

An Iterative Approach to Work Flow Automation & Optimization

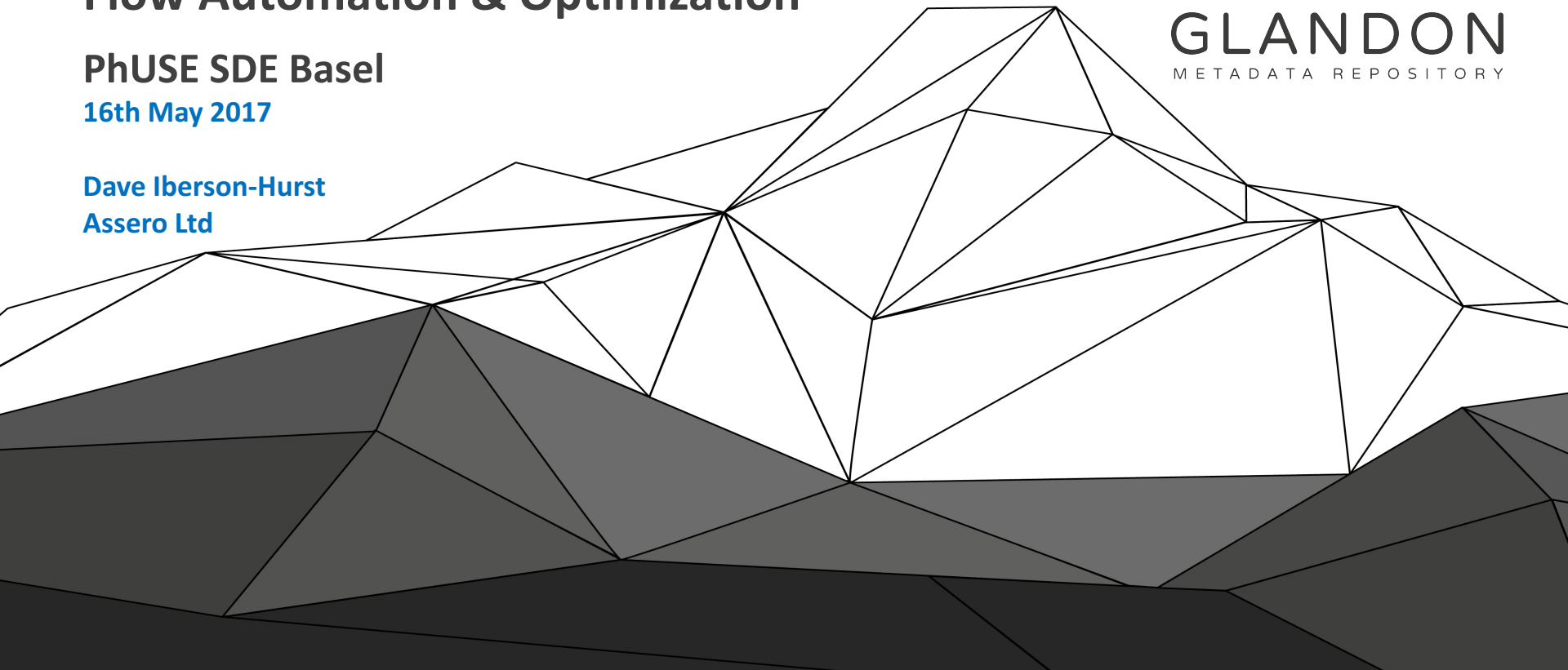
PhUSE SDE Baseline

16th May 2017

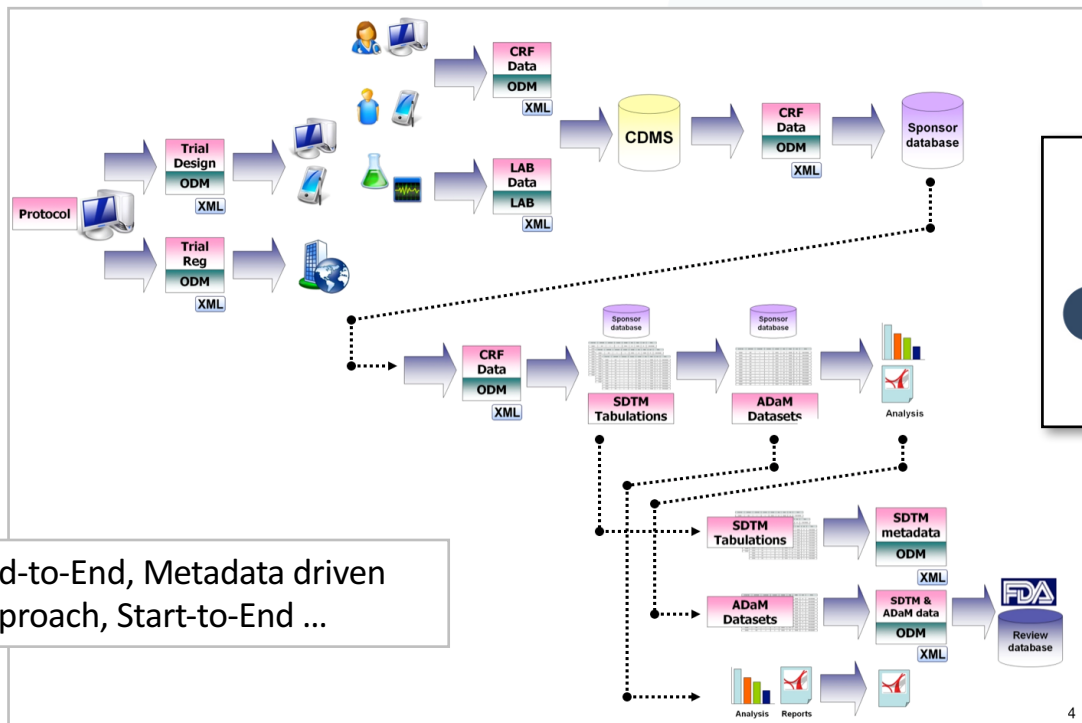
Dave Iberson-Hurst
Assero Ltd



GLANDON
METADATA REPOSITORY



A Very Old Picture



The CDISC Standard

An End-to-End Workshop
23rd and 24th April 2007.
Montreux, Switzerland.

 **CDISC**
Setting the
Global Standard
for Clinical Data

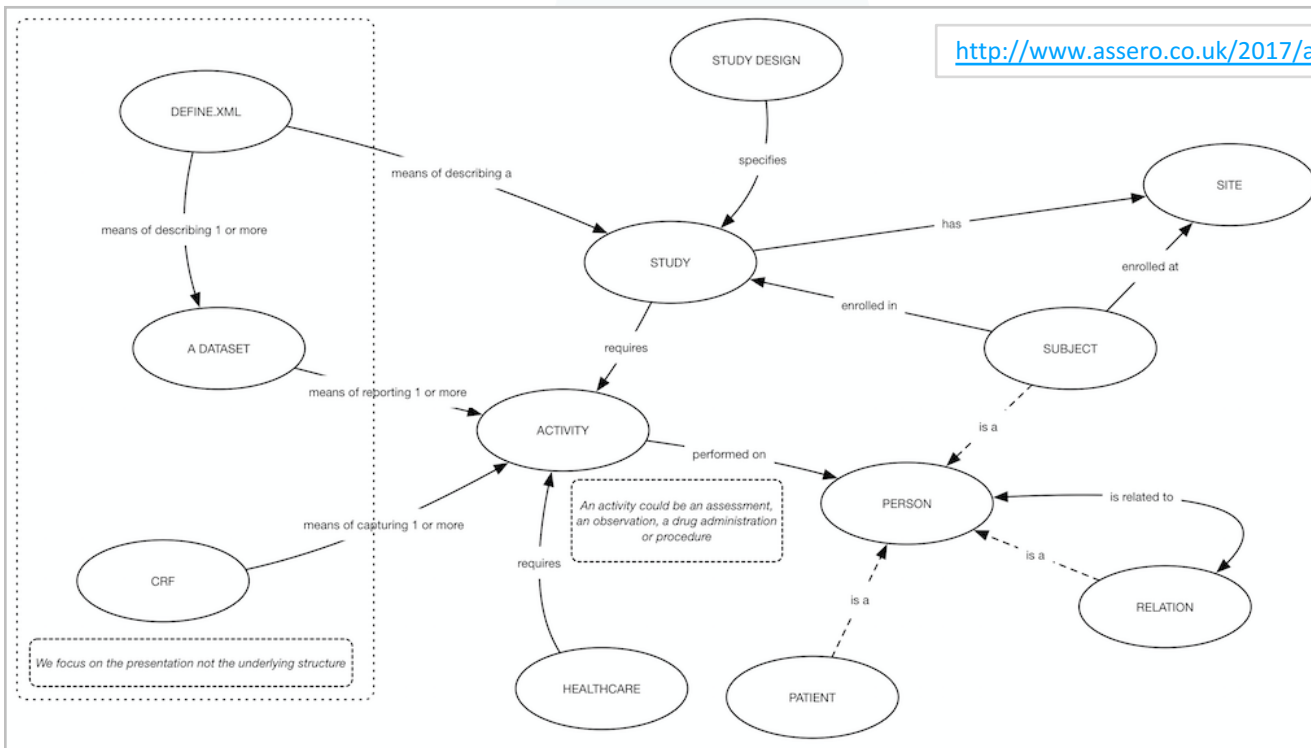
© CDISC, 2007

Left and Right Sides

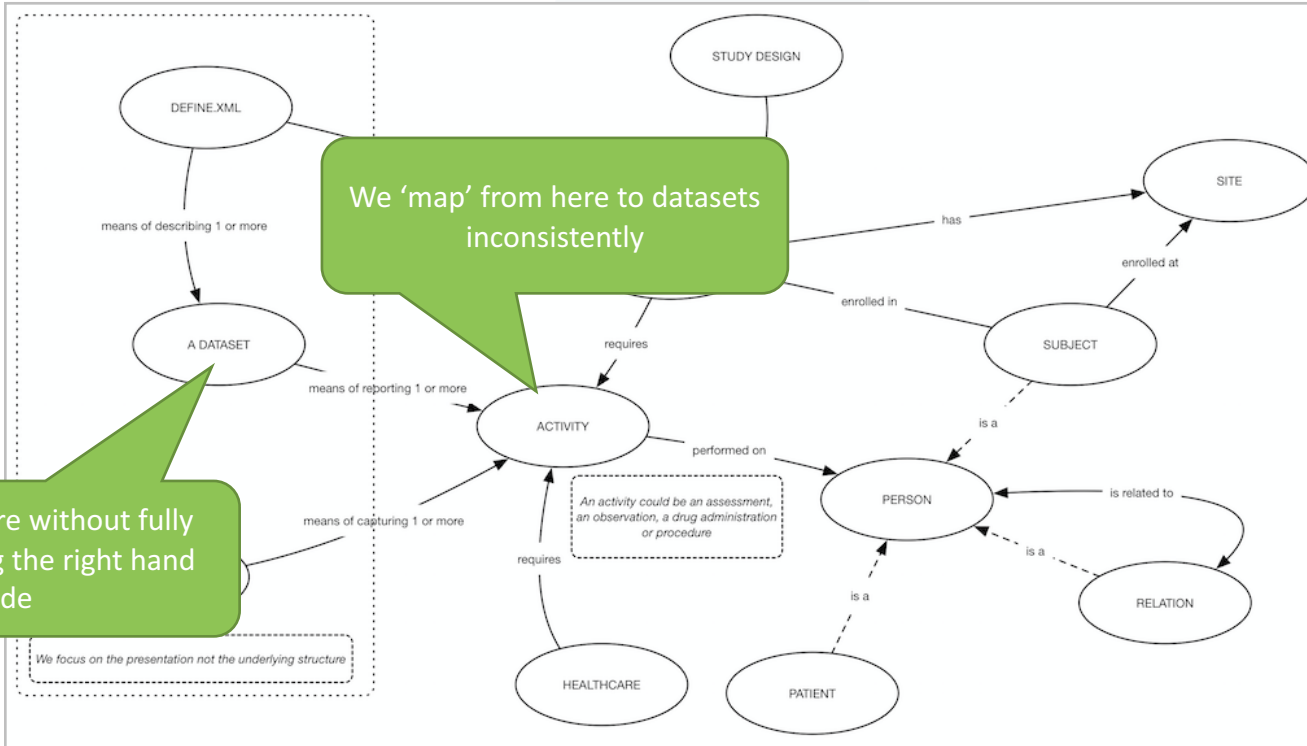


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METADATA REPOSITORY

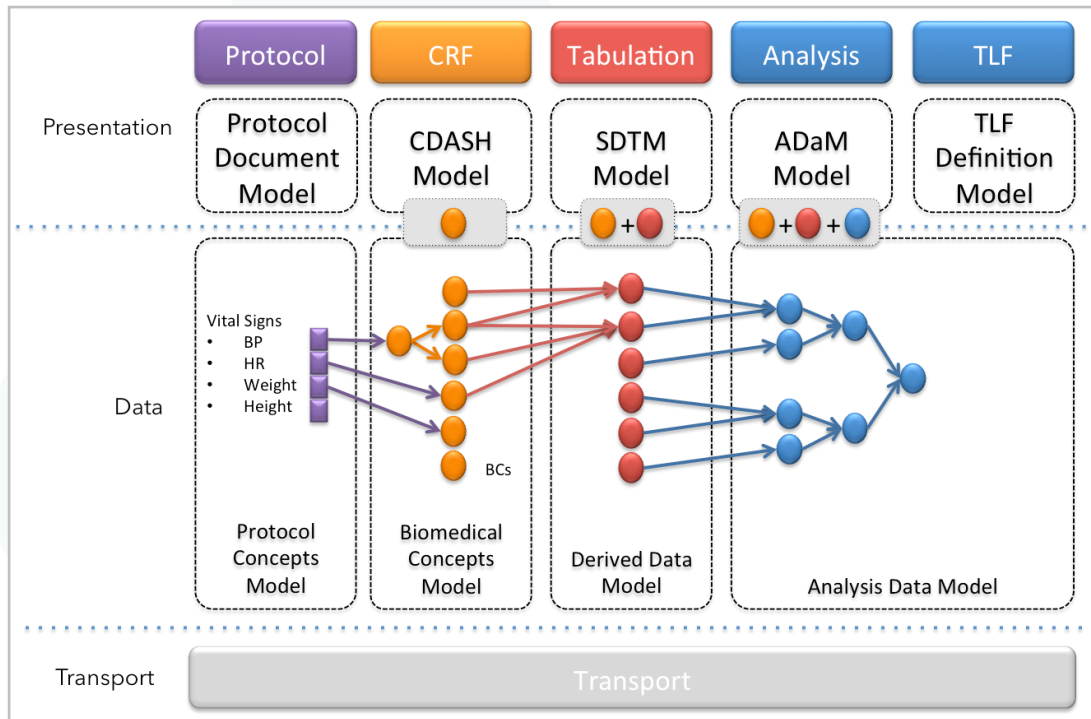
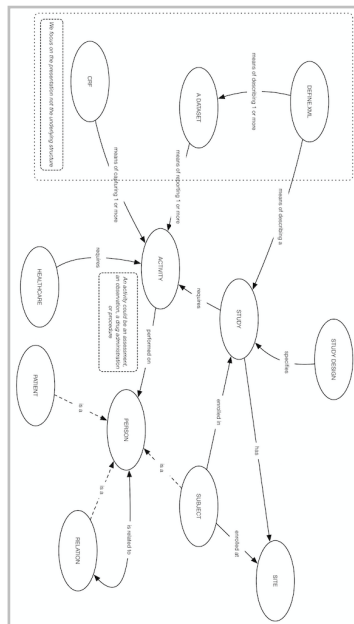
<http://www.assero.co.uk/2017/a-left-side-and-a-right-side/>



Left and Right Sides



Same Picture ... Rotated



FDA @ PhUSE CSS 2016

Define File

- Use Define.xml v2.0
 - Lacking a complete Define file greatly increases the amount of time reviewers spend understanding an application
- Include detailed description of data elements:
 - Detailed, reproducible computational algorithms for derived variables
 - Code lists that describe categories, subcategories, reference time-pts
 - Applicable value level metadata & description of SUPPQUAL domains
 - Explanations of sponsor-defined identifiers (e.g., -SPID, -GRPID)
- Provide separate unit code lists for each domain

Define File

From a presentation by Mary Doi, M.D., M.S. (FDA CDER)

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Items in TCG (continued)

- Use CDISC controlled terminology variables when available (TCG Section 6)
 - **Controlled terminology issues in 62% of applications**
- Include Seriousness Criteria for all serious adverse events (TCG 4.1.1.3)
 - **Missing (or with inconsistencies) in 50% of applications**
 - Important to independently verify that AE was serious
- Include study day variable for all observational datasets (TCG 4.1.4.1)

Items in TCG

10

FDA @ PhUSE CSS 2017

eCTD Technical Validation of Study Data

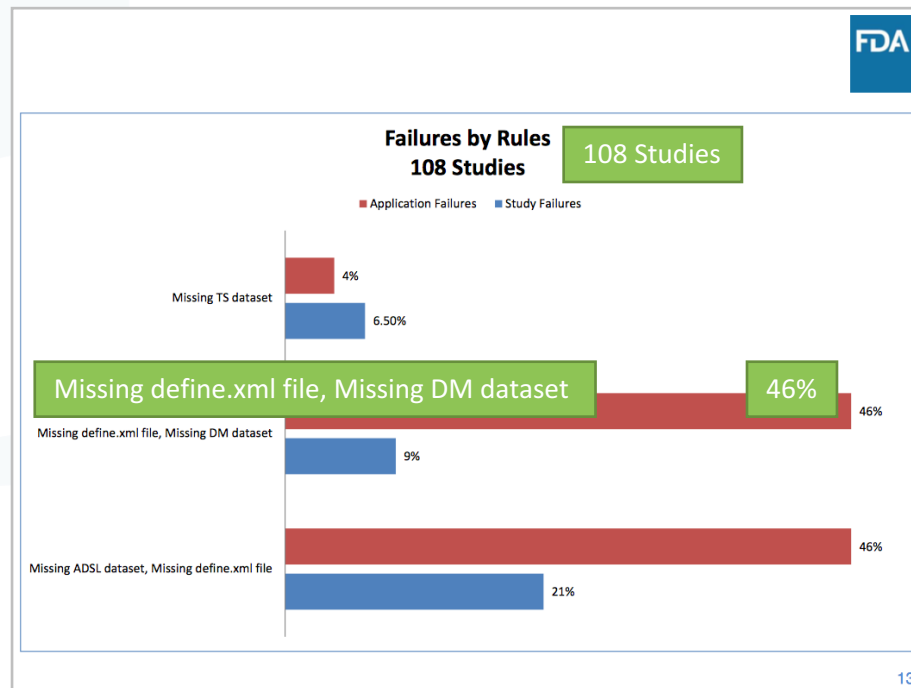
High Level Rule #1	High Level Rule #2
Rule # 1734 : A Trial Summary (TS) dataset must be present for each study in module 4, sections 4.2.3.1, 4.2.3.2, 4.2.3.4 and in module 5, sections 5.3.1.1, 5.3.1.2, 5.3.3.1, 5.3.3.2, 5.3.3.3, 5.3.3.4, 5.3.4, 5.3.5.1, 5.3.5.2	Rule #1736: DM dataset and define.xml must be submitted in module 4, sections 4.2.3.1, 4.2.3.2, 4.2.3.4. DM dataset, ADSL dataset, define.xml must be submitted in module 5, sections 5.3.1.1, 5.3.1.2, 5.3.3.1, 5.3.3.2, 5.3.3.3, 5.3.3.4, 5.3.4, 5.3.5.1, 5.3.5.2

<https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM523539.pdf>

From a presentation by Crystal Allard, Special Assistant to the Director
Office of Computational Science

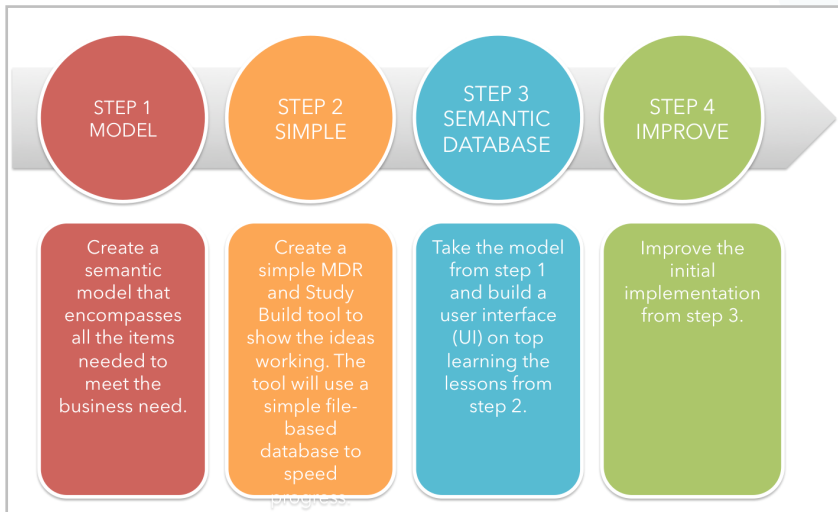
FDA

11

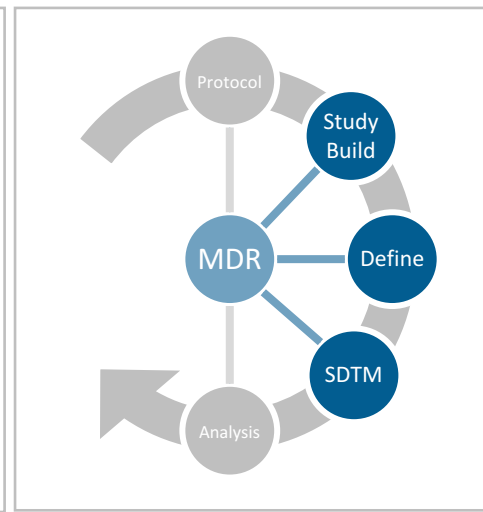


13

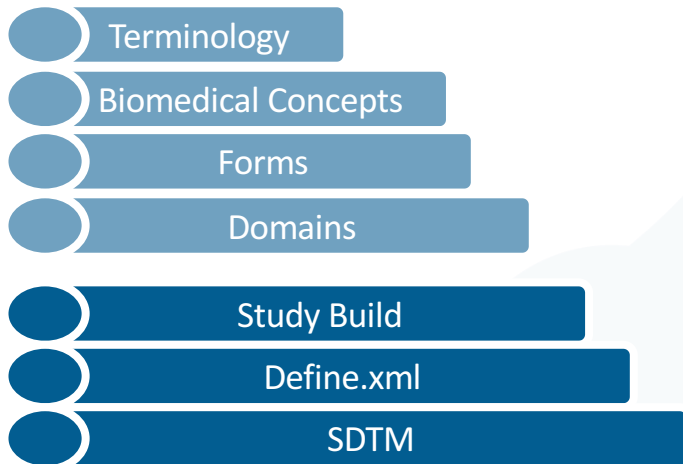
Iterative Approach



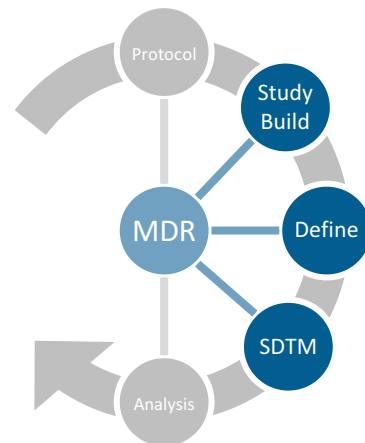
- Drivers
 - Control (new versions, rate-of-change)
 - Precision (which version)
 - Visibility (what changed)
 - Ease-of-use, make it seasier
- Need a solid foundation, a model
- Implement in an MDR
- 'Hide' the new world underneath the user interface
- Present to the user in ways they currently understand
- Utilize graph technologies
- Then build tools to use the solid foundation accessed vi an API
- Iterate, learn, adjust, increase capability



Iterative Approach



- MDR
 - Handle terminologies including CDISC
 - Manage the new Biomedical Concepts
 - Major aim was to investigate BCs and their use
 - Manage Forms
 - Managed SDTM Domains
 - Expand as needed by tools
- Study Build using definitions held by the MDR
- Produce define.xml from the study build information
- Step into SDTM data



Terminology

History: CDISC Terminology

Show entries

Search:

Version	Label	Identifier	Version Label	Owner							Status		C		
35.0.0	CDISC Terminology 2014-03-28	CDISC Terminology	2014-03-28	CDISC	Show	Search					Standard	Status			T Gr- Gr+
36.0.0	CDISC Terminology 2014-06-27	CDISC Terminology	2014-06-27	CDISC	Show	Search					Standard	Status			T Gr- Gr+
37.0.0	CDISC Terminology 2014-09-24	CDISC Terminology	2014-09-24	CDISC	Show	Search					Standard	Status			T Gr- Gr+
38.0.0	CDISC Terminology 2014-10-06	CDISC Terminology	2014-10-06	CDISC	Show	Search					Standard	Status			T Gr- Gr+
39.0.0	CDISC Terminology 2014-12-16	CDISC Terminology	2014-12-16	CDISC	Show	Search					Standard	Status			T Gr- Gr+
40.0.0	CDISC Terminology 2015-03-27	CDISC Terminology	2015-03-27	CDISC	Show	Search					Standard	Status			T Gr- Gr+
41.0.0	CDISC Terminology 2015-06-26	CDISC Terminology	2015-06-26	CDISC	Show	Search					Standard	Status			T Gr- Gr+
42.0.0	CDISC Terminology 2015-09-25	CDISC Terminology	2015-09-25	CDISC	Show	Search					Standard	Status			T Gr- Gr+
43.0.0	CDISC Terminology 2015-12-18	CDISC Terminology	2015-12-18	CDISC	Show	Search					Standard	Status	✓		T Gr- Gr+
44.0.0	CDISC Terminology 2016-03-25	CDISC Terminology	2016-03-25	CDISC	Show	Search					Standard	Status			T Gr- Gr+
45.0.0	CDISC Terminology 2016-06-24	CDISC Terminology	2016-06-24	CDISC	Show	Search					Standard	Status			T Gr- Gr+
46.0.0	CDISC Terminology 2016-09-30	CDISC Terminology	2016-09-30	CDISC	Show	Search					Standard	Status			T Gr- Gr+
47.0.0	CDISC Terminology 2016-12-13	CDISC Terminology	2016-12-13	CDISC	Show	Search					Standard	Status			T Gr- Gr+
48.0.0	CDISC Terminology 2017-03-31	CDISC Terminology	2017-03-31	CDISC	Show	Search					Standard	Status			T Gr- Gr+

Showing 1 to 14 of 14 entries

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[Import](#)
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Terminology Changes

Changes: CDISC Terminology CDISC Terminology

Show 10 entries

Search:

Identifier	Label	Submission Value	2015-06-26	2015-09-25	2015-12-18	2016-03-25	2016-06-24	2016-09-30	2016-12-13	2017-03-31	
C100129	CDISC Questionnaire Category Terminology	QSCAT									Changes
C100130	CDISC SDTM Relationship to Subject Terminology	RELSUB	-	-	-	-		-			Changes
C100131	CDISC Questionnaire ADAS-Cog CDISC Version Test Name Terminology	ADCTN	-	-			-	-	-	-	Changes
C100132	CDISC Questionnaire ADAS-Cog CDISC Version Test Code Terminology	ADCTC	-	-			-	-	-	-	Changes
C100133	CDISC Questionnaire BPRS-A Test Name Terminology	BPR01TN	-	-			-	-	-	-	Changes
C100134	CDISC Questionnaire BPRS-A Test Code Terminology	BPR01TC	-	-			-	-	-	-	Changes
C100135	CDISC Questionnaire EQ-5D-3L Test Name Terminology	EQ5D01TN	-	-			-	-	-	-	Changes
C100136	CDISC Questionnaire EQ-5D-3L Test Code Terminology	EQ5D01TC	-	-			-	-		-	Changes
C100137	CDISC Clinical Classification HAMD 17 Test Name Terminology	HAMD1TN	-	-				-	-	-	Changes
C100138	CDISC Clinical Classification HAMD 17 Test Code Terminology	HAMD1TC	-	-				-	-	-	Changes

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Code List Changes I

Changes: CDISC Questionnaire Category Terminology C100129

Code List Changes

Show 15 entries

Search:

Version	Date	Identifier	Submission Value	Preferred Term	Synonym	Extensible	Definition
35	2014-03-28	C100129	QSCAT	CDISC Questionnaire Category Terminology	Questionnaire Category	✓	A grouping of observations within the Questionnaire domain.
36	2014-06-27	↓	↓	↓	Questionnaire Category Category of Questionnaire	↓	↓
37	2014-09-24	↓	↓	↓	↓	↓	↓
38	2014-10-06	↓	↓	↓	↓	↓	↓
39	2014-12-16	↓	↓	↓	↓	↓	↓
40	2015-03-27	↓	↓	↓	↓	↓	↓
41	2015-06-26	↓	↓	↓	↓	↓	↓
42	2015-09-25	↓	↓	↓	↓	↓	↓
43	2015-12-18	↓	↓	↓	↓	↓	↓
44	2016-03-25	↓	↓	↓	↓	↓	↓
45	2016-06-24	↓	↓	↓	↓	↓	↓
46	2016-09-30	↓	↓	↓	↓	↓	↓
47	2016-12-13	↓	↓	↓	↓	↓	↓
48	2017-03-31	↓	↓	↓	↓	↓	↓

Showing 1 to 14 of 14 entries

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Code List Changes II

Code List Item Changes

Show 15 entries Search:

Identifier	Label	Submission Value	2015-06-26	2015-09-25	2015-12-18	2016-03-25	2016-06-24	2016-09-30	2016-12-13	2017-03-31	
C100759	Brief Pain Inventory Questionnaire	BPI	-	-	-	-	-	-	-	-	Changes
C100760	Brief Pain Inventory Short Form Questionnaire	BPI SHORT FORM	-	-	-	-	-	-	-	-	Changes
C100761	Brief Psychiatric Rating Scale A Questionnaire	BPRS-A	-	-	-	-	-	-	-	-	Changes
C100762	Alzheimer's Disease Assessment Scale-Cognitive CDISC Version Questionnaire	ADAS-COG	-	-	-	-	-	-	-	-	Changes
C100763	Clinical Global Impression Questionnaire	CGI	-	-	-	-	-	-	-	-	Changes
C100764	Current Opioid Misuse Measure Questionnaire	COMM	-	-	-	-	-	-	-	-	Changes
C100765	Columbia-Suicide Severity Rating Scale Baseline Questionnaire	C-SSRS BASELINE	-	📄	-	-	-	-	-	-	Changes
C100766	Faces Pain Scale Revised Questionnaire	FPSR	-	-	-	-	-	-	-	-	Changes
C100767	Hamilton Depression Rating Scale 17 Item Questionnaire	HAMD 17	-	-	-	-	✖				Changes
C100768	Karnofsky Performance Status Scale Questionnaire	KPS SCALE	-	-	-	-	-	-	-	-	Changes
C100769	Movement Disorder Society Unified Parkinson's Disease Rating Scale Questionnaire	MDS-UPDRS	-	-	-	-	-	-	-	-	Changes
C100771	Michigan Neuropathy Screening Instrument Questionnaire	MNSI	-	-	-	-	-	-	-	-	Changes
C100772	Neuropsychiatric Inventory Questionnaire	NPI	-	-	-	-	-	-	-	-	Changes
C100773	Parkinson's Disease Quality of Life Scale Questionnaire	PDQUALIF	-	-	-	-	-	-	-	-	Changes
C100774	Roland Morris Disability Questionnaire	RDQ	-	-	-	-	-	-	-	-	Changes

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[→](#)
[Close](#)

Code List Item Changes

Changes: Columbia-Suicide Severity Rating Scale Baseline Questionnaire C100765

Code List Item Full History

Show 15 entries Search:

Version	Date	Identifier	Submission Value	Preferred Term	Synonym	Definition
35	2014-03-28	C100765	C-SSRS BASELINE	Columbia-Suicidality Severity Rating Scale Baseline Questionnaire	CSS01	Columbia-Suicidality Severity Rating Scale (C-SSRS) Baseline Version 2009-01-14 (Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.; copyright 2008 The Research Foundation for Mental Hygiene, Inc.).
36	2014-06-27	↓	↓	↓	↓	↓
37	2014-09-24	↓	↓	↓	↓	↓
38	2014-10-06	↓	↓	↓	↓	↓
39	2014-12-16	↓	↓	↓	↓	↓
40	2015-03-27	↓	↓	↓	↓	↓
41	2015-06-26	↓	↓	↓	↓	↓
42	2015-09-25	↓	↓	Columbia-Suicidality Severity Rating Scale Baseline Questionnaire	↓	Columbia-Suicidality Severity Rating Scale (C-SSRS) Baseline Version 2009-01-14 (Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.; copyright 2008 The Research Foundation for Mental Hygiene, Inc.). Columbia-Suicide Severity Rating Scale (C-SSRS) Baseline Version 2009-01-14 (Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.; copyright 2008 The Research Foundation for Mental Hygiene, Inc.).
43	2015-12-18	↓	↓	↓	↓	↓
44	2016-03-25	↓	↓	↓	↓	↓
45	2016-06-24	↓	↓	↓	↓	↓
46	2016-09-30	↓	↓	↓	↓	↓
47	2016-12-13	↓	↓	↓	↓	↓
48	2017-03-31	↓	↓	↓	↓	↓

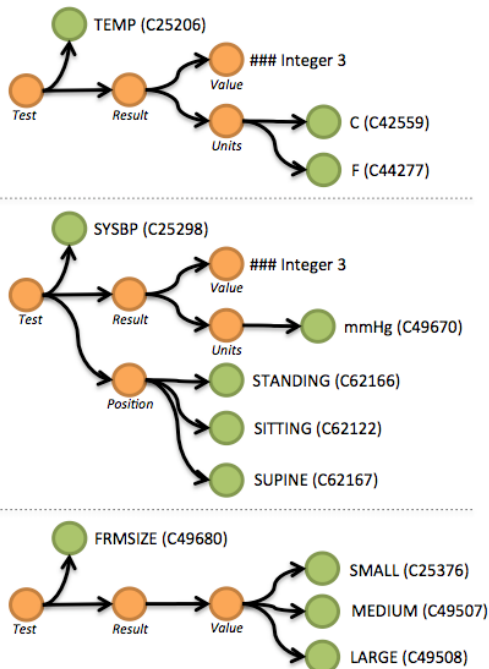
Showing 1 to 14 of 14 entries

Previous 1 Next

Close

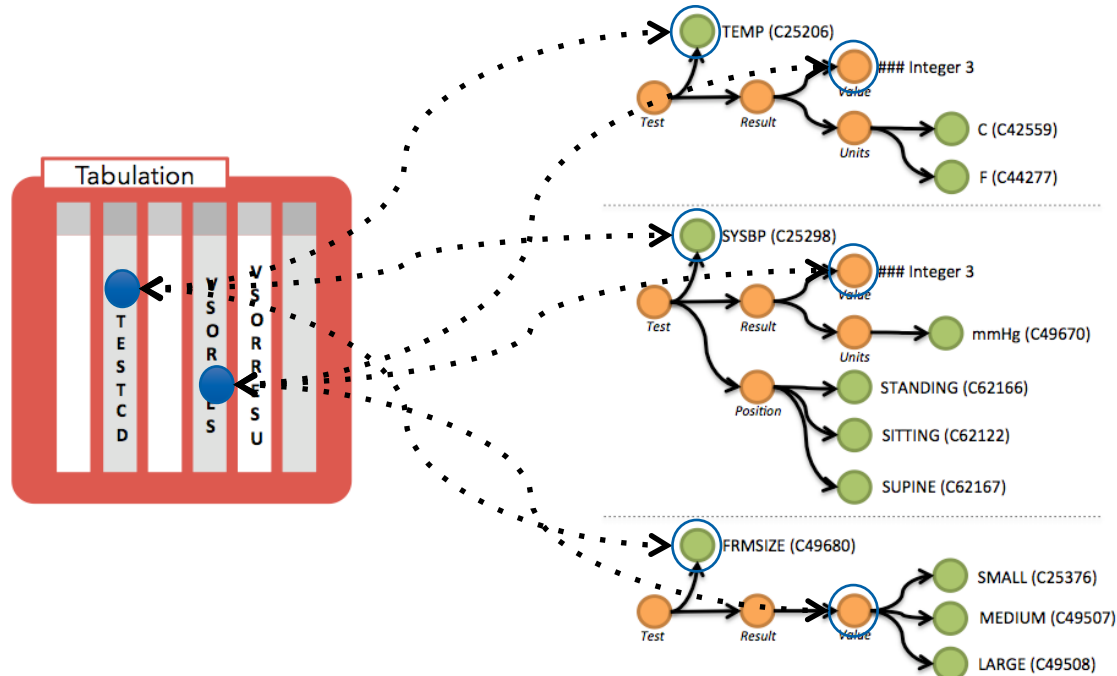
Biomedical Concepts

- Better structure and relationships, not just individual variables 'floating'. A collection of variables with logical structure.
- Consistent structure
- Note the definition of value level metadata
- CDISC have just released an updated SHARE model for review/comment containing BCs
- BCs derived from concept maps as seen in TA User Guides
- Can exist independent of SDTM & CDASH



Biomedical Concepts

Note: Only a couple of relationships shown so as to convey the principle

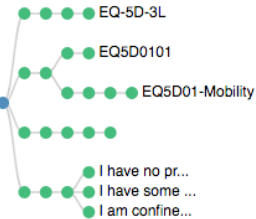


Biomedical Concepts

Edit: EQ-5D-3L Mobility BC C100392 (V1.1.0, 2, Incomplete)

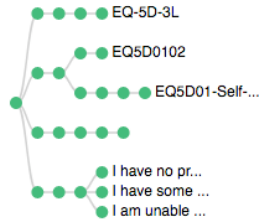
All Biomedical Concepts

[1] EQ-5D-3L Mobility



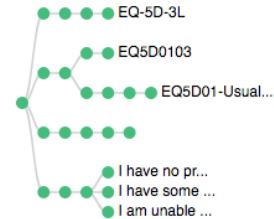
Close

[2] EQ-5D-3L Self-Care



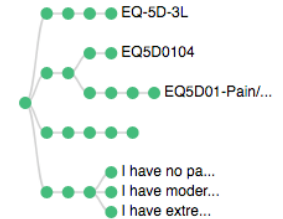
Close

[3] EQ-5D-3L Usual Activities



Close

[4] EQ-5D-3L Pain/Discomfort



Close

4

Save

Close

<

>

Biomedical Concepts

Current Biomedical Concept

Show 15 entries

Search:

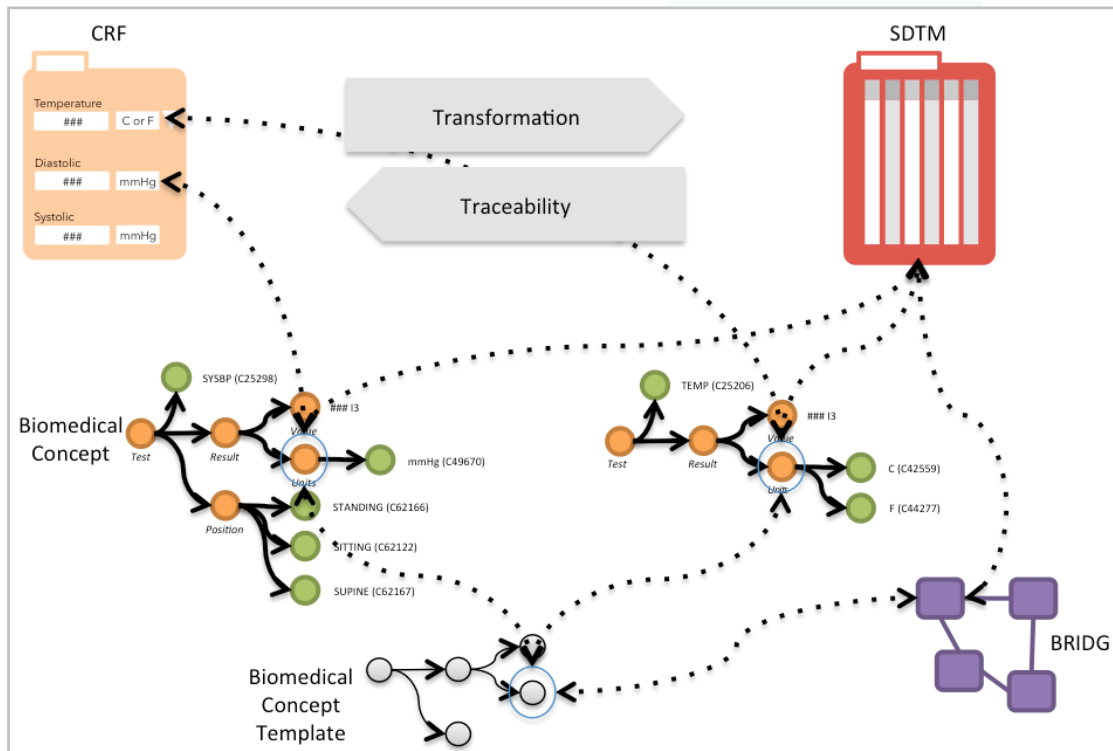
Alias	Question Text	Prompt Text	Enabled	Collect	Datatype	Format	Terminology
Baseline (--BLFL)			✗	✗	boolean		
Body Position (--POS)			✗	✗	string [coded]		
Category (--CAT)			✓	✗	string [coded]		EQ-5D-3L [C66957] T
Date Time (--DTC)	Date & Time		✓	✓	dateTime		
Laterality (--LAT)			✗	✗	string [coded]		
Method (--METHOD)			✗	✗	string [coded]		
Reason Not Done (--REASND)			✗	✗	string [coded]		
Result Value (--ORRES)	Mobility		✓	✓	string [coded]		I have no problems in walking about [EQ5D3L.MOBILITY.NONE] I have some problems in walking about [EQ5D3L.MOBILITY.SOME] I am confined to bed [EQ5D3L.MOBILITY.CONFINED] T
Site Of Administration (--LOC)			✗	✗	string [coded]		
Subcategory (--SCAT)			✗	✗	string [coded]		
Test Code (--TESTCD)			✓	✗	string [coded]		EQ5D0101 [C100392] T
Test Name (--TEST)			✓	✗	string [coded]		EQ5D01-Mobility [C100392] T

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- Biomedical Concept shown as a 'flattened structure' with alias names to relate it to the current world
- Note that terminology is bound in and defined as part of BC.

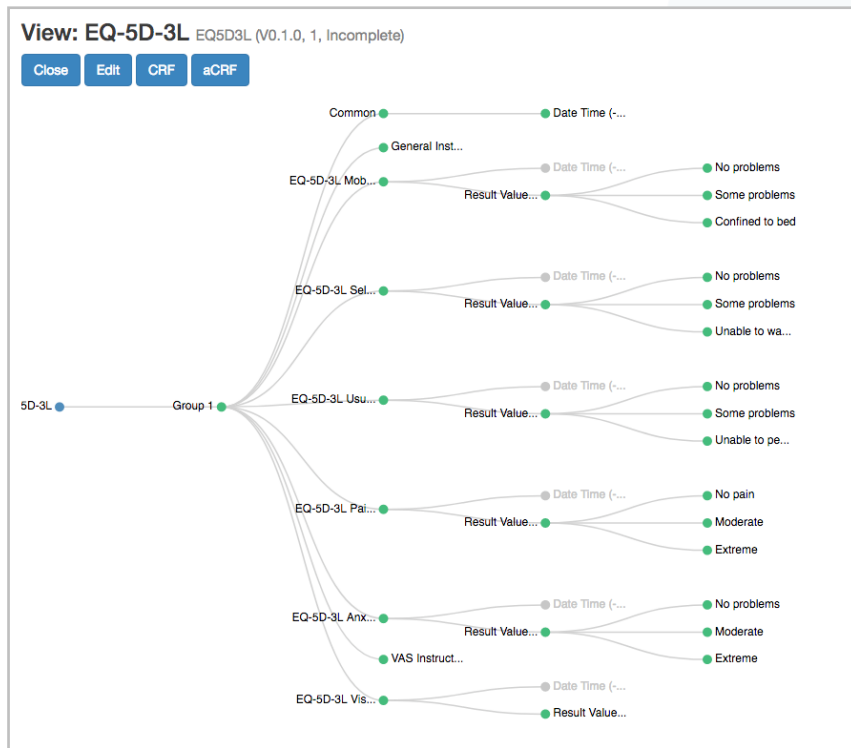
Using Biomedical Concepts



Notes:

1. A template is used to build BCs. There will be many templates.
2. The template is based on the BRIDG model.
3. BRIDG provides an invisible reference framework.
4. The dotted links provide machine capable automated processing and traceability.
5. Biomedical Concepts need only be associated with the target domain, the machine can link the individual pieces itself

Forms

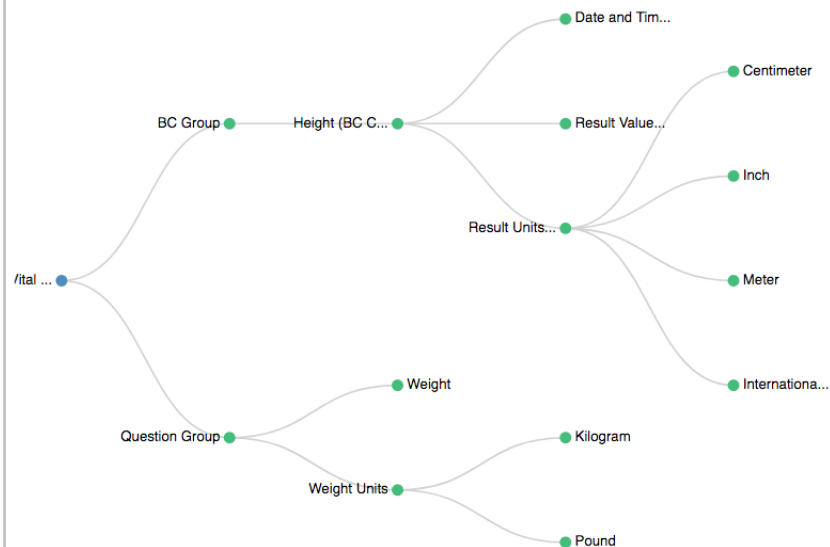


1. Use the Biomedical Concepts to build forms
2. Example here is EQ-5D-3L using 6 concepts that each use a mix of CDISC and sponsor terminology
3. Makes it easy to build forms
4. When a Biomedical Concept is used on two or more forms then definitions will be consistent across those forms, including use of terminology
5. Results in less variation

Iterative Forms

View: Mixed Vital Signs MIXED VS (V0.1.0, 1, Incomplete)

Close Edit CRF aCRF



1. Ability to mix Biomedical Concepts and 'traditional' individual questions and mappings
2. This is essential to allow for iterative development of Biomedical Concepts.
3. Need to be able to mix the old and the new
4. Not all Biomedical Concepts will be available immediately so we will require flexibility

Annotated CRF

Annotated CRF: Mixed Vital Signs MIXED VS (V0.1.0, 1, Incomplete)

Mixed Vital Signs		VS=Vital Signs
BC Group		
Height (BC C25347)		
Question text	VSDTC where VSTESTCD=HEIGHT	D D / M M / Y Y Y Y H H M M
Result value?	VSORRES where VSTESTCD=HEIGHT	# # # #
Result units?	VSORRESU where VSTESTCD=HEIGHT	☐ Centimeter ☐ Inch ☐ Meter ☐ International Foot
Question Group		
Weight?	VSORRES	# # # #
Units	VSORRESU	☐ Kilogram ☐ Pound
Report Close		

1. Having the definitions allows for annotation of CRFs
2. Use of Biomedical Concepts allows for auto-annotation using the links shown in previous slides
3. Use of 'traditional' questions allows for the mapping information to be exposed

SDTM

Show: Demographics SDTM IG DM (V3.2.0, 3, Standard)

Details

Identifier	Label	Owner	Version	Version Label
SDTM IG DM	Demographics	CDISC	3.2.0	3.2

Variables

Show entries

Search:

Ordinal	Name	Label	Datatype	CT or Format	Role	Sub Role	Notes	Core
16	BRTHDTC	Date/Time of Birth	Char	ISO 8601	Qualifier	Record Qualifier	Date/time of birth of the subject.	Permissible
17	AGE	Age	Num		Qualifier	Record Qualifier	Age expressed in AGEU. May be derived from RFSTDTC and BRTHDTC, but BRTHDTC may not be available in all cases (due to subject privacy concerns).	Expected
18	AGEU	Age Units	Char	AGEU	Qualifier	Record Qualifier	Units associated with AGE.	Expected
19	SEX	Sex	Char	SEX	Qualifier	Record Qualifier	Sex of the subject.	Required
20	RACE	Race	Char	RACE	Qualifier	Record Qualifier	Race of the subject. Sponsors should refer to "Collection of Race and Ethnicity Data in Clinical Trials" (FDA, September 2005) for guidance regarding the collection of race (http://www.fda.gov/RegulatoryInformation/Guidances/ucm126340.htm) See Assumption below regarding RACE.	Expected

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[Clone](#) [Export JSON](#) [Export Turtle](#)

1. SDTM Definitions held by the MDR
 1. SDTM Model
 2. SDTM IG
 3. SDTM IG Domains
2. Allows for sponsor domains to be created based on IG domains

Impact Analysis

Impact Analysis: EQ-5D-3L - Mobility

Items Impacted

Show 15 entries

Search:

Identifier	Label	Version	Version Label	
BC C100392	EQ-5D-3L Mobility	1.0.0		Show
CDISC Terminology	CDISC Terminology 2015-12-18	43.0.0	2015-12-18	Show
EQ5D3L	EQ-5D-3L	0.1.0		Show
MIXED	Mixed Form	0.1.0		Show
QS Domain	Questionnaires	0.1.0		Show

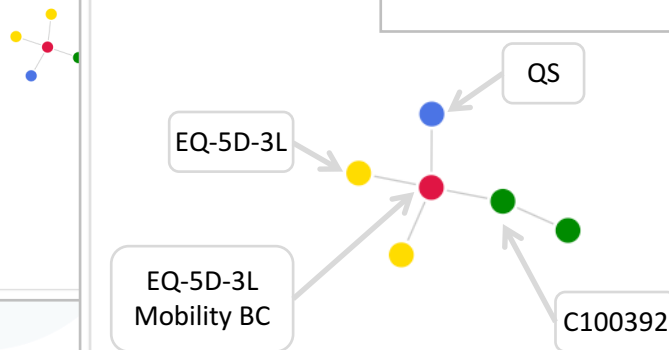
Showing 1 to 5 of 5 entries

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Close

Impact Graph

Impact Graph



1. All of the definitions, and the linked nature of the definitions, allows impact analysis to be performed.
2. Simple example of terminology change. If C100392 (EQ-5D-3L TESTCD) changes what is impacted.
3. The items are
 1. The Biomedical Concept
 2. Two forms that use the concept
 3. The QS Domain where the captured data will go



Iteration: Study Builds

[Study Information](#)
[Schedule of Assessments](#)
[Study Detail](#)
[Case Report Form](#)
[Annotated CRF](#)

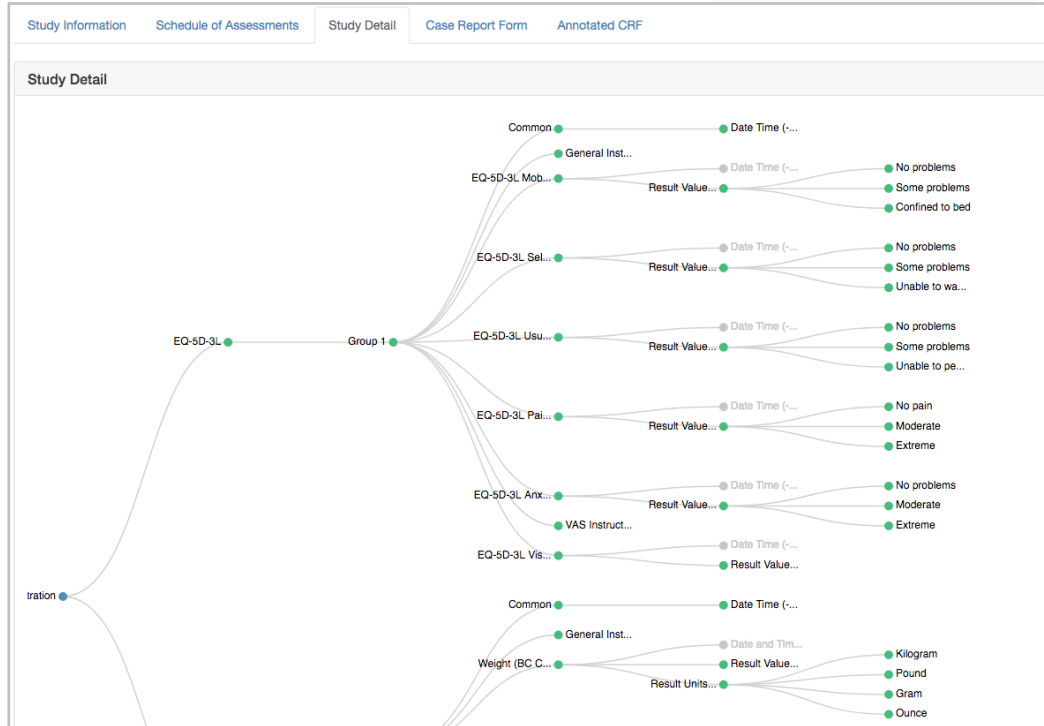
Schedule of Assessments

SoA	V1	V2	V3
EQ-5D-3L	✓		
Mixed Form	✓	✓	✓

V+ V- ← → F- ↑ ↓ 🔍 🔄

1. With solid foundation of definitions we are now in a position to undertake the functions required by the business
2. Build studies, using the form definitions held within the MDR (accessed via the MDR API)
3. Build the Schedule of Assessments

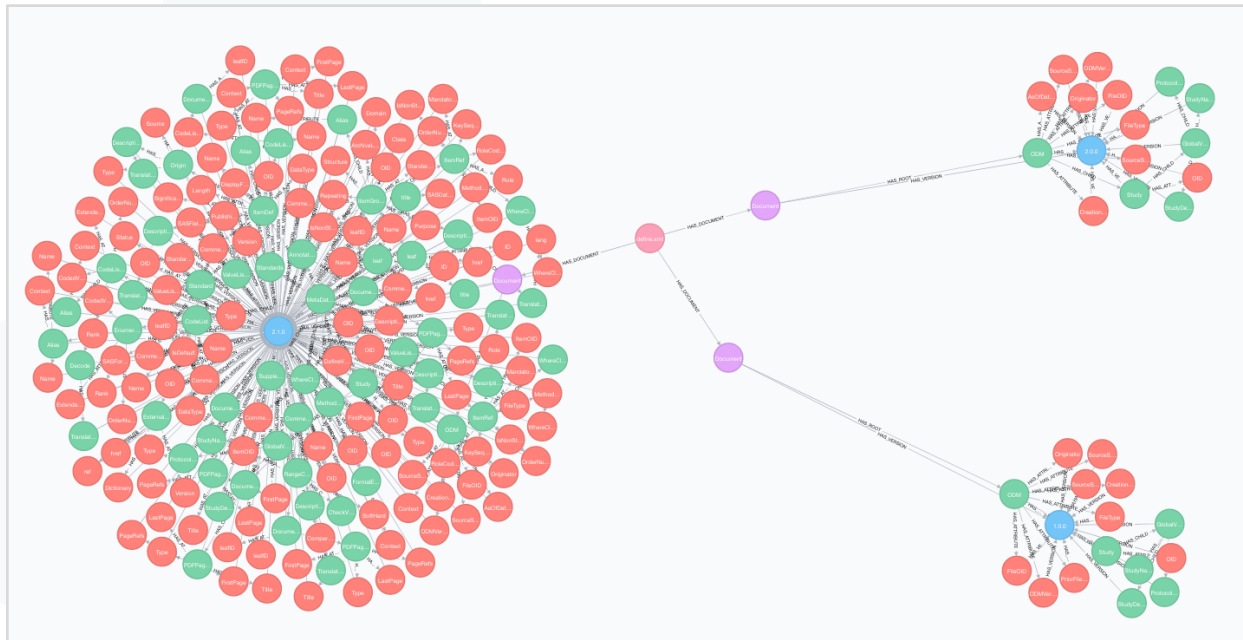
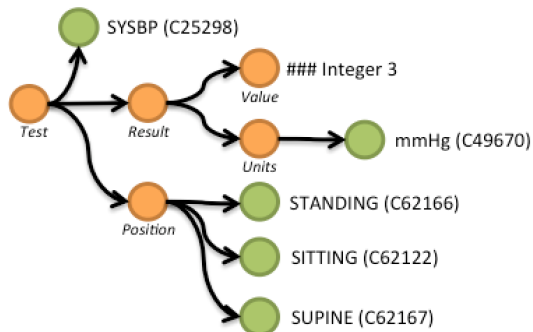
Iteration: Study Builds



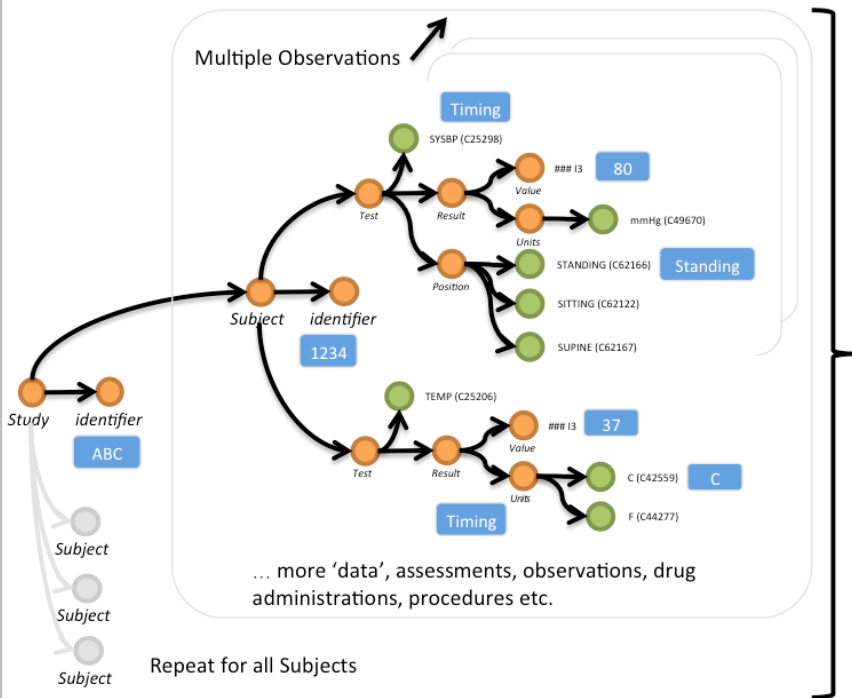
1. The tool can then turn that automatically into the detail
2. Can export it to EDC systems (ALS, ODM, JSON)
3. Allows for study-specific changes
4. Produce the aCRF automatically
5. The study build contains all the version information (forms, terminology etc)

Iteration: Define.xml

1. With a study build that contains a lot of detail we can move towards a full automation of the define.xml
2. We also are able to support manual creation of define.xml. By having all the definitions that the MDR holds the tooling can help build definitions (e.g. VLM from Biomedical Concepts).
3. This is the current work focus



Iteration: SDTM Data



Query to
present as
SDTM



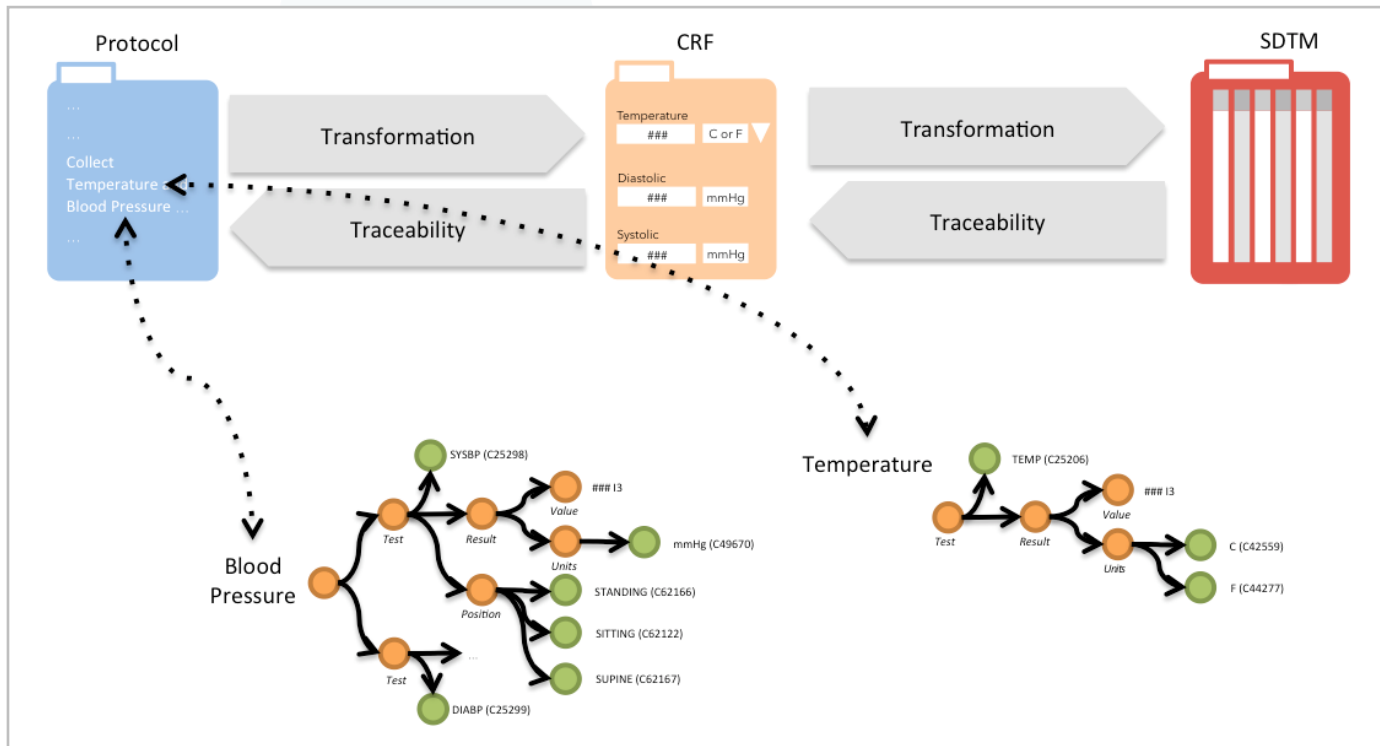
1. The next step is to start generating domains automatically from data
2. Having a machine representation of the metadata (the study definition) allows for the data to be 'attached'
3. Then significant parts of a domain can be created via a query. SDTM is a view of the data
4. The data can be used for other purposes
5. Learn and iterate to allow for the other variables to be created automatically
6. **This is the subject of a FDA/PhUSE CSS Project**
7. Also, if several studies stored in the same way, bigger pools of data can be created with much less effort

ABC	VS	ABC-1234	SYSBP	Standing	80	mmHg	...	Timing
ABC	VS	ABC-1234	TEMP		37	C	...	Timing

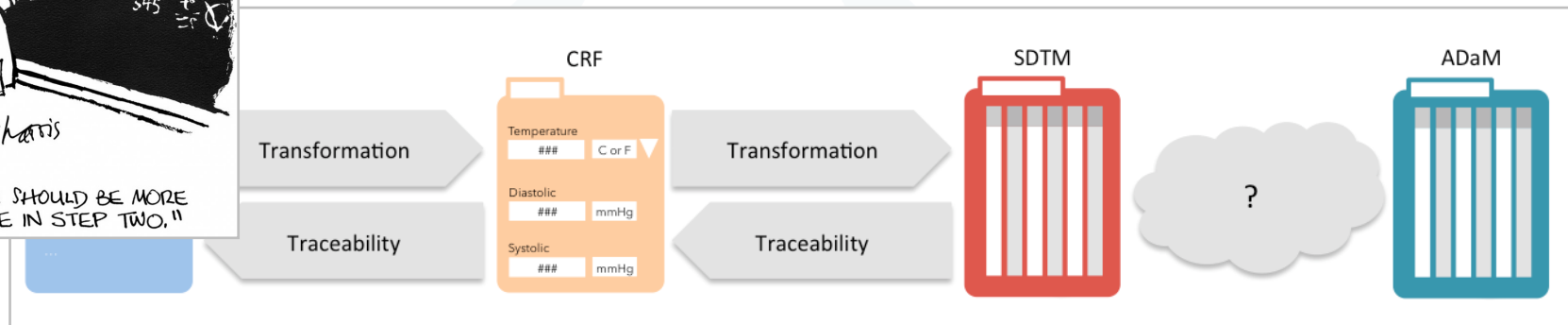
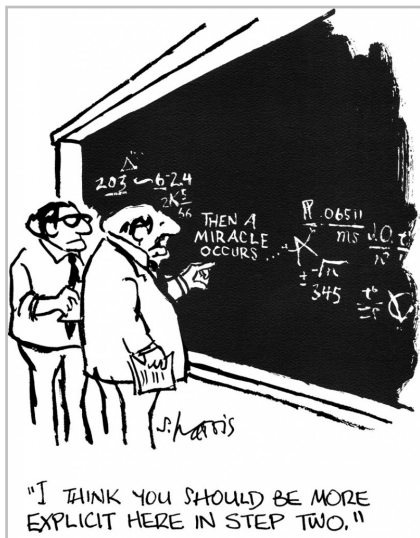
Standard Results & Units, Status,
Baseline & Derived

Iteration: Protocol

1. Link the names of the concepts back into the protocol document.
2. From a quick initial examination this looks possible with the TransCelerate protocol tool



Iteration: Analysis



Summary

- Good progress in moving towards an end-to-end vision
- Graph technologies allows for an iterative approach, easier to amend existing work and add new content
- Solid foundation of high-quality definitions consistent across the life-cycle present opportunities for automation and breaking down the silos.

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