The CDISC vision is to inform patient care & safety through higher quality medical research.
The CDISC Moonshot - Can we do it?

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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 anywhere - 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 FRMIZE - really?

• Refusal to use controlled terminology from the medical world
  ▪ LOINC
  ▪ UCUM
  ▪ ICDx
  ▪ SNOMED
  ▪ …
An example using UMLS RESTful web services

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

Height and Weight are not in this diagram!
"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
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?

```xml
<XML4PharmaServerWebServiceResponse ServerDateTime="2017-02-08T16:22:02">
  <WebServiceRequest>
    http://www.xml4pharmaserver.com:8080/CDISCCTSService/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**

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:
- Result:
Better / smarter validation tools

False positives

But you can always describe the **false positives** in the Reviewer's Guide, isn't it?
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

```xml
<query 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";

  let $base := '/db/fda_submissions/cdisc01/'
  let $define := 'define2-0-0-example-sdtm.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" variable="{data($varname)}" recordnumber="{data($recnum)}">
          No data found for required variable {data($varname)} in record number {data($recnum)}
        </error>
  </query>
```

Already implemented in the "Smart Dataset-XML Viewer"
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.
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" program.

• 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
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The next step …?

Thank you for your attention!
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