CLINICAL DATA INTERCHANGE STANDARDS CONSORTIUM

The CDISC vision is to inform patient care & safety through higher quality medical research.

Strength *through Collaboration*

The CDISC Moonshot - Can we do it?

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XML 4Pharma

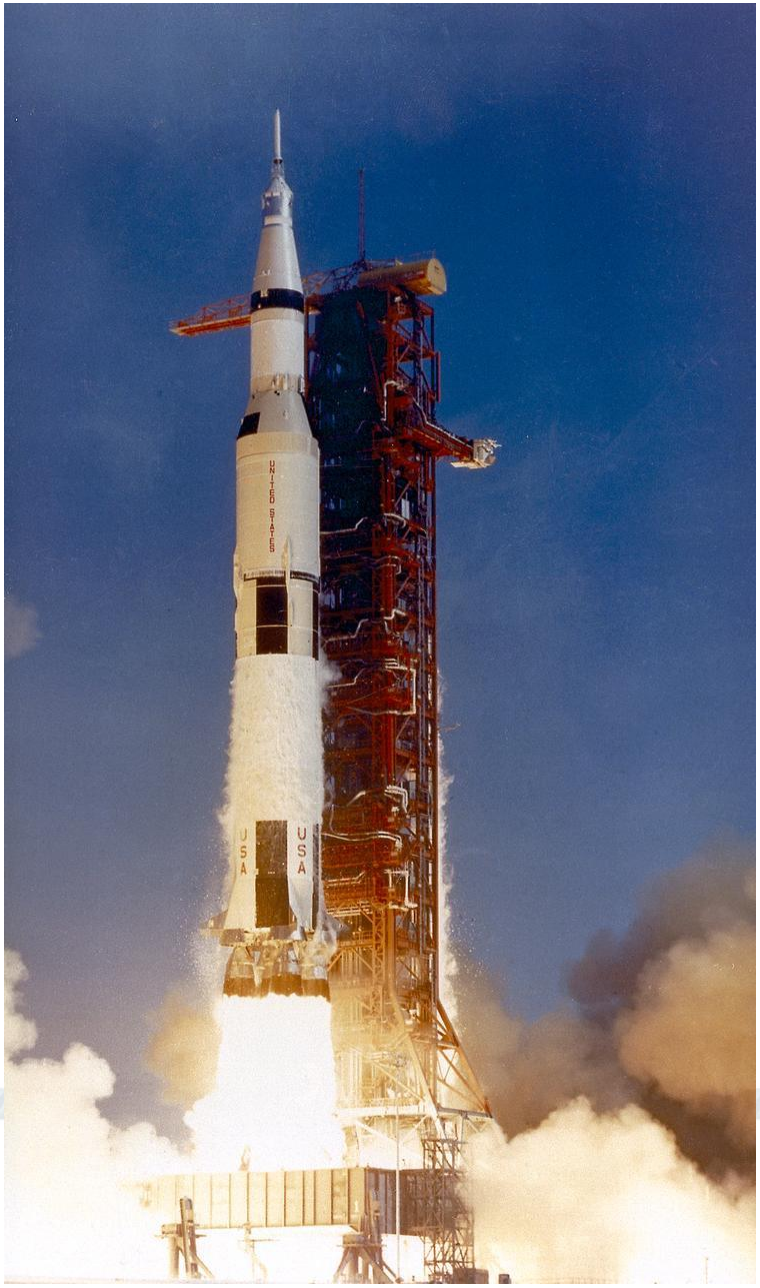
Strength *through Collaboration*

CDISC has grown …

But it is time to take the next step …

The CDISC Moonshot

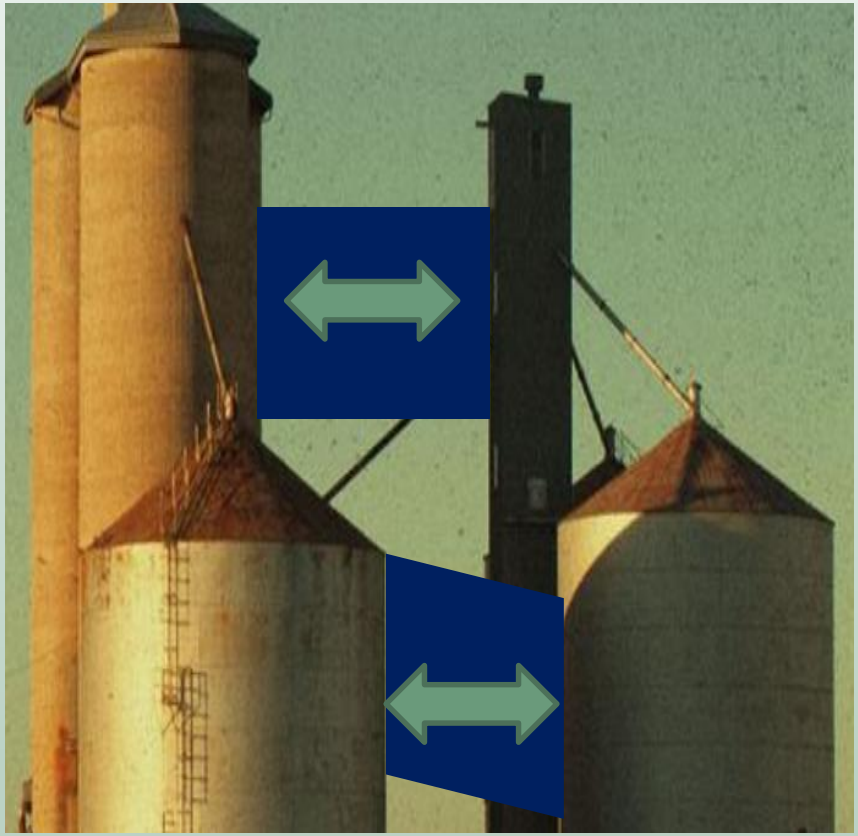
The next great step …



From the CDISC website …

Are these stages of a CDISC rocket?

Oh no … these are CDISC silos …



From silos to rocket stages

- Most of our standards have their origin in the last century …
- Are not according to "current state of the art" in (bio)medical informatics
- Have developed along the same lines and traditions we had almost 20 years ago
- Don't we need a modernization?

The CDISC ODM Standard

- 20 years old, only minor updates
  - And some extensions (Define-XML, SDM-XML, Dataset-XML, CTR-XML)
- No support for:
  - RESTful web services
  - Flexible and complicated study designs
  - Wearables, insideables
- Little support for electronic health records
- Based on the concept of "files"
  - Who still needs data files? We need "data services"

ODM 2.0 - the first rocket stage

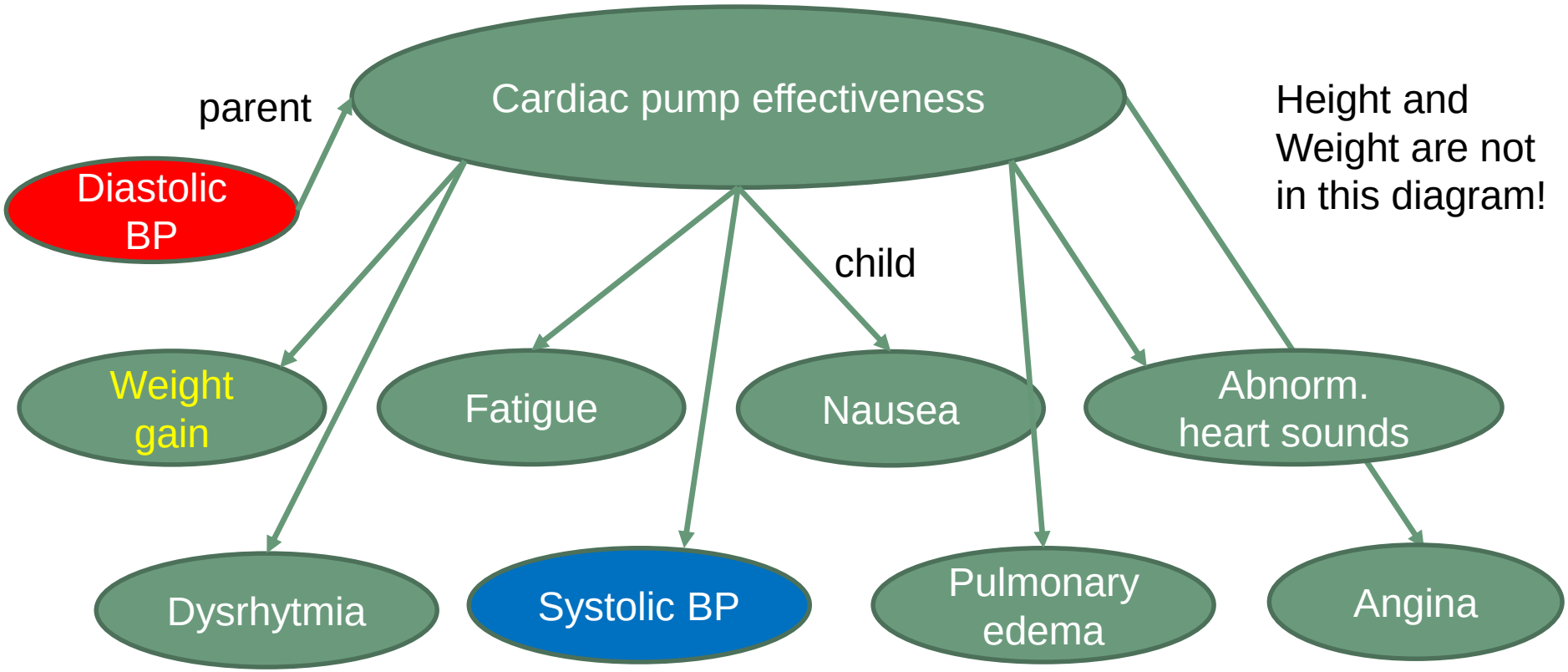
- Support for RESTful web services
  - The data can be anyware - not necessarily in files
- Full integration of electronic health records
- We need some concepts that are also used by FHIR
  - But clinical research is more complicated (protocol based)
- Downward compatible
- Can ODM and FHIR be one standard in 10 years from now?

CDISC controlled terminology

- "Lists" of terms with little of no links between them
- DIABP and SYSBP are as much related as DIABP with FRMSIZE - really?
- Refusal to use controlled terminology from the medical world
  - LOINC
  - UCUM
  - ICDx
  - SNOMED
  - …

An example using UMLS RESTful web services

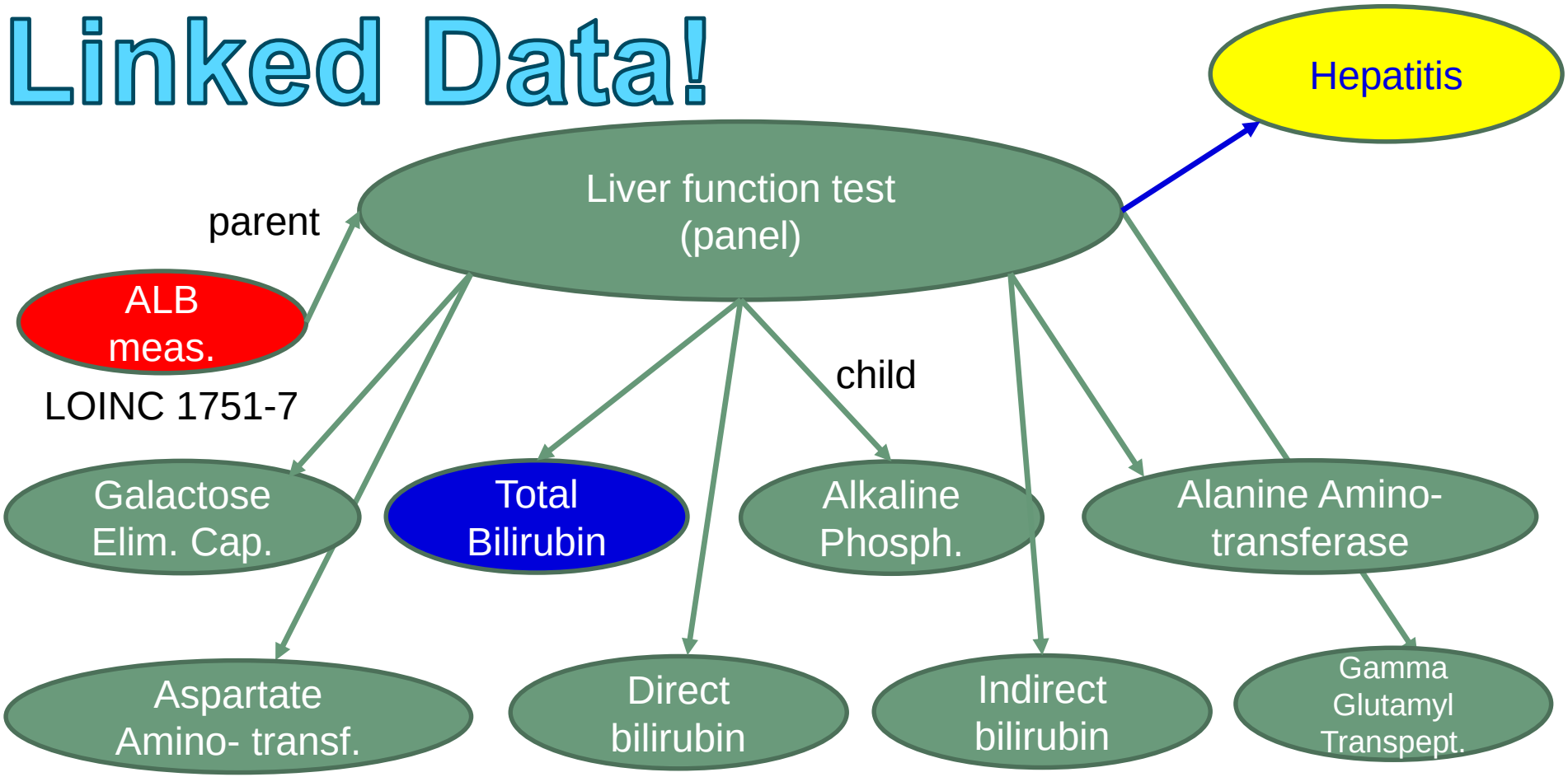
Linked Data!



"DIABP" and "SYSBP" are related through e.g. "*cardiac pump effectiveness*"
There is no way ever to find out using CDISC-CT alone…

A LOINC example using UMLS RESTful web services

Linked Data!



"ALB" and "BILI" are related through e.g. "Liver function test"
There is no way ever to find out using CDISC-CT alone…

Units

- How much cm is 1 inch?
  - Does CDISC-CT know?

Answer:

http://www.xml4pharmaserver.com:8080/CDISCCTService/rest/ucumtransform/[in_i]/to/cm

UCUM Transformation Web Services

```
- <XML4PharmaServerWebServiceResponse ServerDateTime="2017-02-08T16:13:28">
  - <WebServiceRequest>
      http://www.xml4pharmaserver.com:8080/CDISCCTService/rest/ucumtransform/1/from/%5Bin_i%5D/to/cm
    </WebServiceRequest>
  - <Response>
      <SourceQuantity>1.0</SourceQuantity>
      <SourceUnit>[in_i]</SourceUnit>
      <TargetUnit>cm</TargetUnit>
      <ResultQuantity>2.54</ResultQuantity>
    </Response>
  </XML4PharmaServerWebServiceResponse>
```

Units

- How much is 1 "international unit" pro mg "supercompound" pro g pro kg of "chicken" pro hour in: "international unit" pro ounce "supercompound" pro g pro pound of "chicken" per day ?

```
− <XML4PharmaServerWebServiceResponse ServerDateTime="2017-02-08T16:22:02">
  − <WebServiceRequest>
      http://www.xml4pharmaserver.com:8080/CDISCCTService/rest/ucumtransform/1/from/%5BiU%
      %5D%7Bchicken%7D/d)
    </WebServiceRequest>
  − <Response>
      <SourceQuantity>1.0</SourceQuantity>
      <SourceUnit>[iU]/mg{supercompound}/(g/kg{chicken}/h)</SourceUnit>
    − <TargetUnit>
        m[iU]/[oz_av]{supercompound}/(g/[lb_av]{chicken}/d)
      </TargetUnit>
      <ResultQuantity>2604166.7</ResultQuantity>
    </Response>
  </XML4PharmaServerWebServiceResponse>
```

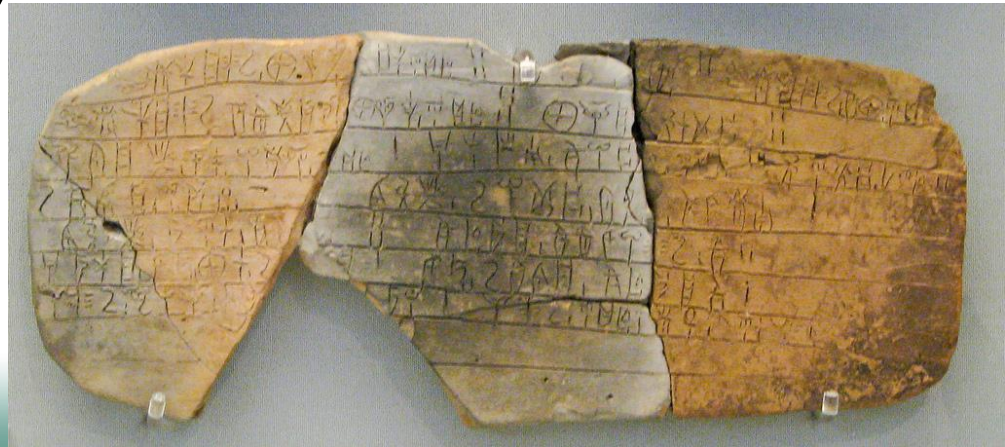
Forget about doing this when using CDISC "units"

CDISC Controlled Terminology

- CT is our "rocket fuel"
- And we can't afford not to get the highest quality fuel
- If there is better fuel than "our own invented one", we need to use that
- Some of our "fuel" is OK, but the most important part isn't

SDTM / SEND / ADaM

- Two dimensional tables
- Breaking almost any rule of "good database design"
- Massive amount of data redundancy
  - 30-40% of the variables could be removed
- Very limited amount of traceability (only through define.xml)
- Pretty bad (outdated) data model



Smart tools can replace data redundancy

DOMAIN	USUBJID	SUBJID	RFSTDTC	RFENDTC
DM	01-701-1015	1015	2014-01-02	2014-07-02
DM	01-701-1023	1023	2012-08-05	2012-09-0a
DM	01-701-1028	1028	2013-07-19	2014-01-14
DM	01-701-1033	1033	2014-03-18	2014-04-14
DM	01-701-1034	1034	2014-07-01	2014-12-30
DM	01-701-			
DM	01-701-			
DM	01-701-			
DM	01-701-1111	1111	2012-09-07	2012-09-17

01-701-1033 (USUBJID)
First date of study treatment exposure = Tue Mar 18 2014
Last date of study treatment exposure = Mon Mar 31 2014

COUNTRY	DMDTC
USA	2013-12-26
USA	2012-07-22
USA	2013-07-11
USA	2014-03-10
USA	
USA	

2013-07-11 (DMDTC)
DMDY = -8

VS

USUBJID	VSSEQ	VSTESTCD	VSPOS	VSO
01-701-1015	7	DIABP	SUPINE	56
01-701-1015	8	DIABP	STANDING	51
01-701-1015	9	DIABP	STANDING	61
01-701-1015	10	DIABP		
01-701-1015	11	DIABP		
01-701-1015	12	DIABP		

DIABP (VSTESTCD)
Diastolic Blood Pressure
NCI: C25299

VISITNUM	VSDTC	VSTPT
6	2014-02-01	AFTER LYIN
6	2014-02-01	AFTER STAN
6	2014-02-01	AFTER STAN
7		AFTER LYIN
7		AFTER STAN
7		AFTER STAN

6 (VISITNUM)
Visit: AMBUL ECG REMOVAL
Planned Study Day of Visit: 30

VISITNUM	LBDTC
9	2014-03-26T15:15
10	2014-05-07T11:21
11	2014-06-21T10:58

2014-05-07T11:21 (LBDTC)
LBDY = 125
Element = PBO (Placebo) - Epoch = Treatment

Reviewers should start using these tools…

Smart Dataset-XML Viewer

SDTM / SEND / ADaM

- Due to data redundancy and 2-D tables
  our submission standards have too much weight …
- Like that, we will never reach the moon …
- CDISC should never have given up first principles
  because of (silly) requests from reviewers who use completely outdated tools
- It is not too late to slim down SDTM/SEND/ADaM
- And we should start thinking about alternatives
  - Some people do, but their work is mostly ignored

Is SDTM ready for the future?

- More and more trials with "wearables" and "insideables"
  - "CRF free"
- Remote clinical trials without any "visits"
  - But SDTM still requires us to submit VISITNUM
- Clinical trials with virtual sites
- Read Doug Bain's and Kai Langel's blogs (ClinPal)

- Shouldn't we rethink a good number of SDTM (outdated) assumptions?

Better / smarter validation tools

- Current process:

External company

Validation Software

- Result:

Better / smarter validation tools

The "Open Rules for CDISC Standards" Initiative

FDA,PMDA,CDISC rules implemented as:

- Transparent rules
- Human-readable and machine-executable
- Use RESTful web services
  - In future also using the SHARE API
- Updates/corrections over a RESTful web service
  - No more "waiting for the next release"
- Anyone can develop his own validation system

"Open Rules for CDISC Standards"

Example - Rule FDAC017

```
(: Rule FDAC017-FDAC018: SDTM Required variable not found - Variables described in SDTM as Required
 must be included in the dataset :)
(: The following Query relies on that the define.xml is complete and
 that Mandatory='Yes' is set for each required variable :)
xquery version "3.0";
declare namespace def = "http://www.cdisc.org/ns/def/v2.0";
declare namespace odm="http://www.cdisc.org/ns/odm/v1.3";
declare namespace data="http://www.cdisc.org/ns/Dataset-XML/v1.0";
declare namespace xlink="http://www.w3.org/1999/xlink";
declare namespace request="http://exist-db.org/xquery/request";
(: "declare variable ... external" allows to pass $base and $define from an external programm :)
(: declare variable $base external; :)
(: declare variable $define external; :)
let $base := '/db/fda_submissions/cdisc01/'
let $define := 'define2-0-0-example-sdtm.xml'
(: iterate over all datasets mentioned in the define.xml :)
for $itemgroup in doc(concat($base,$define))//odm:ItemGroupDef
    (: get all the ItemRef-OIDs which have 'Mandatory="Yes" :)
    let $mandatory := $itemgroup/odm:ItemRef[@Mandatory='Yes']/@ItemOID
    (: get the dataset itself :)
    let $datasetfilename := $itemgroup/def:leaf/@xlink:href
    let $dataset := doc(concat($base,$datasetfilename))
    let $datasetname := $itemgroup/@Name
    (: iterate over all the records :)
    for $record in $dataset//odm:ItemGroupData
        let $recnum := $record/@data:ItemGroupDataSeq
         (: iterate over the 'mandatory' OIDs  :)
         for $m in $mandatory
             (: and give an error when there is no such ItemData/@ItemOID  :)
             let $varname := doc(concat($base,$define))//odm:ItemDef[@OID=$m]/@Name
             where not($record/odm:ItemData[@ItemOID=$m])
             return <error rule="FDAC017" datasetname="{$datasetname}" variable="{data($varname)}"
             rulelastupdate="2015-08-31" recordnumber="{$recnum}">
             No data found for required variable {data($varname)} in record number {data($recnum)}
             in dataset {data($datasetname)}</error>
```

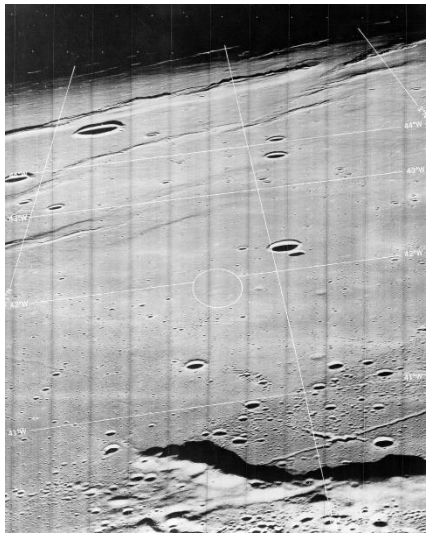
Already implemented in the "Smart Dataset-XML Viewer"

http://xml4pharmaserver.com/RulesXQuery/index.html

The final stage: landing on the moon

- On average, our spacecraft is circling 6 months (the review time) around the moon before landing

- The crew is told they are free to use any tools they brought with them,
  even when they are completely outdated …



How can review be shortened

without any loss of quality - even with quality increase

- Reviewers should not be allowed to use files anymore
- All submissions in a single (set of) database(s)
  - E.g. native XML databases
  - The database is the only allowed source of information
- CDISC volunteers can provide modern tools (e.g. open-source) to regulators that reviewers must at least use

STUDYID	DOMAIN	USUBJID	LBSEQ	LBTESTCD	LI
CDISCPILOT01	LB	01-701-1015	233	BASO	264
CDISCPILOT01	LB	01-701-1015	263	BASO	264
CDISCPILOT01	LB	01-701-1015	298	BASO	264
CDISCPILOT01	LB	01-701-1015	7	BILI	197
CDISCPILOT01	LB	01-701-1015	44	BILI	
CDISCPILOT01	LB	01-701			
CDISCPILOT01	LB	01-701			
CDISCPILOT01	LB	01-701			
CDISCPILOT01	LB	01-701			

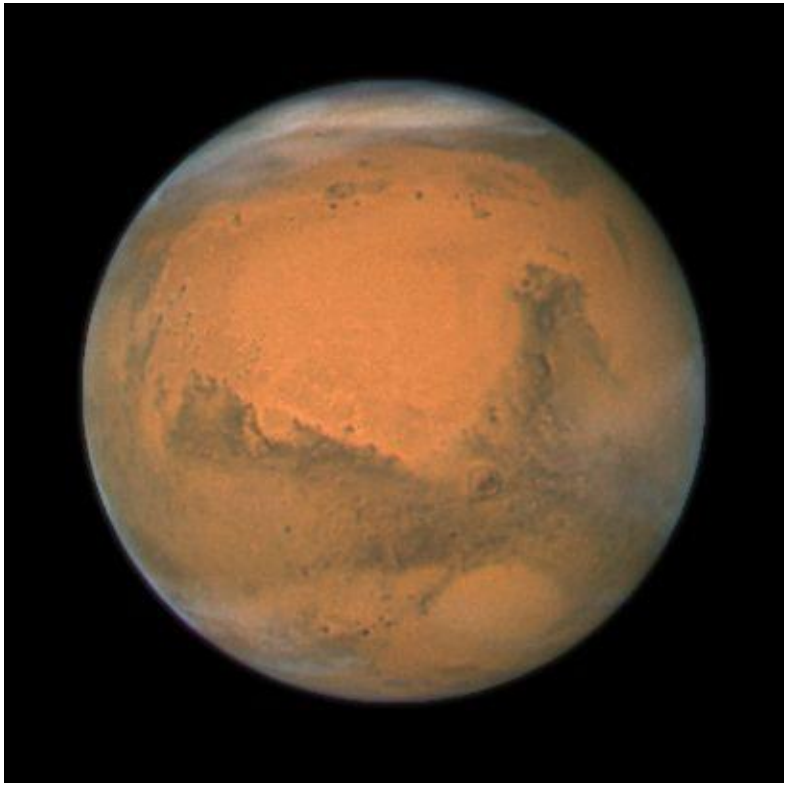
01-701-1015 (USUBJID)
ACTARMCD: Pbo
AGE: 61 years
SEX: Female

LBSEQ	LBTESTCD	LBLOINC	LBCAT	LBORRES	LBORRESU	VISITNUM	LBORNRLO
233	BASO	26444-0	HEMATOLOGY	0.03	THOU/uL	11	0
263	BASO	26444-0	HEMATOLOGY	0.04	THOU/uL	12	0
298	BASO	26444-0	HEMATOLOGY	0.03	THOU/uL	13	0
7	BILI	1975-2	CHEMISTRY	0.6	mg/dL	1	0.2
44	BILI	1975-2	CHEMISTRY	0.5	mg/dL	4	0.2
79	BILI	1975-2					
109	BILI	1975-2					
139	BILI	1975-2					

1975-2 (LBLOINC)
LOINC Common Name: Bilirubin.total [Mass/volume] in Serum or Plasma
Example UCUM Units: mg/dL

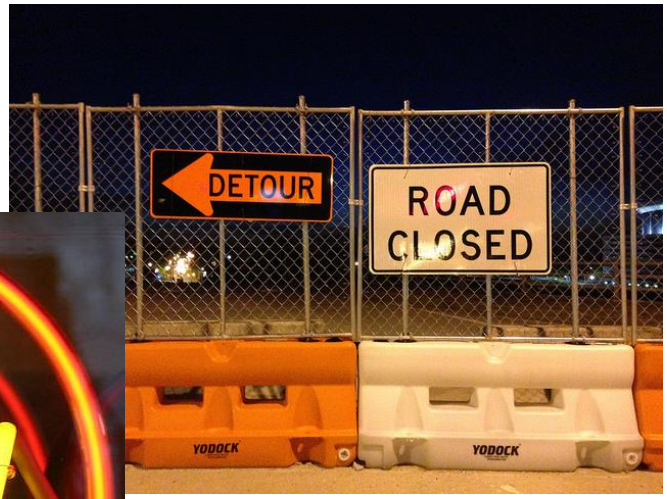
Some are even reaching further …

- Initiatives like:
  - RDF
  - Linked Data
  - SDTM-IG in XML
  - Protocol in XML
  - …
- Mostly not official CDISC activities
  (but shouldn't they?)
- But regulators are still extremely reluctant to even think about these



The Showstoppers … Actions required

- Get rid of SAS-XPT
- Start mandating LOINC and UCUM
- Get rid of "not invented here" syndrome
- Help / convince / force regulatory authorities to use modern technologies



Regulators and the "cancer moonshot"

- FDA is expected to receive US $xx million from the "cancer moonshot" programm
- If they would invest a few % of that in modern technology (computers, non-relational databases, tools) they would make a huge step forward
- And the result could be:

Acknowledgements

- All volunteers that fight
  - FOR getting things done better, simpler, more efficient
  - AGAINST "not invented here", "do it as we always have done" mentality

Photo credit: NASA/Kim Shiflett

Further Acknowledgements

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The next step …?

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