



Managing complexity towards submission

Phuse US Connect 2019-02-27

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Outline

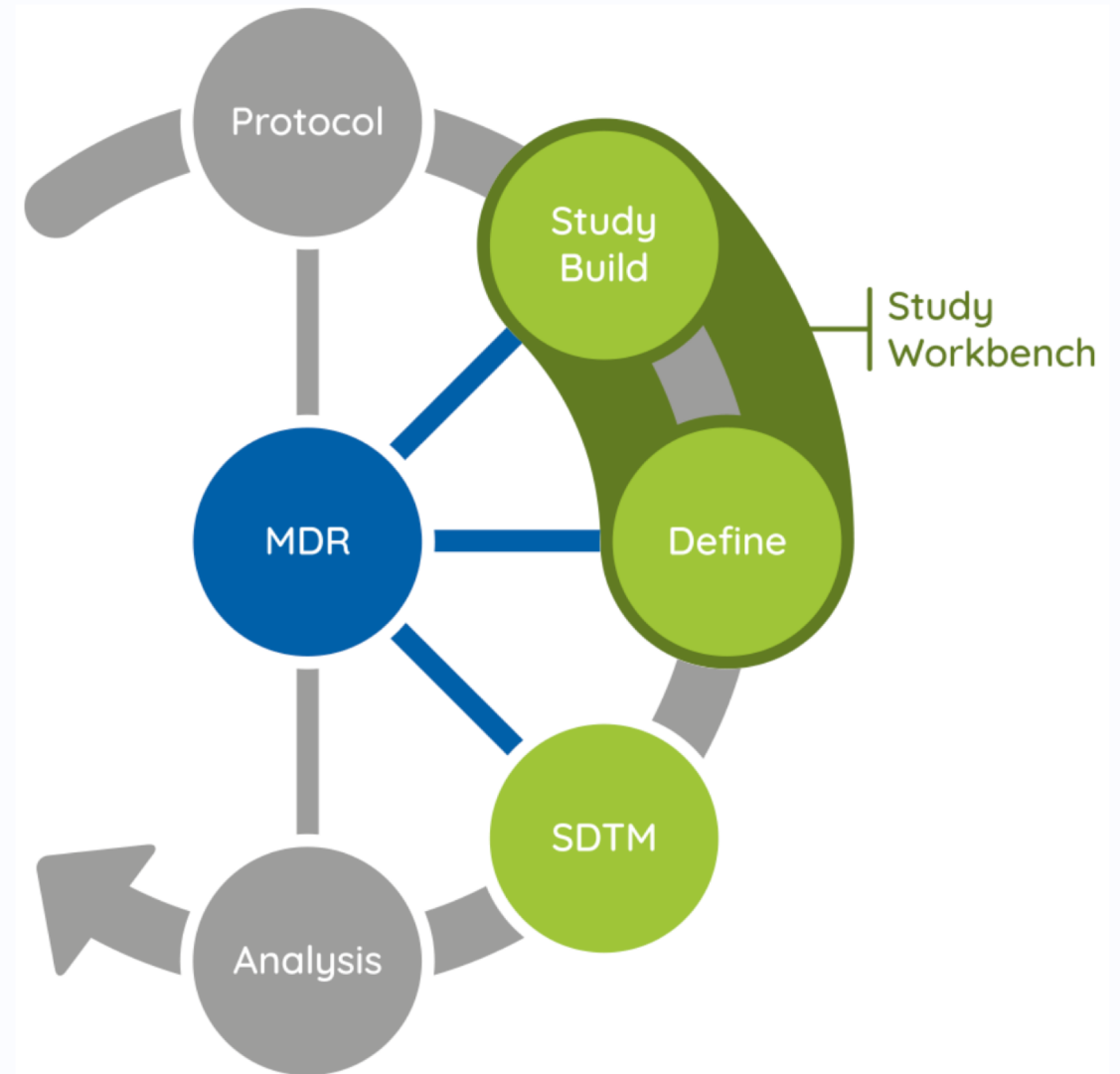
- Managing complexity
- Challenges in study setup ...
 - ... and reporting
 - ... and submitting
- Biomedical Concepts: What? Why?
- Summary



Overview

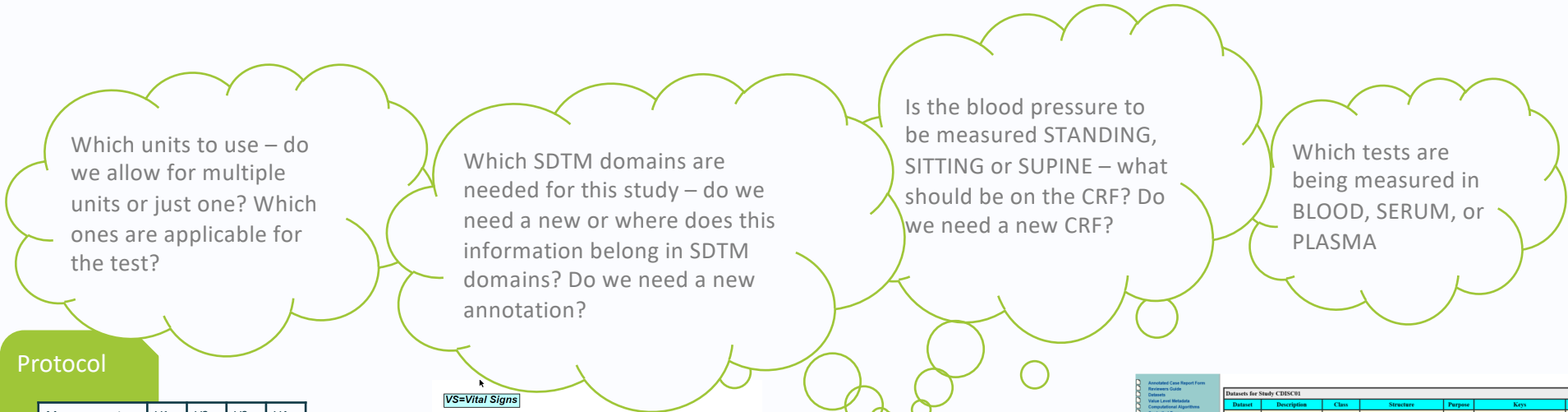
A suite of tools

- An MDR at the center providing a single source of knowledge
 - Terminology
 - Biomedical Concepts (BCs)
 - Forms
 - SDTM domains
- Provides an API to other tools
- A study workbench tool
 - To construct clinical studies
 - And automate define creation
- A tool to generate SDTM datasets (planned)
- Then expand across lifecycle
- Also, not shown, an experimental tool linking healthcare and clinical research prototyping the SDTM auto generation



Study Setup

Translating study specifications to reality



Protocol

Measurements	V1	V2	V3	V4
Demographics	x			
Vital signs	x			x
CT Scan		x		
Dosing		x	x	x
EQ-5D	x			x
Lipids	x			x
Haemoglobin	x			x
Adverse Events	x	x	x	x

VS=Vital Signs

CDISC Study: CDISC01 Assessment Date:

VITAL SIGNS

VSTEST

Height ☐ cm ☐ in
(VSORRES / VSORRESU when VTESTCD = HEIGHT)

Weight ☐ kg ☐ lbs
(VSORRES / VSORRESU when VTESTCD = WEIGHT)

VSPOS

Sitting Blood Pressure ☐ mmHg
Systolic / Diastolic
(VSORRES / VSORRESU when VTESTCD = SYSBP, DIABP)

Radial Pulse Rate ☐ bpm
(VSORRES / VSORRESU when VTESTCD = PULSE)

☐ Small ☐ Medium ☐ Large
(VSORRES when VTESTCD = FRMSIZE)

EDC, Labs etc.



Assembled Case Report Form
Revisions Guide
Data Entry
Visit Level Metadata
Consentment Algorithms
Calculated Items

Dataset	Description	Class	Structure	Purpose	Keys	Location
TA	Trial Arms	Trial Design	One record per planned Element per Arm	Tabulation	STUDYID, ARMCID, TAITFORD	ts.tbl
TE	Trial Elements	Trial Design	One record per planned Element	Tabulation	STUDYID, ETCD	te.tbl
TI	Trial Inclusion/Exclusion Criteria	Trial Design	One record per IE criterion	Tabulation	STUDYID, IETESTCD	ti.tbl
TS	Trial Summary	Trial Design	One record per trial summary parameter value	Tabulation	STUDYID, TSPARMCD, TSSEQ	ts.tbl
TV	Trial Visits	Trial Design	One record per planned Visit per Arm	Tabulation	STUDYID, VISITNUM, ARMCID	tv.tbl
DM	Demographics	Special Purpose	One record per subject	Tabulation	STUDYID, USUBID	dm.tbl
SE	Subject Elements	Special Purpose	One record per actual Element per subject	Tabulation	STUDYID, USUBID, SESTDTC, SEENDTC, TAITFORD, ETCD	se.tbl
SV	Subject Visits	Special Purpose	One record per actual visit per subject	Tabulation	STUDYID, USUBID, SVSTDTC, VISITNUM	sv.tbl

STUDYID	DOMAIN	USUBID	VSSEQ	VSTESTCD	VSTEST	VSPOS	VSORRES	VSORRESU	VSTRESC	VSTRESCU	VSTRESN	VSTRESU
CDISC01	VS	CDISC01.100008	1	DIABP	Diastolic Blood Pr.	SITTING	74	mmHg	74	mmHg	74	mmHg
CDISC01	VS	CDISC01.100008	2	DIABP	Diastolic Blood Pr.	SITTING	88	mmHg	88	mmHg	88	mmHg
CDISC01	VS	CDISC01.100008	3	DIABP	Diastolic Blood Pr.	SITTING	78	mmHg	78	mmHg	78	mmHg
CDISC01	VS	CDISC01.100008	4	DIABP	Diastolic Blood Pr.	SITTING	90	mmHg	90	mmHg	90	mmHg
CDISC01	VS	CDISC01.100008	5	FRMSIZE	Body Frame Size		LARGE		LARGE			
CDISC01	VS	CDISC01.100008	6	HEIGHT	Height		66	IN	167.6		167.6	cm
CDISC01	VS	CDISC01.100008	7	PULSE	Pulse Rate		74	BEATS/MIN	74		74	BEATS/MIN
CDISC01	VS	CDISC01.100008	8	PULSE	Pulse Rate		84	BEATS/MIN	84		84	BEATS/MIN
CDISC01	VS	CDISC01.100008	9	PULSE	Pulse Rate		76	BEATS/MIN	76		76	BEATS/MIN
CDISC01	VS	CDISC01.100008	10	PULSE	Pulse Rate		80	BEATS/MIN	80		80	BEATS/MIN
CDISC01	VS	CDISC01.100008	11	SYSBP	Systolic Blood Pr.	SITTING	122	mmHg	122		122	mmHg
CDISC01	VS	CDISC01.100008	12	SYSBP	Systolic Blood Pr.	SITTING	148	mmHg	148		148	mmHg

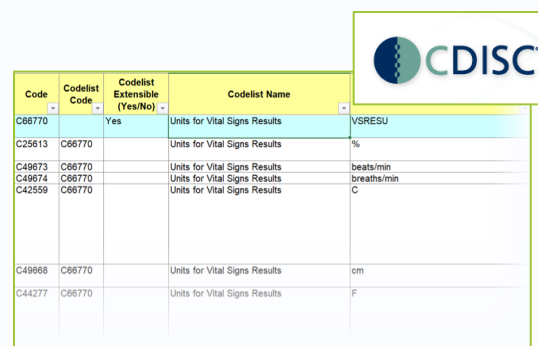
protocol -> data collection -> reporting

Standards ... but not connected



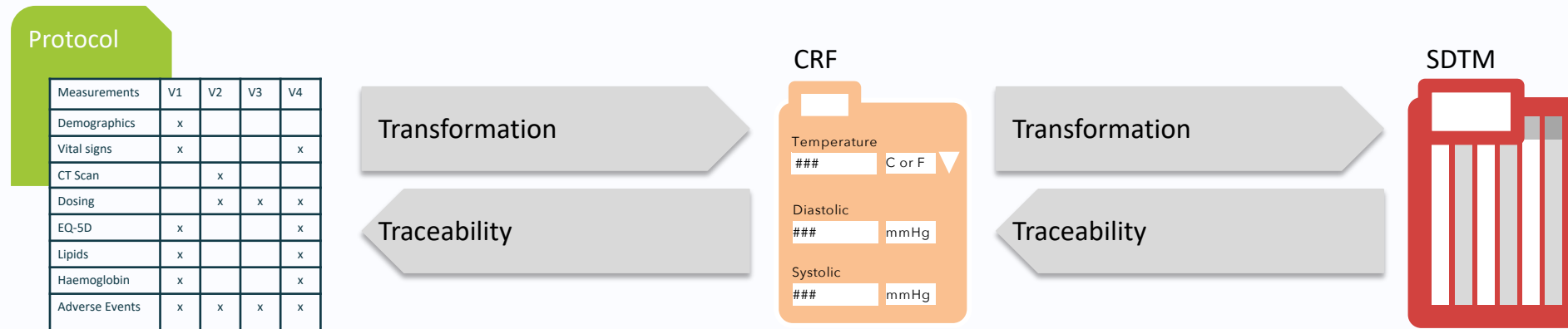
protocol -> data collection -> reporting

Standards ... but not connected



Study Setup

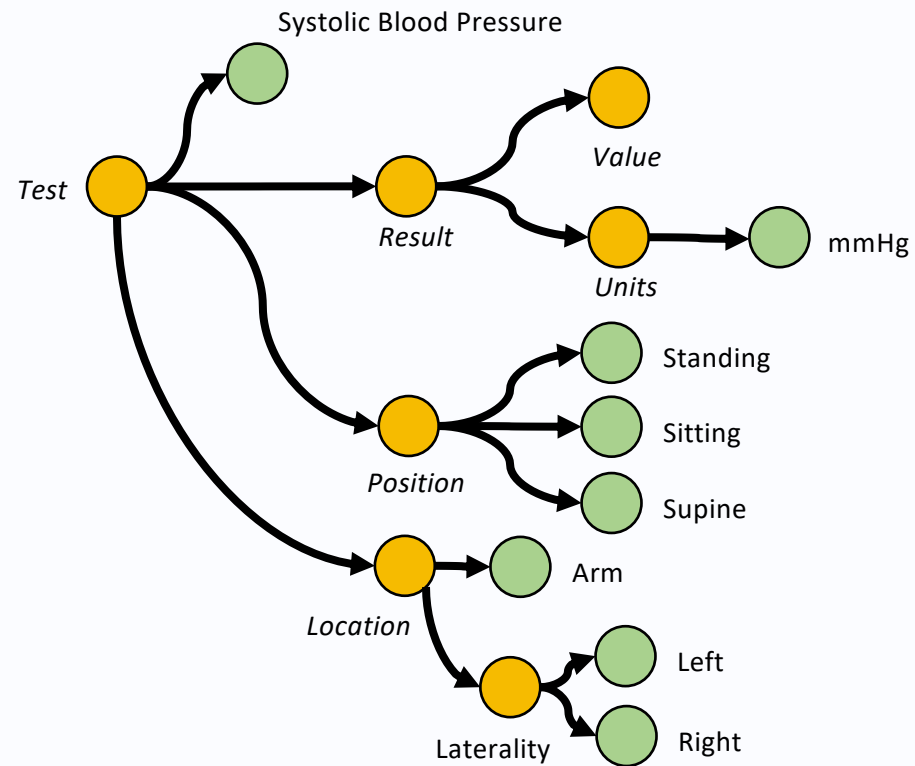
Challenge – maintaining transformations and traceability effectively



Biomedical Concepts (BCs) break down the “silos” and facilitate a consistent way of collecting the data across studies

What is a Biomedical Concept?

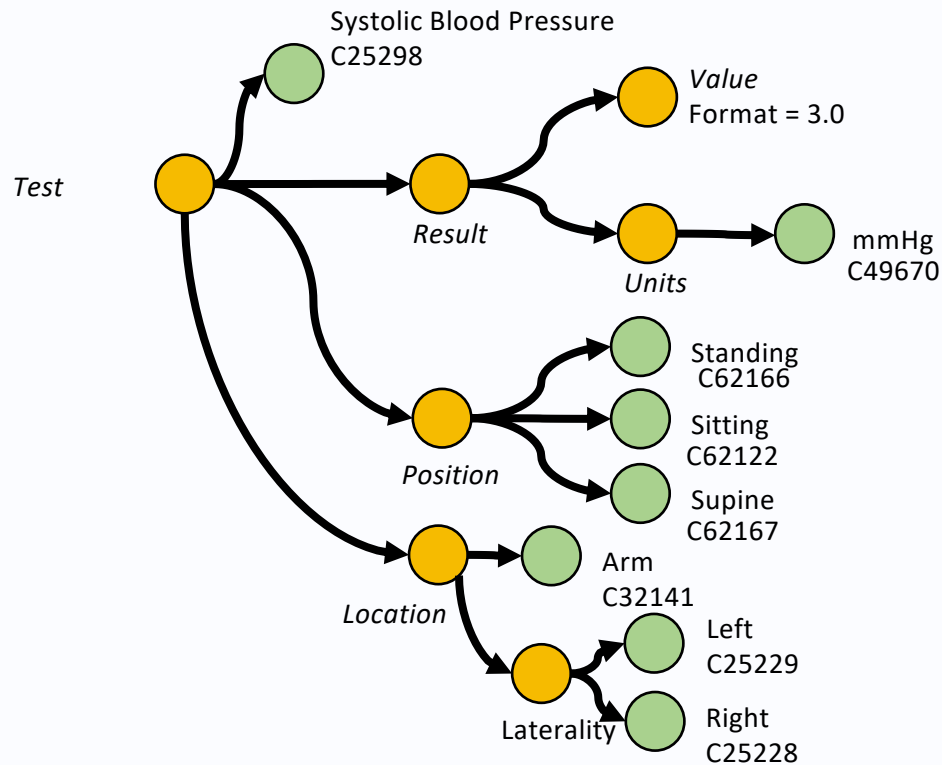
Clinical view



- A collection of variables
- A real-world entity
- Something a physician would recognize

What is a Biomedical Concept?

Data Manager / Programmer view



- Some more detail
- Linked to the CDISC terminology
- Consistent information with views tailored to user
- Present in a way that is meaningful to the consumer

Biomedical Concepts

Implementation

Show: Systolic Blood Pressure (BC C25298) BC C25298 (V3.1.0, 4, Incomplete)

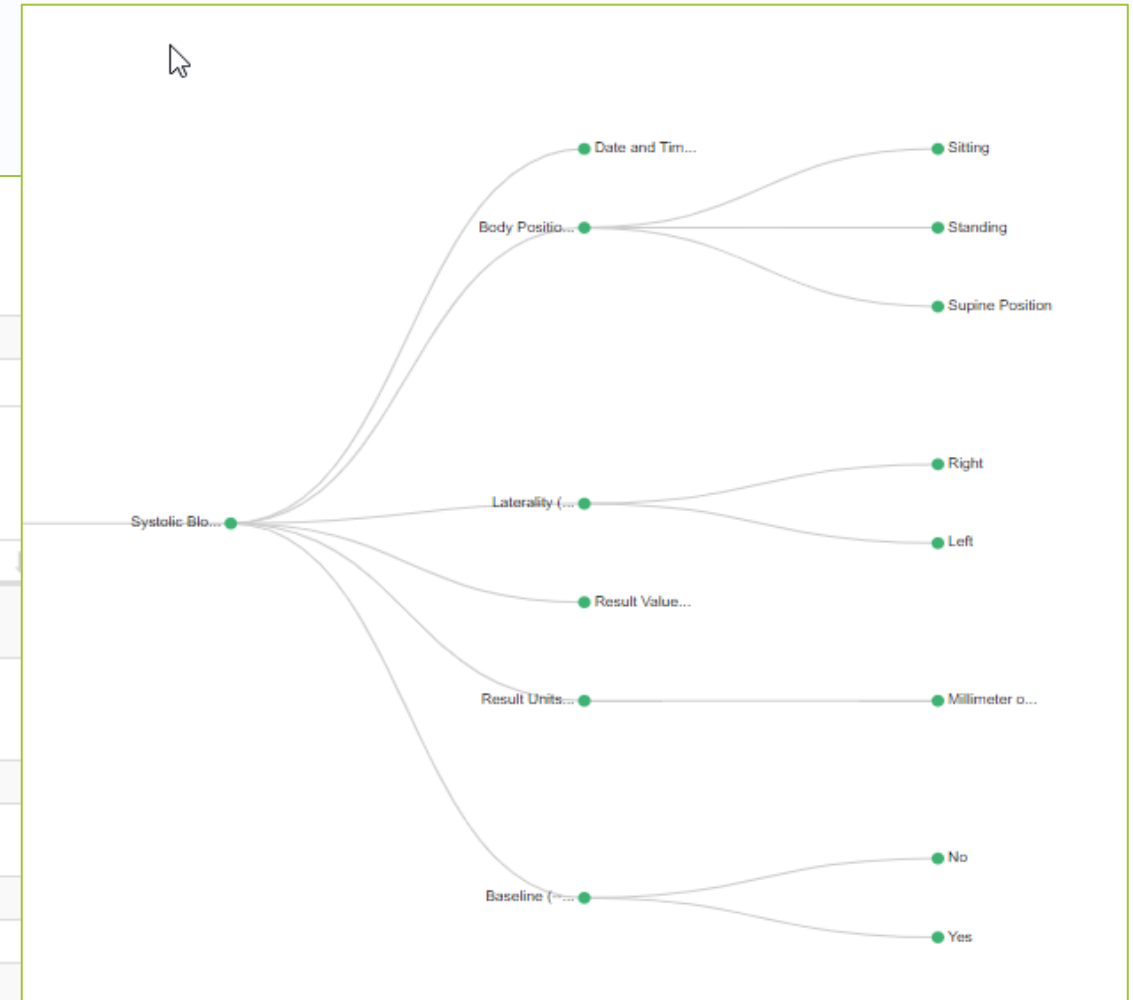
Details

Identifier	Label	Owner
BC C25298	Systolic Blood Pressure (BC C25298)	ACME

Items

Show 10 entries

Alias	Question Text	Prompt Text
Baseline (--BLFL)	Is this a baseline value?	Baseline
Body Position (--POS)	In what position was the subject during the measurement?	Position
Date and Time (--DTC)	On what date were the measurement performed?	Date
Laterality (--LAT)	Which arm?	Arm
Location (--LOC)	The location of the measurement	Location
Method Code (--METHOD)		
Result Units (--ORRESU)	The unit of the measurement	Units
Result Value (--ORRES)	What was the result of the measurement?	Result
Test Code (--TESTCD)		
Test Name (--TEST)		



✓	✓	float	3	
✓	✗	string		SYSBP (C25298)
✓	✗	string		Systolic Blood Pressure (C25298)

Refer domains to Biomedical Concepts

Where does the collected information belong?

- Multiple domains can refer to the same BC.
- The context of the study will then determine which domain is used
- **IMPORTANT:** The domain referrers to the BC. They BC DOES NOT refer to the domain. Can be used with any appropriate SDTM domain of the correct class

Show: Vital Signs VS Domain (V1.0.0, 2, Standard)

Details

Identifier	Label	Owner	Internal Version	Version
VS Domain	Vital Signs	ACME	1.0.0	

Notes

Used Variables

Show 10 entries Search:

Ordinal	Name	Label	Datatype	CT	Format	Role	Sub Role	IG Notes	Notes	Core
1	STUDYID	Study Identifier	Char			Identifier		Unique identifier for a study.		Required
2	DOMAIN	Domain Abbreviation	Char	DOMAIN		Identifier		Two-character abbreviation for the domain.		Required
3	USUBJID	Unique Subject Identifier	Char			Identifier		Identifier used to uniquely identify a subject across all studies for all applications or submissions involving the product.		Required
4	VSSEQ	Sequence Number	Num			Identifier		Sequence Number given to ensure uniqueness of subject records within a domain. May be any valid number.		Required
5	VSGRPID	Group ID	Char			Identifier		Used to tie together a block of related records in a single domain for a subject.		Permissible
6	VSSPID	Sponsor-Defined Identifier	Char			Identifier		Sponsor-defined reference number. Perhaps pre-printed on the CRF as an explicit line identifier or defined in the sponsor's operational database.		Permissible
7	VSTESTCD	Vital Signs Test Short Name	Char	VSTESTCD		Topic		Short name of the measurement, test, or examination described in VSTEST. It can be used as a column name when converting a dataset from a vertical to a horizontal format. The value in VSTESTCD cannot be longer than 8 characters, nor can it start with a number (e.g. "1TEST"). VSTESTCD cannot contain characters other than letters, numbers, or underscores. Examples: SYSBP, DIABP, BMI.		Required
8	VSTEST	Vital Signs Test Name	Char	VSTEST		Qualifier	Synonym Qualifier	Verbatim name of the test or examination used to obtain the measurement or finding. The value in VSTEST cannot be longer than 40 characters. Examples: Systolic Blood Pressure, Diastolic Blood Pressure, Body Mass Index.		Required
9	VSCAT	Category for Vital Signs	Char			Qualifier	Grouping Qualifier	Used to define a category of related records.		Permissible
10	VSSCAT	Subcategory for Vital Signs	Char			Qualifier	Grouping Qualifier	A further categorization of a measurement or examination.		Permissible

Showing 1 to 10 of 32 entries Previous 1 2 3 4 Next

Unused Variables

Show 10 entries Search:

No data available in table

Showing 0 to 0 of 0 entries Previous Next

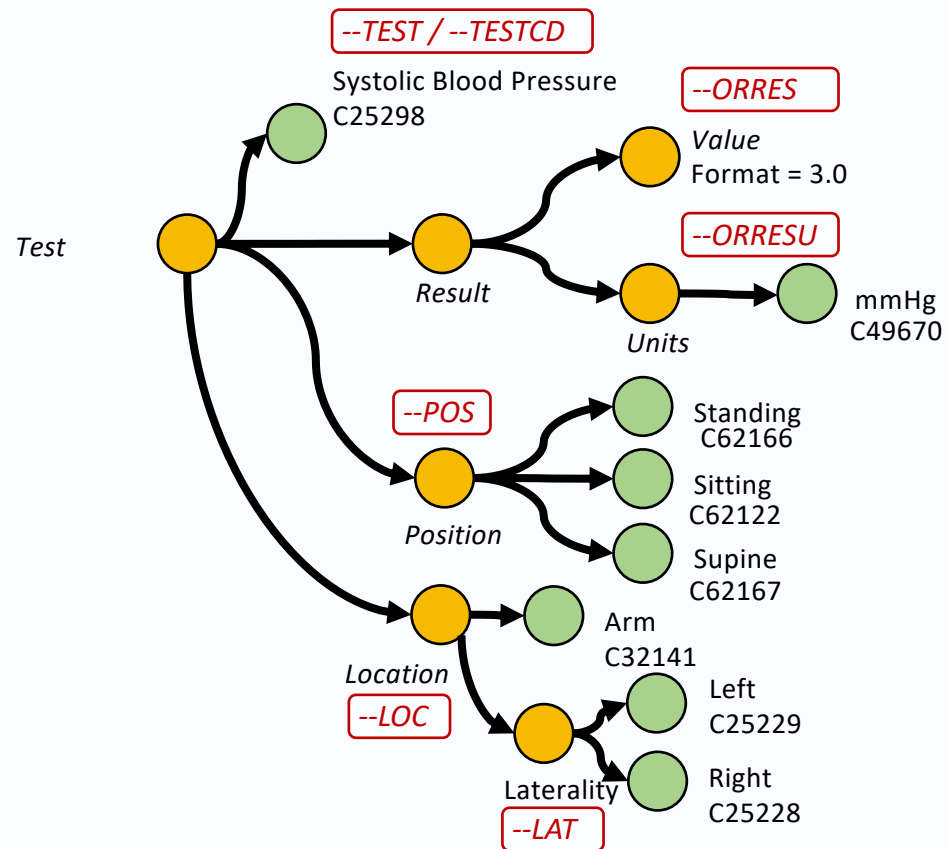
Biomedical Concepts

Show 10 entries Search: pressure

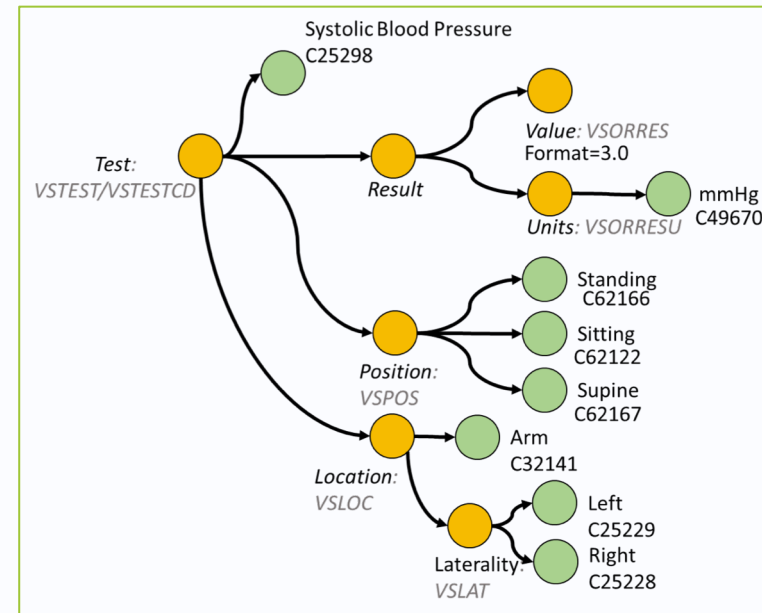
Identifier	Label	Owner	Version	Version Label
BC C25298	Systolic Blood Pressure (BC C25298)	ACME	2.0.0	0.2
BC C25298	Systolic Blood Pressure (BC C25298)	ACME	3.0.0	0.3
BC C25299	Diastolic Blood Pressure (BC C25299)	ACME	2.0.0	0.2

Biomedical Concepts

Domain relationship

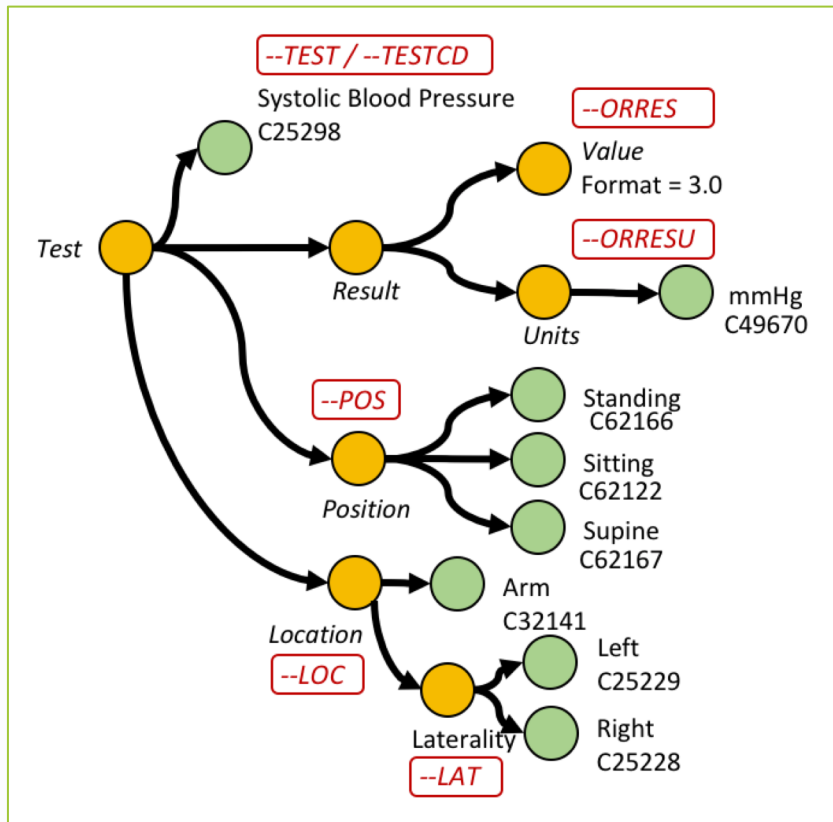


- We can automatically add these “mappings” because the BC is linked to a domain
- In reality linked to a class hence the “--” rather than “VS”

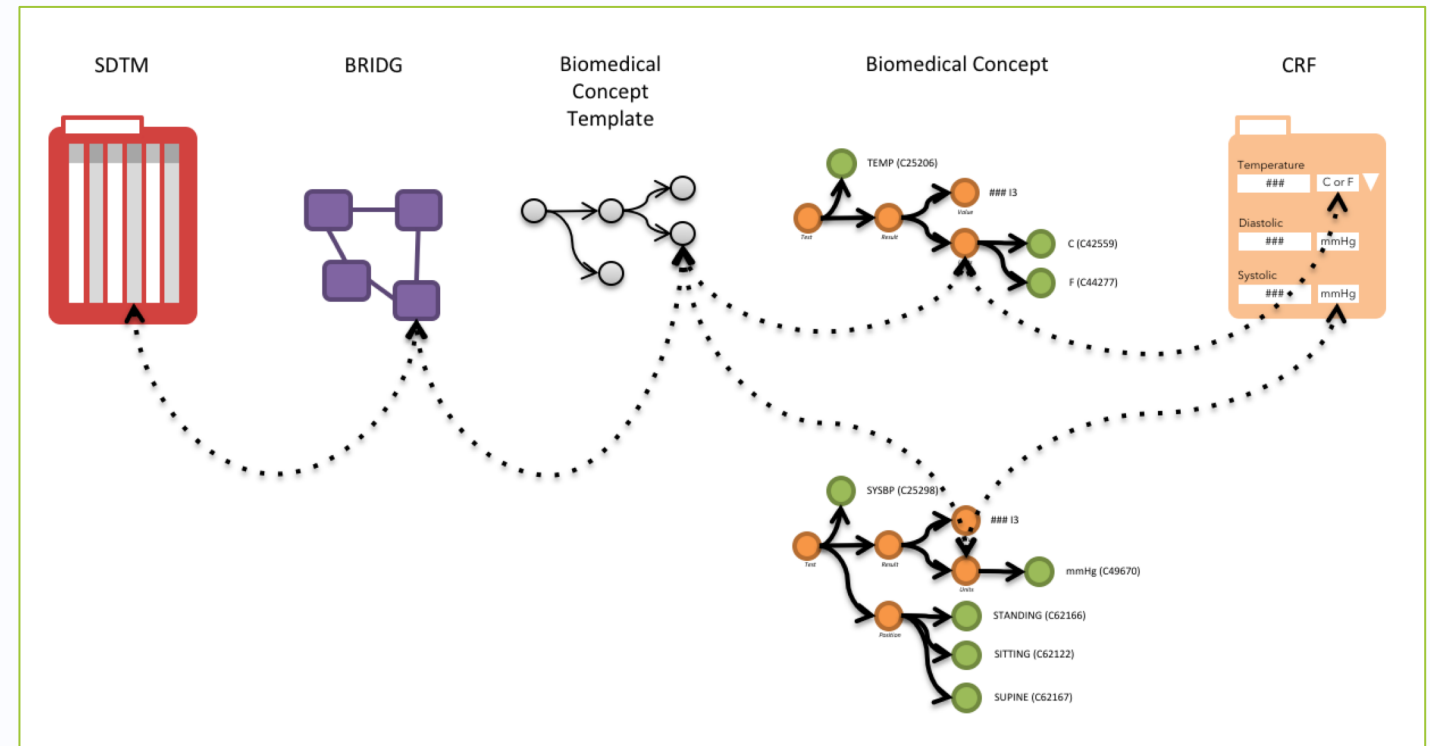


Biomedical Concepts

Domain relationship

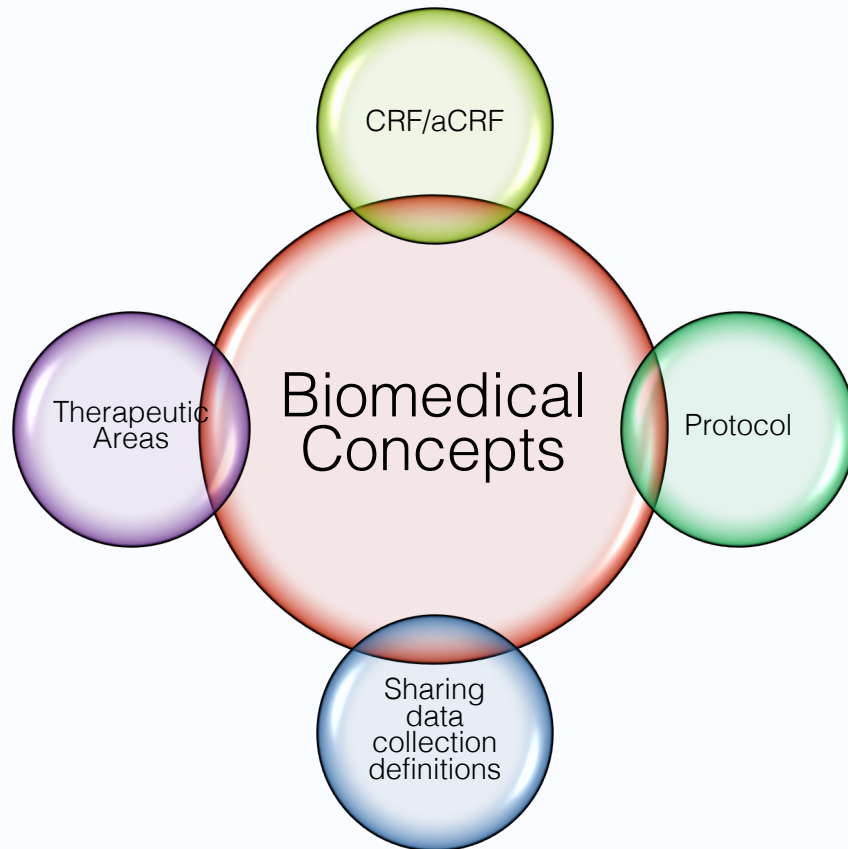


- We use a framework (BRIDG) and templates to ensure consistency of approach

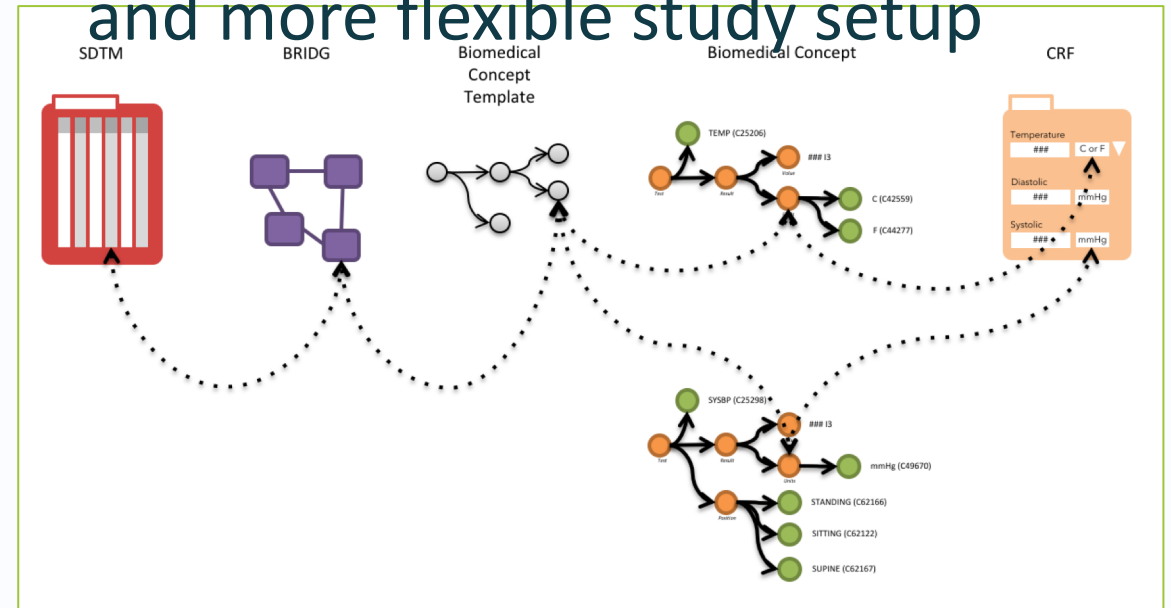


Why bother?

Consistency across the life-cycle



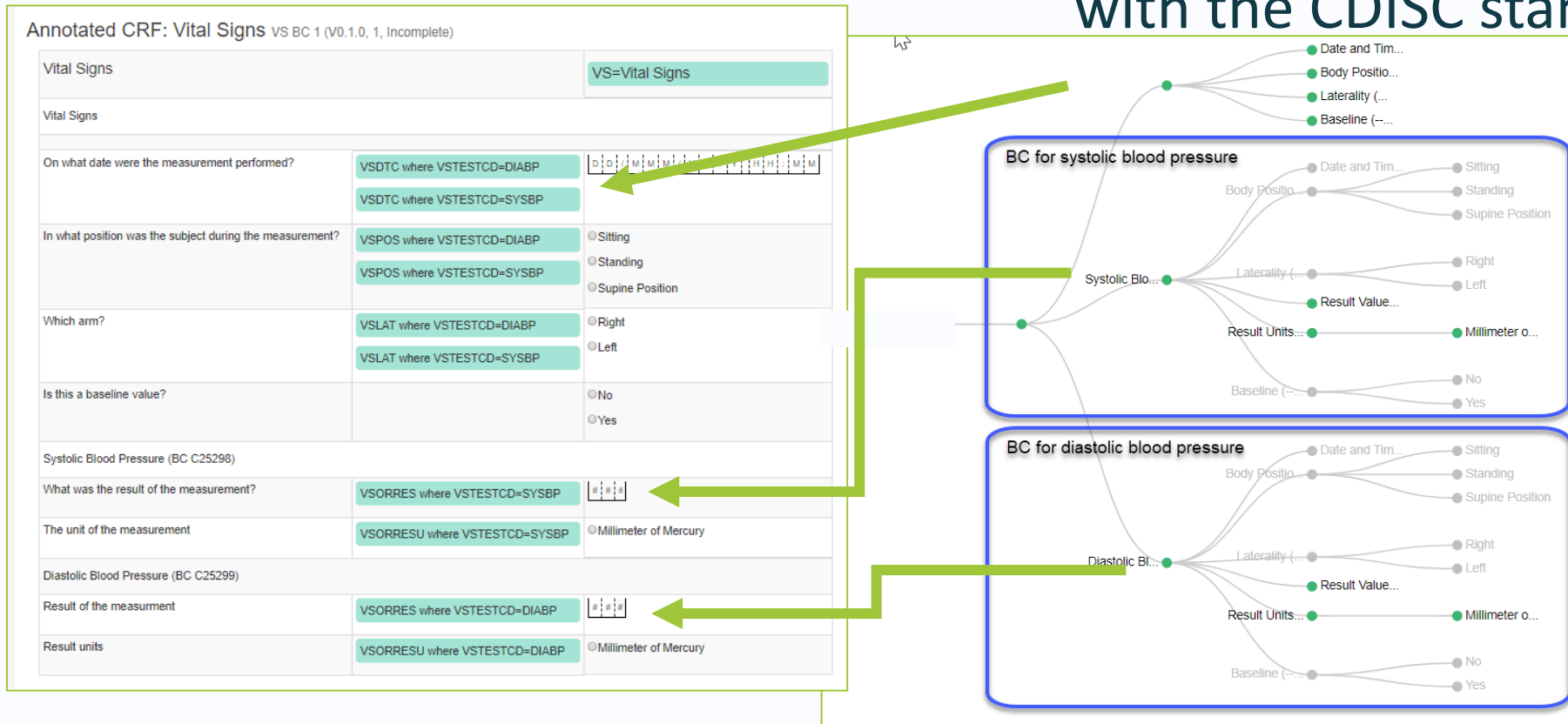
- BC is a standardised definition that can be used for various purpose and facilitates faster and more flexible study setup



Standardisation - From Forms to BCs

Flexible form creation

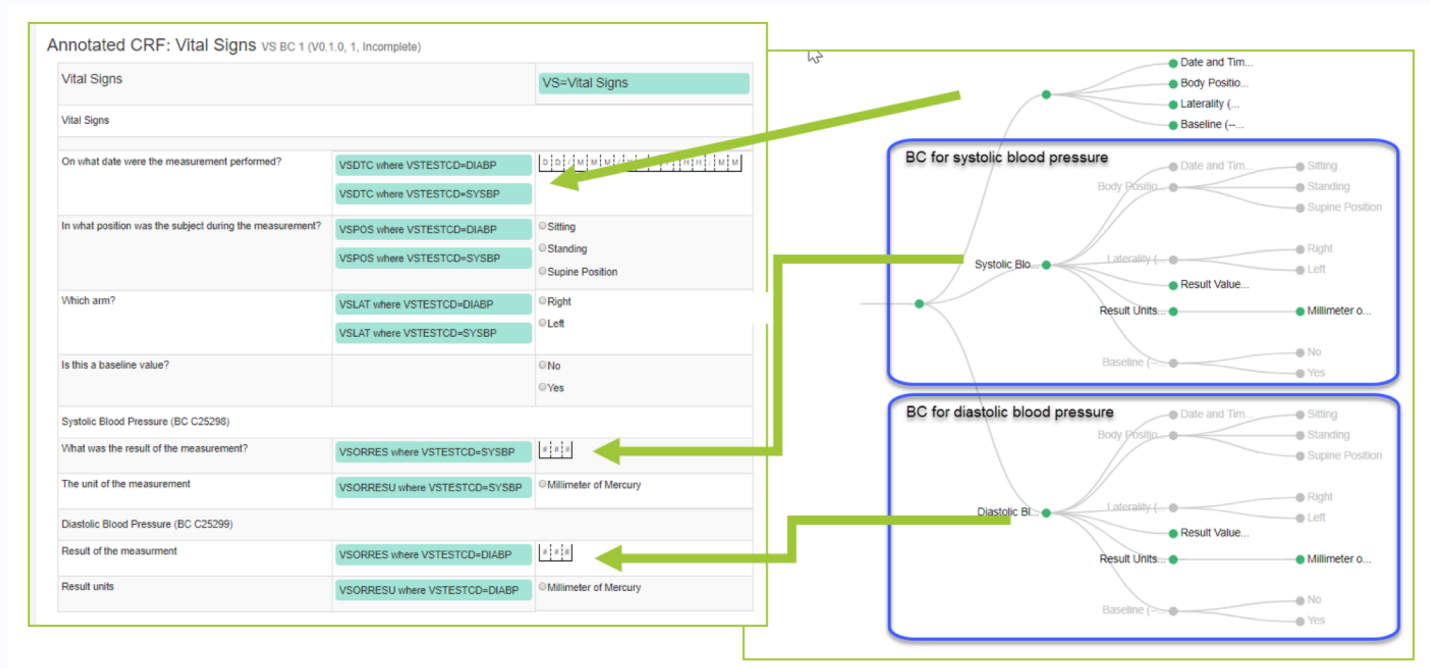
- Ensures we have compliance with the CDISC standards



Demo

Standardisation - From Forms to BCs

Flexible form creation



The flexibility is achieved on 3 levels:

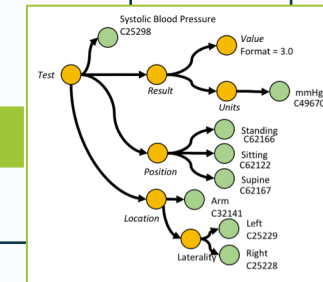
1. The user can decide which BCs to add to a Vital Signs form, i.e. which questions are included in the vital sign page
2. The user can enable/disable data elements in a BC, e.g. decide not to use the baseline flag question if not relevant, i.e. what the level of response is needed for the question
3. The user can decide if questions and/or responses are optional/mandatory

Upstream Standardisation

BCs in Protocols

Assessments	Screening	Baseline	Treatment	EndOfTrial
Demographics	x			
Vital signs	x			
CT Scan		x		
Dosing		x	x	x
EQ-5D	x			x
Lipids	x			x
Haemoglobin	x			x
Adverse Events	x	x	x	x

Assessments	BC	Screening	Baseline	Treatment	EndOfTrial
Demographics	Age Race Date of Birth Sex	x			
Vital signs	Height Weight Heart Rate Temperature Systolic Blood Pressure Diastolic Blood Pressure	x			x
CT Scan	CT scan timing				
Dosing	Number of dosing units		x	x	x
EQ-5D	Mobility	x			x
Lipids	LDL HDL Total Cholesterol	x			x
Haemoglobin	Haemoglobin	x			x
Adverse Events	Adverse Events	x	x	x	x



Upstream Standardisation

BCs in Protocols

The screenshots show a CRF interface with multiple tabs for 'Vital Signs'. The first tab shows a list of BCs (Best Practices) for Vital Signs. The second tab shows a list of BCs for Blood Pressure. The third tab shows a list of BCs for Blood Glucose. A green arrow points from these forms towards the table on the right.

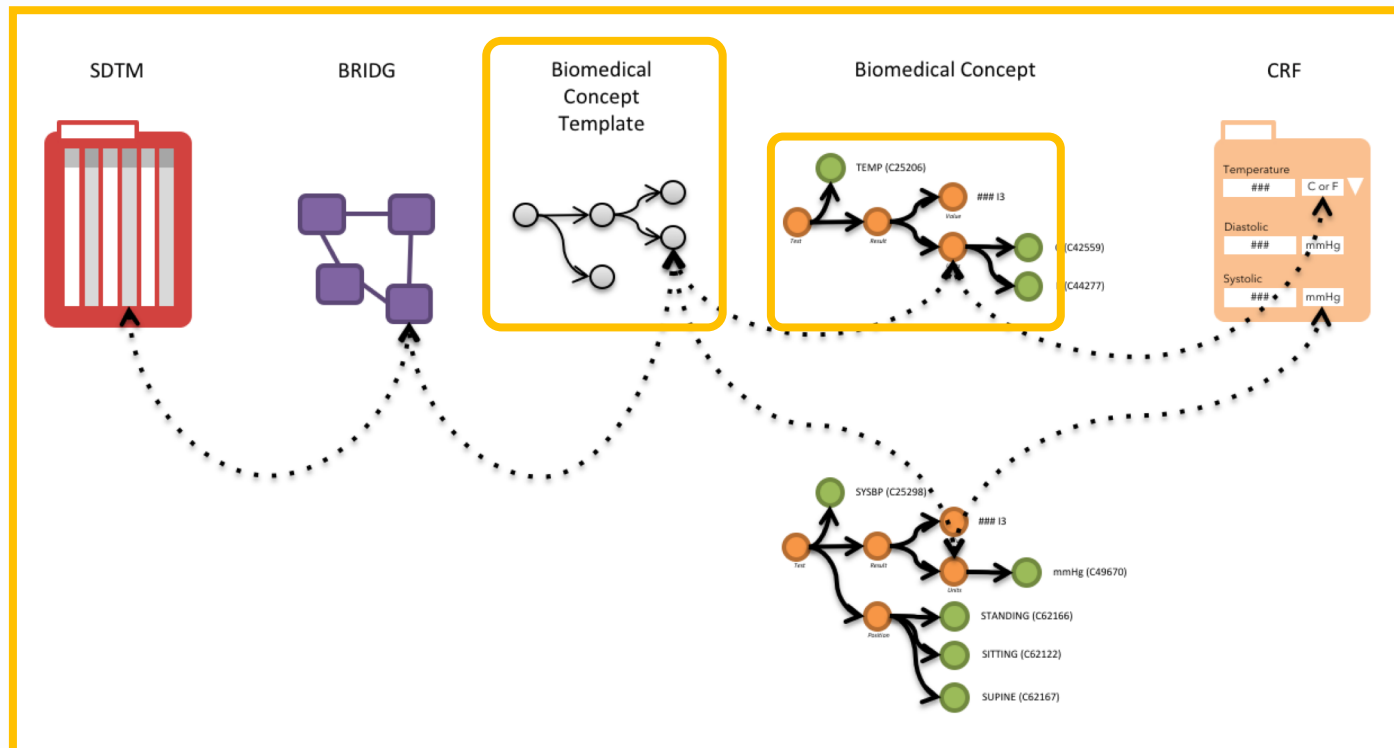
- Forms containing these BCs will then be listed and the CRF designer would then pick the appropriate CRF.
- CRF reviewed early by the study group allowing for adjustments to the protocol if needed.

Assessments	BC	Screening	Baseline	Treatment	EndOfTrial
Demographics	Age Race Date of Birth Sex	X			
Vital signs	Height Weight Heart Rate Temperature Systolic Blood Pressure Diastolic Blood Pressure	X			X
CT Scan	CT scan timing		X		
Dosing	Number of dosing units		X	X	X
EQ-5D	Mobility	X			X
Lipids	LDL HDL Total Cholesterol	X			X
Haemoglobin	Haemoglobin	X			X
Adverse Events	Adverse Events	X	X	X	X

Sharing BCs

Common definitions based on templates

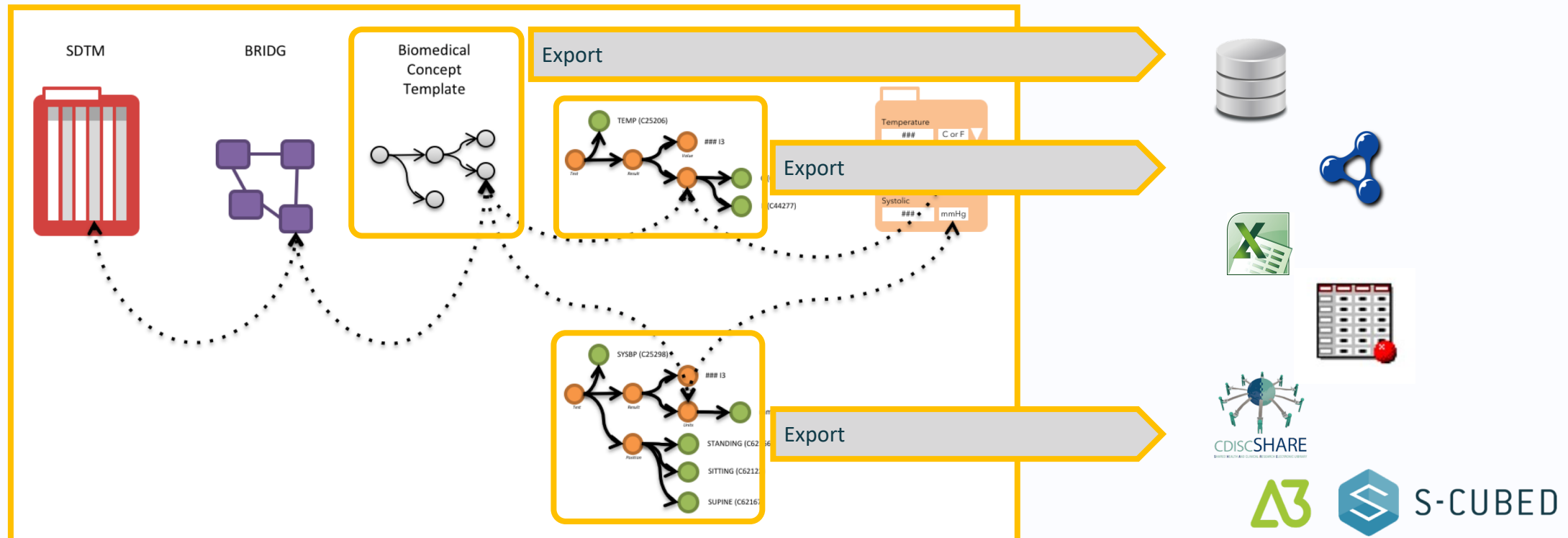
- BCs should be made based on templates to ensure consistency.
- Contributors could be both pharmaceutical companies, CROs as well as regulators.
- Sharing the definition of a BC does not disclose any intellectual property or any sensitive data that needs de-identification



Sharing BCs

Common definitions based on templates

- Distribute the information via SAS tables, linked data, spreadsheets (MS Excel), database loads etc.
- Share with CDISC



BCs For Defining Therapeutic Areas (TAs)

Current metadata for TAs – a BC template

Domain	Question Text	Prompt	SDTM or CDASH Variable Name	BRIDG	Definition	Codelist	CRF Completion Instructions	Core	Data Type
VS	What is the vital sign test name?	<Test>	VSTEST	PerformedActivity.PerformedObservation > PlannedActivity > StudyActivity > DefinedActivity.DefinedObservation.nameCode.CD.originalText	Verbatim name of the test or examination used to obtain the measurement or finding. {VSTEST} (See Section 2.2.)	VSTEST	Record the name of the vital sign test if not pre-printed on the CRF.	Highly Recommended	Char
VS	What was the unit of the measurement?	<Units>	VSORRESU	PerformedObservation > PerformedObservationResult.value.ANY=> PQ.translation.PQR.code	Original units in which the data were collected. {VSRESU} (See Section 2.2.)	VSRESU	'Record or select the unit of measure associated with the test, if not pre-printed on the CRF.'	Recommended /Conditional	Char

Doesn't define the possible/required tests for the TA

Doesn't define the possible/required units for the test

BCs For Defining Therapeutic Areas (TAs)

TAs as a set of BCs

Domain	Question Text	Prompt	SDTM or CDASH Variable Name	BRIDG	Definition	Codelist	CRF Completion Instructions	Core	Data Type
VS	What is the vital sign test name?	<Test>	VSTEST	PerformedActivity.PerformedObservation > PlannedActivity > StudyActivity > DefinedActivity.DefinedObservation.nameCode.CD.originalText	Verbatim name of the test or examination used to obtain the measurement or finding. {VSTEST} (See Section 2.2.)	VSTEST	Record the name of the vital sign test if not pre-printed on the CRF.	Highly Recommended	Char
VS	What was the unit of the measurement?	<Units>	VSORRESU	PerformedObservation > PerformedObservationResult.value.ANY=> PQ.translation.PQR.code	Original units in which the data were collected. {VSRESU} (See Section 2.2.)	VSRESU	Record or select the unit of measure associated	Recommended /Conditional	Char

- TAs could be defined as a set of BCs
- Also a set of relationships with target domains
- Those domain relationships might change in TAs!

Show: Systolic Blood Pressure (BC C25298) BC C25298 (V3.1.0, 4, Incomplete)

Identifier	Label	Owner	Status	Version	Version Label	Impact
BC C25298	Systolic Blood Pressure (BC C25298)	ACME	Incomplete	3.1.0	0.3	Impact

Items

Show 10 entries

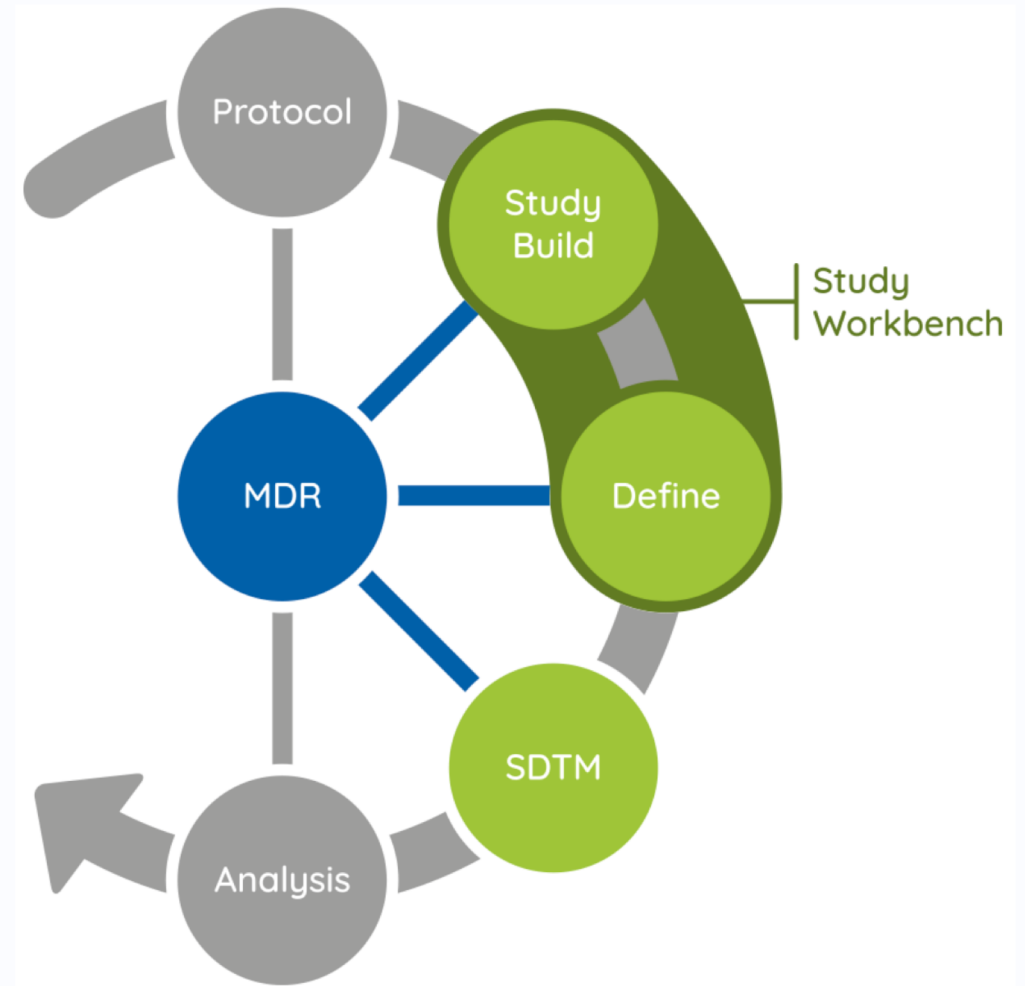
Alias	Question Text	Prompt Text	Enabled	Collect	Datatype	Format	Terminology
Baseline (-BLFL)	Is this a baseline value?	Baseline	✓	✓	boolean		N (C49487) Y (C49488)
Body Position (-POS)	In what position was the subject during the measurement?	Position	✓	✓	string		SITTING (C62122) STANDING (C62166) SUPINE (C62167)
Date and Time (-DTC)	On what date were the measurement performed?	Date	✓	✓	dateTime		
Laterality (-LAT)	Which arm?	Arm	✓	✓	string		RIGHT (C25228) LEFT (C25229)
Location (-LOC)	The location of the measurement	Location	✓	✗	string		ARM (C32141)
Method Code (-METHOD)			✗	✗	string		
Result Units (-ORRESU)	The unit of the measurement	Units	✓	✓	string		mmHg (C49670)
Result Value (-ORRES)	What was the result of the measurement?	Result	✓	✓	float	3	
Test Code (-TESTCD)			✓	✗	string		SYSBP (C25298)
Test Name (-TEST)			✓	✗	string		Systolic Blood Pressure (C25298)

Demo

Summary

S-Cubed A3 suite

- Solid foundation based around the MDR
- The old world can co-exist with BC's
- Allow for other tools to access exports or APIs
- Deployment should not require large-scale IT projects such that all sponsors can benefit from high-quality definitions.
- Web-based tools



Thank you for listening



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