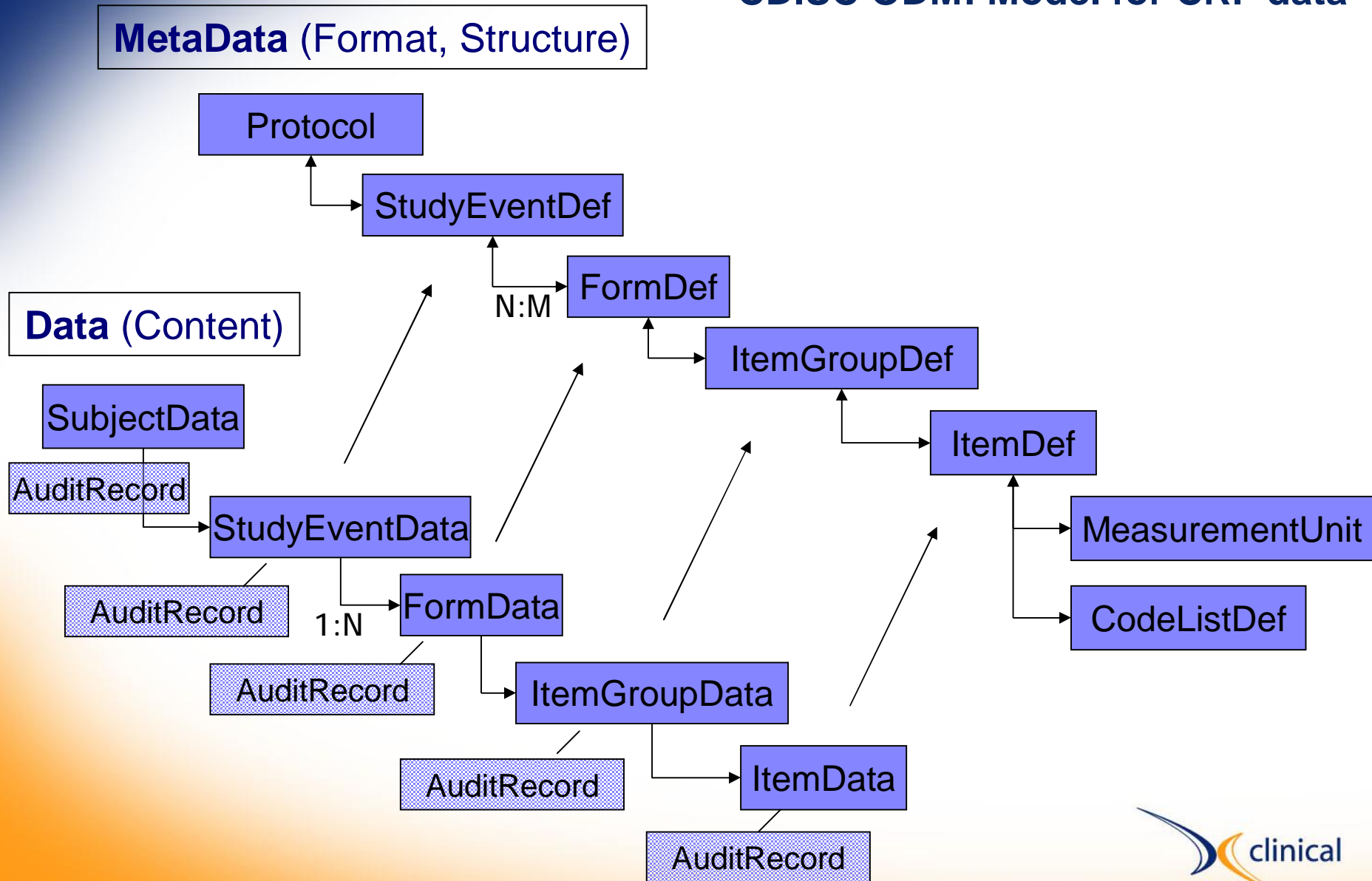


End-to end use of CDISC along the clinical trial process

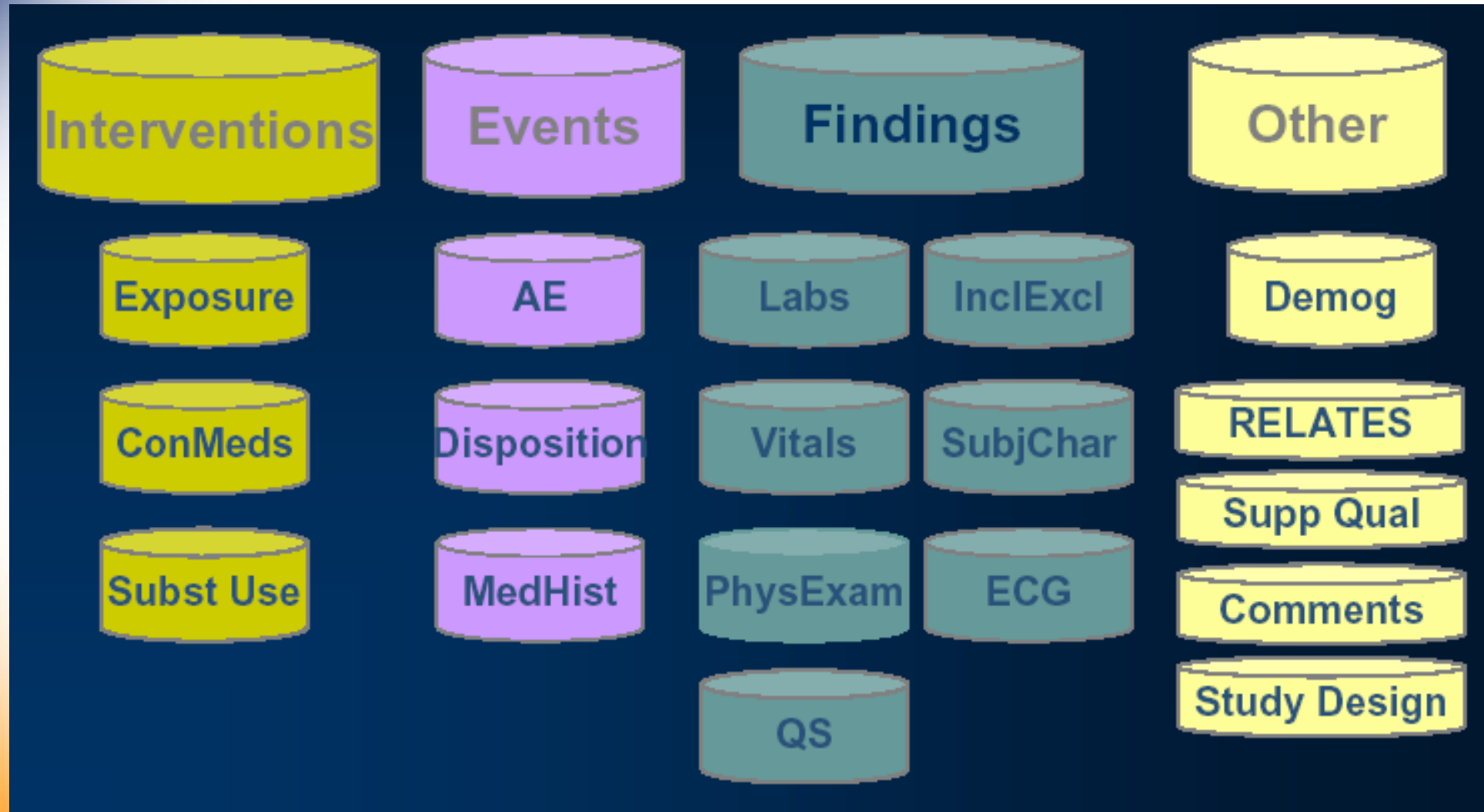
Clinical trial process (simplified)



CDISC ODM: Model for CRF data



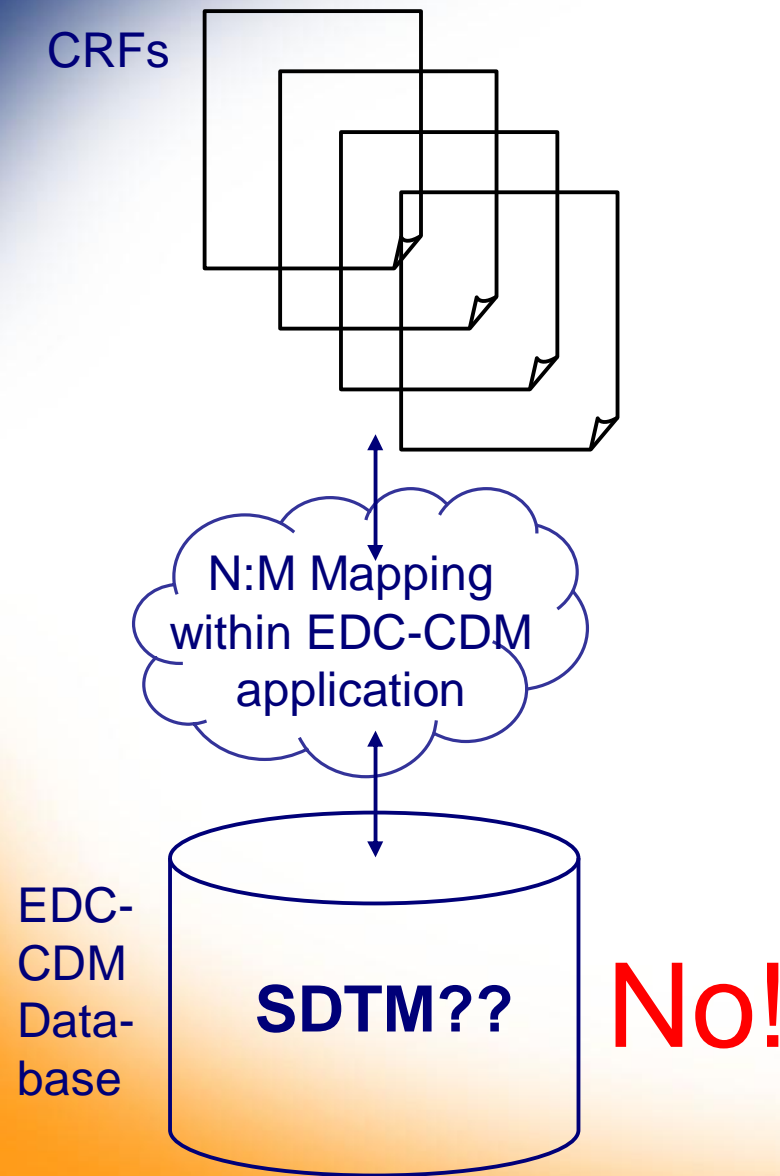
CDISC SDTM: Model for data tabulations



Courtesy: CDISC

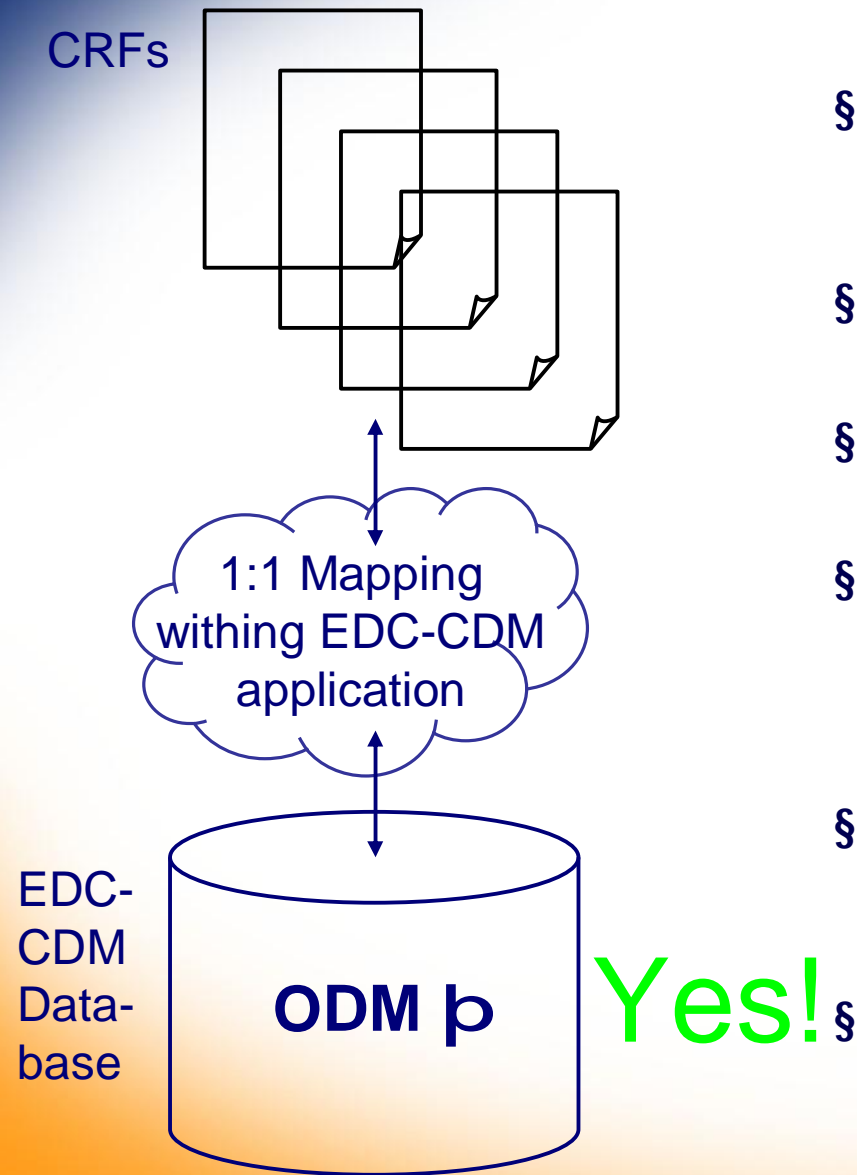


Shouldn't we just use SDTM in the EDC-CDM database?



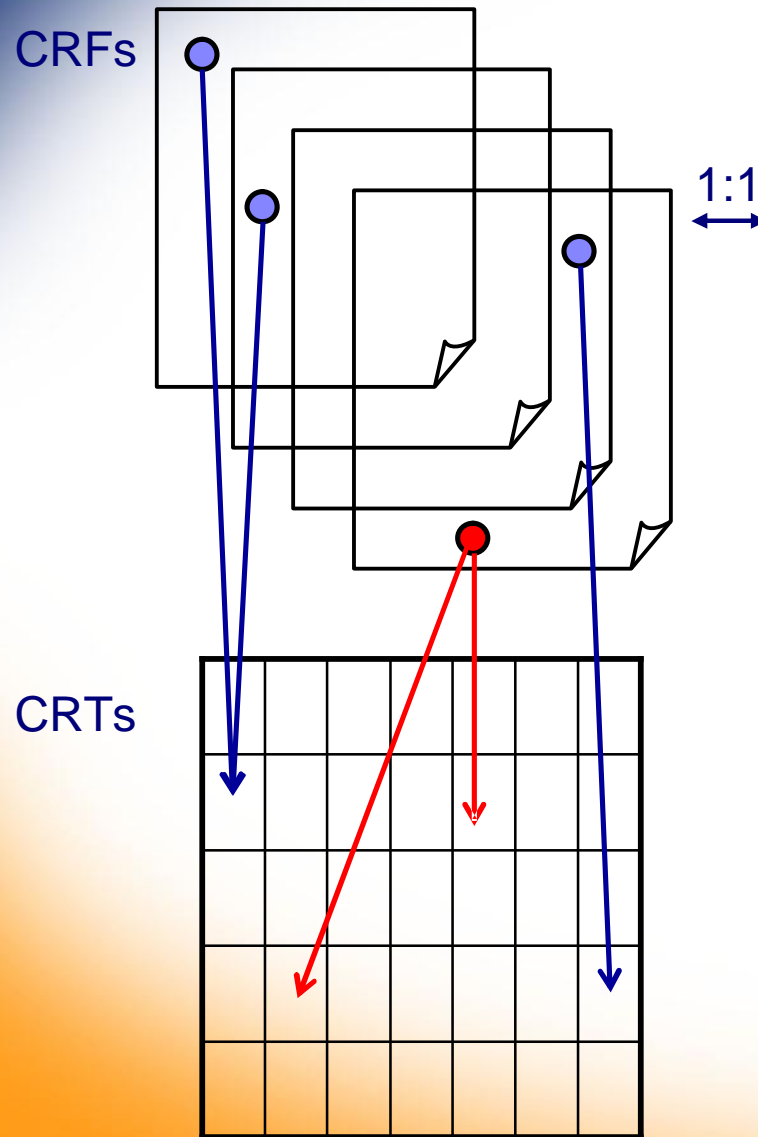
- § SDTM does not contain an audit trail
- § Mapping between SDTM and CRFs needs to be redone for every new trial
- § Such mapping would be proprietary within each EDC-CDM system
- § Audit trailing, signatures, administrative data would have a proprietary format within the EDC-CDM application
- § SDTM controlled terminology can be used within an ODM database

Advantages of using ODM for EDC-CDM



- § ODM is extremely flexible to adapt to any kind of CRFs (no need to have all domain variables on the same page ...)
- § ODM contains audit trail, signatures, internationalization, ...
- § Mapping between ODM and CRFs is trivial (1:1)
- § N:M Mapping between ODM and SDTM can be done with standard XML technology and reused for other trials with little effort
- § ODM contains XML-based value-level metadata that can be used for SDTM submission
- § ODM can integrate the SDTM controlled terminology

N:M mapping between ODM and SDTM



ODM = CRF metadata and data =
Visits, Forms, ItemGroups, Items



SDTM = Case Report Tabulations
= **different** (!!) „ItemGroups“, Items

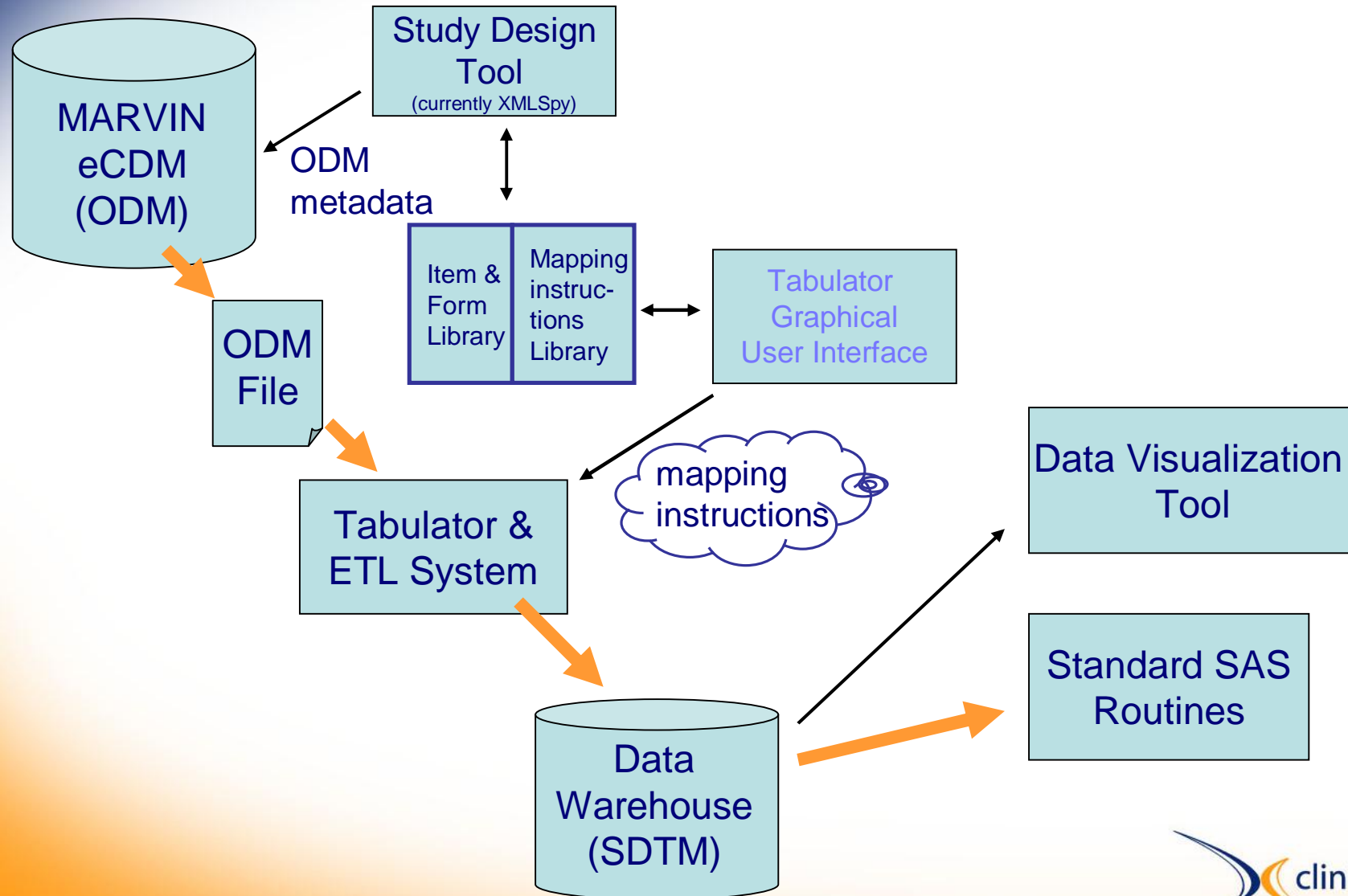
Sponsor's objectives

- § CDISC SDTM based data warehouse
- § should store all data
 - § cross-trial
 - § independent of the particular EDC-CDM system being used
 - § including measurement device data
- § for a number of purposes
 - § central storage and access (rapid retrieval)
 - § data dictionary (controlled terminology)
 - § CRF-CRT (i.e. ODM-SDTM) mapping dictionary
 - § source for standardized SAS analysis
 - § source for submission datasets
 - § archiving

Rationale of an ODM-SDTM transformation tool

- § Transformation between ODM data export files and SDTM datasets should be:
 - § automatic
 - § reproducible
 - § independent of the source system (EDC-CDM) and the target system (SDTM data warehouse)
 - § based on mapping instructions documented in machine readable format
 - § based on ODM and SDTM metadata (define.xml)
 - § based on standard XML technology
- § Make setup of mapping instructions easier:
 - § drag-and-drop / point-and-click
 - § share value-level metadata between ODM and SDTM as much as possible (ItemDefs, CodeListDefs, MeasurementUnitDefs); if needed, do renaming and/or recoding
 - § use SDTM controlled terminology as early as possible (at e-CRF setup)

Production implementation (end-to-end)



Use cases of an ODM-SDTM transformation tool

- § load and validate ODM file (trial-specific)
- § load and validate define.xml file (cross-trial)
- § copy ItemDefs, CodeListDefs, MeasurementUnitDefs from ODM metadata to define.xml (and rename them or create new elements)
- § create/update ValueListDefs
- § define N:M mapping instructions including derivations (calculations, recoding, etc.)
- § to resume mapping work later:
 - § store new version of define.xml
 - § store trial-specific mapping instructions
- § show which parts of the ODM data have already been mapped to SDTM and which are still missing
- § support all of the above with a graphical user interface (drag-and-drop and/or point-and-click)
- § execute the mapping instructions to transform the trial ODM export file into SDTM datasets (first XML data, then SQL)



Use Cases for the SDTM data warehouse loading routines

- § transform define.xml ItemGroupDefs to SQL create table statements
- § create new tables for new domains based on latest define.xml
- § notify warehouse administrator in case of table creation conflicts (trial not complying with the SDTM domain definitions of previous trials)
- § transform SDTM XML datasets to SQL insert statements (XSLT)
- § load data by study ID
- § validate compliance with previous value-level metadata
- § delete data by study ID (no update; delete and reload)

Example of an ODM export file

```
<ClinicalData StudyOID="██████████" MetadataVersionOID="MDU.0.7">
  <SubjectData SubjectKey="556_520_862">
    <SiteRef LocationOID="Center.002"/>
    <StudyEventData StudyEventOID="Event.SCREENING">
      <FormData FormOID="Form.DEMOG">
        <ItemGroupData ItemGroupOID="IG.SCREENING_DATE">
          <ItemData ItemOID="Item.DATE_U" Value="2005-07-28"/>
        </ItemGroupData>
        <ItemGroupData ItemGroupOID="IG.ORIG_COLOR">
          <ItemData ItemOID="Item.ORIG_COLOR" Value="A-red"/>
        </ItemGroupData>
        <ItemGroupData ItemGroupOID="IG.BASE">
          <ItemData ItemOID="Item.PROBMR" Value="HFSMS000366"/>
          <ItemData ItemOID="Item.SEX" Value="F"/>
          <ItemData ItemOID="Item.BIRTHDT" Value="1982-02-18"/>
          <ItemData ItemOID="Item.SCRNR" Value="SCR1-A1-rot"/>
          <ItemData ItemOID="Item.INCLUSION_1" Value="Y"/>
          <ItemData ItemOID="Item.DATE_IC" Value="2005-07-28"/>
          <ItemData ItemOID="Item.QUESTCOMPL" Value="Y"/>
          <ItemData ItemOID="Item.QUESTOK" Value="Y"/>
          <ItemData ItemOID="Item.BLSAMPLE" Value="Y"/>
          <ItemData ItemOID="Item.BLTIME" Value="07:44:00"/>
        </ItemGroupData>
      </FormData>
      <FormData FormOID="Form.oGTT">
        <ItemGroupData ItemGroupOID="IG.t0">
          <ItemData ItemOID="Item.COLOR" Value="A-red"/>
          <ItemData ItemOID="Item.TARGETTIME" Value="09:00:00"/>
          <ItemData ItemOID="Item.ACTUALTIME" Value="09:00:00"/>
          <ItemData ItemOID="Item.BGcompact" Value="73">
            <MeasurementUnitRef MeasurementUnitOID="MeasurementUnit.mgpd1"/>
          </ItemData>
          <ItemData ItemOID="Item.CAPA" Value="Y"/>
          <ItemData ItemOID="Item.CAPB" Value="Y"/>
          <ItemData ItemOID="Item.BGLABa" Value="68.6">
            <MeasurementUnitRef MeasurementUnitOID="MeasurementUnit.mgpd1"/>
          </ItemData>
          <ItemData ItemOID="Item.BGLABb" Value="76.1">
            <MeasurementUnitRef MeasurementUnitOID="MeasurementUnit.mgpd1"/>
          </ItemData>
          <ItemData ItemOID="Item.BGLABav" Value="72.35">
            <MeasurementUnitRef MeasurementUnitOID="MeasurementUnit.mgpd1"/>
          </ItemData>
        </ItemGroupData>
      </FormData>
    </StudyEventData>
  </SubjectData>
</ClinicalData>
```

Example of ODM-SDTM mapping instructions (“tabulator.xml”)

```
<tbt:Select ContextPath="/SubjectData">
  <tbt:Write TargetItemOID="STUDYID" Value="██████████" />
  <tbt:Write TargetItemOID="DOMAIN" Value="DM" />
  <tbt:Write TargetItemOID="USUBJID">
    <xc:Function Function="concat">
      <xc:Value DataType="text" Value="██████████" />
      <xc:ElementPath>@SubjectKey</xc:ElementPath>
    </xc:Function>
  </tbt:Write>
  <tbt:Write TargetItemOID="SUBJID" Path="@SubjectKey" />
  <tbt:Write TargetItemOID="RFSTDTC" Path="StudyEventData[@OID='Event.Day1']//ItemData[@OID='Item.DATE_U']" />
  <tbt:Write TargetItemOID="RFENDTC" Path="StudyEventData[@OID='Event.Day5']//ItemData[@OID='Item.DATE_U']" />

  <tbt:Write TargetItemOID="SITEID" Value="SiteRef/@LocationOID" />
  <tbt:Write TargetItemOID="INUID" Value="DEU-0001" />
  <tbt:Write TargetItemOID="INUNAM" Value="██████████ ID" />

  <tbt:Write TargetItemOID="BRTHDTC" Path="//ItemData[@OID='Item.BIRTHDTC']" />
  <tbt:Write TargetItemOID="AGE">
    <xc:Calculation Operator="floor">
      <xc:Function Function="yearsDiff">
        <xc:ElementPath>StudyEventData[@OID='Event.SCREENING']//ItemData[@OID='Item.DATE_U']</xc:ElementPath>
        <xc:ElementPath>StudyEventData[@OID='Event.SCREENING']//ItemData[@OID='Item.BIRTHDTC']</xc:ElementPath>
      </xc:Function>
    </xc:Calculation>
  </tbt:Write>
  <tbt:Write TargetItemOID="AGEU" Value="YEARS" />
  <tbt:Write TargetItemOID="SEX" Path="StudyEventData[@OID='Event.SCREENING']/FormData[@OID='Form.DEMOG']//ItemData[@OID='Item.S

  <tbt:Write TargetItemOID="RACE" Value="Caucasian" />
  <tbt:Write TargetItemOID="COUNTRY" Value="DEU" />
  <tbt:Write TargetItemOID="DMDTC" Path="StudyEventData[@OID='Event.SCREENING']//ItemData[@OID='Item.DATE_U']" />
  <tbt:Write TargetItemOID="DMDY" >
    <xc:Calculation Operator="floor">
      <xc:Choose>
        <xc:When>
          <xc:Test Comparator="GE">
            <xc:ElementPath>StudyEventData[@OID='Event.SCREENING']/FormData[@OID='Form.DEMOG']//ItemData[@OID='Item.DATE_U']</xc:ElementPat
          </xc:Test>
            <xc:ElementPath>StudyEventData[@OID='Event.Day1']/FormData[@OID='Form.MEASURES']//ItemData[@OID='Item.DATE_U']</xc:ElementPath>
          </xc:Test>
          <xc:Calculation Operator="sum">
            <xc:Value DataType="integer">1</xc:Value>
            <xc:Function Function="daysDiff">
              <xc:ElementPath>StudyEventData[@OID='Event.SCREENING']/FormData[@OID='Form.DEMOG']//ItemData[@O
              <xc:ElementPath>StudyEventData[@OID='Event.Day1']/FormData[@OID='Form.MEASURES']//ItemData[@OID

            </xc:Function>
          </xc:Calculation>
        </xc:When>
      </xc:Choose>
    </xc:Calculation>
  </tbt:Write>
  <xc:Otherwise>
```

Screenshot of the SDTM Demographics table

Squirrel SQL Client Version 2.1 final

File Drivers Aliases Plugins Session Windows Help

Connect to: DATA_REP Active Session: 1 - DATA_REP as etms_user_...

1 - DATA_REP as etms_user_02

Objects SQL

Info Content Row Count Columns Primary Key Exported Keys Imported Keys Indexes Privileges Column Privileges Row IDs Versions

STUDYID	D...	USUBJID	SUBJID	RFSTDT	RFENDTC	SITEID	INVID	INVNAM	BRTHDTC	AGE	AGEU	SEX	RACE	COU...	DMDTC	DMDY
DM			061_517_813	2005-08-24	2005-08-28				1979-06-14	26	YEARS	f	Caucasian	DEU	2005-07-28	-27
DM			256_124_431	2005-08-29	2005-09-02				1971-02-05	34	YEARS	f	Caucasian	DEU	2005-07-28	-32
DM			354_514_773	2005-08-24	2005-08-28				1980-03-26	25	YEARS	f	Caucasian	DEU	2005-07-28	-27
DM			358_993_595	2005-09-12	2005-09-16				1986-02-28	19	YEARS	f	Caucasian	DEU	2005-07-28	-46
DM			464_849_509	2005-08-29	2005-09-02				1975-01-19	30	YEARS	f	Caucasian	DEU	2005-07-28	-32
DM			556_520_862	2005-09-18	2005-09-22				1982-02-18	23	YEARS	f	Caucasian	DEU	2005-07-28	-52
DM			641_055_914	2005-09-18	2005-09-22				1976-09-01	29	YEARS	f	Caucasian	DEU	2005-07-28	-52
DM			959_726_103	2005-08-29	2005-09-02				1975-10-08	29	YEARS	m	Caucasian	DEU	2005-07-28	-32
DM			171_816_489	2005-08-29	2005-09-02				1982-08-10	23	YEARS	m	Caucasian	DEU	2005-08-27	-2
DM			272_730_716	2005-09-12	2005-09-16				1980-06-27	25	YEARS	f	Caucasian	DEU	2005-08-27	-16
DM			392_169_658	<null>	<null>				1979-10-17	<null>	YEARS	f	Caucasian	DEU	2005-08-27	<null>
DM			395_339_304	2005-09-12	2005-09-16				1981-07-23	24	YEARS	f	Caucasian	DEU	2005-08-27	-16
DM			434_708_535	2005-09-26	2005-09-30				1980-03-22	25	YEARS	f	Caucasian	DEU	2005-08-27	-30
DM			460_443_815	2005-09-26	2005-09-30				1979-08-21	26	YEARS	f	Caucasian	DEU	2005-08-27	-30
DM			694_108_558	<null>	<null>				1978-10-30	<null>	YEARS	m	Caucasian	DEU	2005-08-27	<null>
DM			744_843_825	2005-09-12	2005-09-16				1979-05-09	26	YEARS	m	Caucasian	DEU	2005-08-27	-16
DM			823_475_855	<null>	<null>				1982-12-11	<null>	YEARS	m	Caucasian	DEU	2005-08-27	<null>
DM			912_797_749	2005-09-18	2005-09-22				1980-06-06	25	YEARS	f	Caucasian	DEU	2005-08-27	-22
DM			141_315_331	2005-10-05	2005-10-09				1974-01-10	31	YEARS	m	Caucasian	DEU	2005-09-16	-19
DM			182_583_601	2005-10-05	2005-10-09				1980-03-26	25	YEARS	m	Caucasian	DEU	2005-09-16	-19
DM			223_706_300	2005-09-26	2005-09-30				1976-05-29	29	YEARS	m	Caucasian	DEU	2005-09-16	-10
DM			267_848_768	2005-10-05	2005-10-09				1975-04-26	30	YEARS	m	Caucasian	DEU	2005-09-16	-19
DM			353_330_636	2005-10-05	2005-10-09				1971-05-03	34	YEARS	m	Caucasian	DEU	2005-09-16	-19
DM			518_819_377	2005-10-17	2005-10-21				1982-02-03	23	YEARS	m	Caucasian	DEU	2005-09-16	-31
DM			709_667_008	<null>	<null>				1983-04-29	<null>	YEARS	f	Caucasian	DEU	2005-09-16	<null>
DM			711_410_619	<null>	<null>				1981-04-10	<null>	YEARS	m	Caucasian	DEU	2005-09-16	<null>
DM			741_621_502	2005-09-26	2005-09-30				1978-02-28	27	YEARS	m	Caucasian	DEU	2005-09-16	-10
DM			797_423_204	2005-10-17	2005-10-21				1977-12-14	27	YEARS	m	Caucasian	DEU	2005-09-16	-31
DM			916_606_956	<null>	<null>				1981-01-29	<null>	YEARS	f	Caucasian	DEU	2005-09-16	<null>
DM			158_413_256	<null>	<null>				1979-07-12	<null>	YEARS	m	Caucasian	DEU	2005-09-27	<null>
DM			210_886_969	2005-10-17	2005-10-21				1980-04-08	25	YEARS	m	Caucasian	DEU	2005-09-27	-20
DM			715_279_853	<null>	<null>				1980-09-18	<null>	YEARS	m	Caucasian	DEU	2005-09-27	<null>



Lessons learnt

- § Most work-intensive tasks:
 - § definition of standard variables with controlled terminology on the SDTM side
 - § decision on which CRF items belong to which SDTM domain, which variables to put in SUPPQUAL, which CRF items to load and not to load into the data warehouse, etc.

- § Once a “data dictionary” with SDTM-compliant ItemDefs is set-up for the first time and when such ItemDefs are used in the EDC-CDM system for the set-up of new trial e-CRFs, the mapping of such new trials becomes a quick and easy task.

- § Need a “source data verification” process between ODM data source and SDTM data warehouse to correct mapping errors

- § The end-to-end CDISC approach really combines the best of two worlds:
 - § the flexibility of ODM to define e-CRFs in whatever shape or form
 - § the controlled terminology and domain set of SDTM for standard analysis and submission to the FDA



Contact

XClinical GmbH

Siegfriedstrasse 8
80803 Munich
Germany

Phone: +49 89 45 22 77 – 5100
Fax: +49 89 45 22 77 – 5900

Web: www.xclinical.com

Email: philippe.verplancke@xclinical.com

XClinical USA

c/o Provantec, LLC
7831 Woodmont Ave, Suite 285
Bethesda, Maryland
20814, USA

Phone: 301 841 7784
Toll free: 866 871 5889
Fax: 301 560 7162

