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The Development of CDISC Biomedical Concepts: Update and Next Steps

Presented by Jon Neville, Senior Director Standards Development, CDISC
Bess LeRoy, Head of Standards Innovation, CDISC

Meet the Speakers

Jon Neville

Title: Senior Director, Standards Development

Organization: CDISC

Jon Neville has 14 years' experience implementing and developing CDISC standards. He has led, co-led, or otherwise participated in many CDISC therapeutic-area data standards projects. Jon got his start in CDISC standards leading a legacy data conversion effort to create an integrated database of 24 Alzheimer's disease clinical trials. He has been participating on CDISC teams since 2010

Bess LeRoy

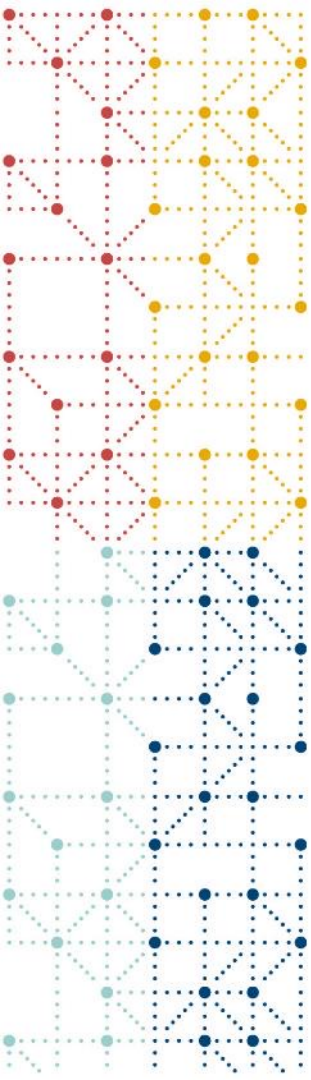
Title: Head of Standards Innovation

Organization: CDISC

Bess LeRoy is the Head of Standards Development at CDISC. Bess has been a CDISC team member since 2011. She has over 15 years' experience working in public health research and has held positions at the Framingham Heart Study, the Rotterdam Study, the Arizona Cancer Center, and the Critical Path Institute.

Agenda

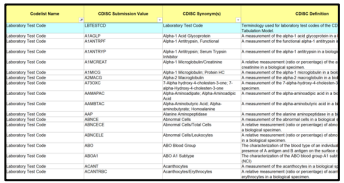
1. Background
2. CDISC Biomedical Concepts
3. Use Cases
4. Looking Towards The Future



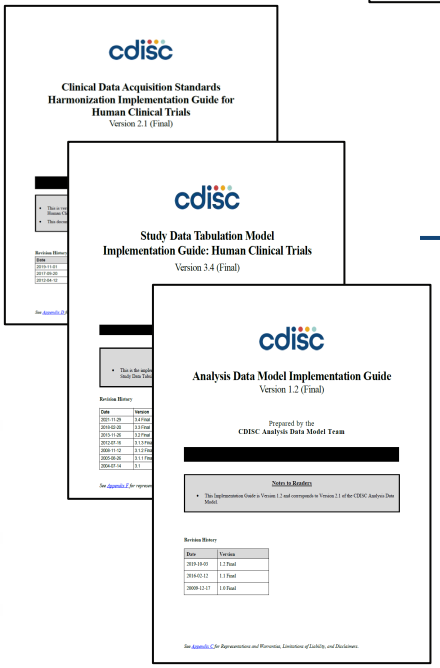
Background

What are biomedical concepts?

How Standards Have Been Historically Implemented

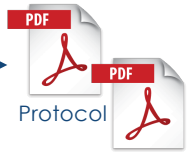


Controlled Terminology



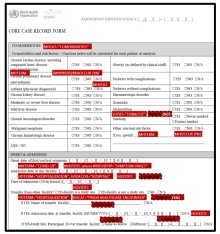
CDISC Implementation Guides

Sponsor MDR



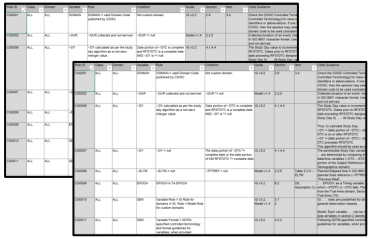
Protocol

SAP



CRFs

Conduct Study



CDISC Conformance Rules

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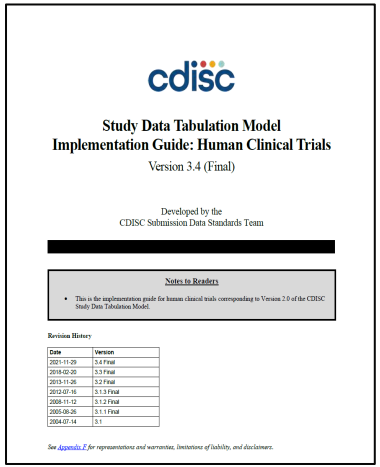
Simple Example…

Representing vital signs in SDTM using this approach



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Study Data Tabulation Model
Implementation Guide: Human Clinical Trials
Version 3.4 (Final)

Developed by the
CDISC Submission Data Standards Team

Notes to Readers

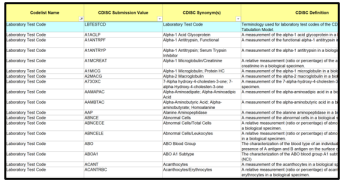
- This is the implementation guide for human clinical trials corresponding to Version 2.0 of the CDISC Study Data Tabulation Model.

Revision History

Date	Version
2021-11-29	3.4 Final
2018-02-20	3.3 Final
2013-11-26	3.2 Final
2012-07-16	3.1.3 Final
2008-11-12	3.1.2 Final
2005-09-26	3.1.1 Final
2004-07-14	3.1

See Appendix F for representations and warranties, limitations of liability, and disclaimers.

SDTMIG: 461 pages



Controlled Terminology

Controlled Terminology:
>35,000 terms in almost 1000 code lists

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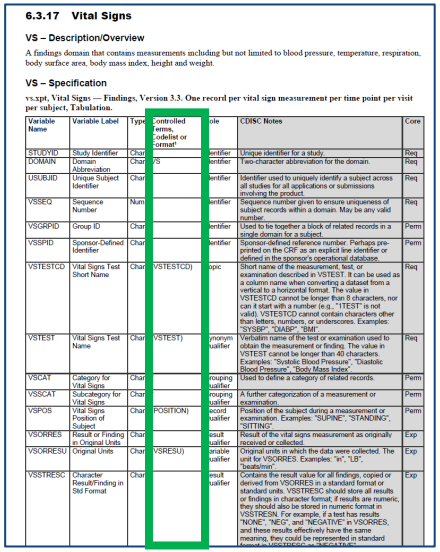


6.3.17 Vital Signs

VS – Description/Overview

A findings domain that contains measurements including but not limited to blood pressure, temperature, respiration, body surface area, body mass index, height and weight.

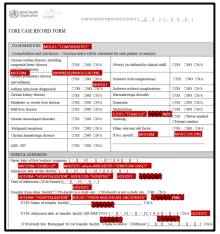
VS – Specification

vs.xpt, Vital Signs — Findings, Version 3.3. One record per vital sign measurement per time point per visit per subject, Tabulation.

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format*	Role	CDISC Notes	Core
STUDYID	Study Identifier	Char		Identifier	Unique identifier for a study.	Req
DOMAIN	Domain Abbreviation	Char	VS	Identifier	Two-character abbreviation for the domain.	Req
USUBJID	Unique Subject Identifier	Char		Identifier	Identifier used to uniquely identify a subject across all studies for all applications or submissions involving the product.	Req
VSSEQ	Sequence Number	Num		Identifier	Sequence number given to ensure uniqueness of subject records within a domain. May be any valid number.	Req
VSGRPID	Group ID	Char		Identifier	Used to tie together a block of related records in a single domain for a subject.	Perm
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.	Perm
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" is not valid). VSTESTCD cannot contain characters other than letters, numbers, or underscores. Examples: "SYSBP", "DIABP", "BMI".	Req
VSTEST	Vital Signs Test Name	Char	VSTEST)	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".	Req
VSCAT	Category for Vital Signs	Char		Grouping Qualifier	Used to define a category of related records.	Perm
VSSCAT	Subcategory for Vital Signs	Char		Grouping Qualifier	A further categorization of a measurement or examination.	Perm
VSPOS	Vital Signs Position of Subject	Char	POSITION)	Record Qualifier	Position of the subject during a measurement or examination. Examples: "SUPINE", "STANDING", "SITTING".	Perm
VSORRES	Result or Finding in Original Units	Char		Result Qualifier	Result of the vital signs measurement as originally received or collected.	Exp
VSORRESU	Original Units	Char	VSRESU)	Variable Qualifier	Original units in which the data were collected. The unit for VSORRES. Examples: "in", "LB", "beats/min".	Exp
VSSTRESC	Character Result/Finding in Std Format	Char		Result Qualifier	Contains the result value for all findings, copied or derived from VSORRES in a standard format or standard units. VSSTRESC should store all results or findings in character format; if results are numeric, they should also be stored in numeric format in VSSTRESN. For example, if a test has results "NONE", "NEG", and "NEGATIVE" in VSORRES, and these results effectively have the same meaning, they could be represented in standard format in VSSTRESC as "NEGATIVE".	Exp

Vital Signs Domain:
Specification for how to construct vital signs data

Repeat 100s of times for all your study data concepts…



CRFs

vs.xpt

Row	STUDYID	DOMAIN	USUBJID	VSSEQ	VSTESTCD	VSTEST	VSPOS	VSORRES	VSORRESU	VSSTRESC	VSSTRESN	VSSTRESU	VSSTAT	VSREASND	VSLOC	VSLOBXFL	VISITNUM	VISIT	VISITDY	VSDTC	VSDY
1	ABC	VS	ABC-001-001	1	SYSBP	Systolic Blood Pressure	SITTING	154	mmHg	154	154	mmHg			BRACHIAL ARTERY	Y	1	Baseline	1	2022-06-19T08:45	1
2	ABC	VS	ABC-001-001	2	DIABP	Diastolic Blood Pressure	SITTING	44	mmHg	44	44	mmHg			BRACHIAL ARTERY	Y	1	Baseline	1	2022-06-19T08:45	1
3	ABC	VS	ABC-001-001	3	HEIGHT	Height		157	cm	157	157	cm				Y	1	Baseline	1	2022-06-19	1
4	ABC	VS	ABC-001-001	4	WEIGHT	Weight		90.5	kg	90.5	90.5	kg				Y	1	Baseline	1	2022-06-19	1
5	ABC	VS	ABC-001-001	5	PULSE	Pulse Rate		72	beats/min	72	72	beats/min			CAROTID ARTERY	Y	1	Baseline	1	2022-06-19	1
6	ABC	VS	ABC-001-001	6	RESP	Respiratory Rate		34	breaths/min	34	34	breaths/min				Y	1	Baseline	1	2022-06-19	1
7	ABC	VS	ABC-001-001	7	TEMP	Temperature		37.1	C	37.1	37.1	C			EAR	Y	1	Baseline	1	2022-06-19	1

Vital Signs Dataset

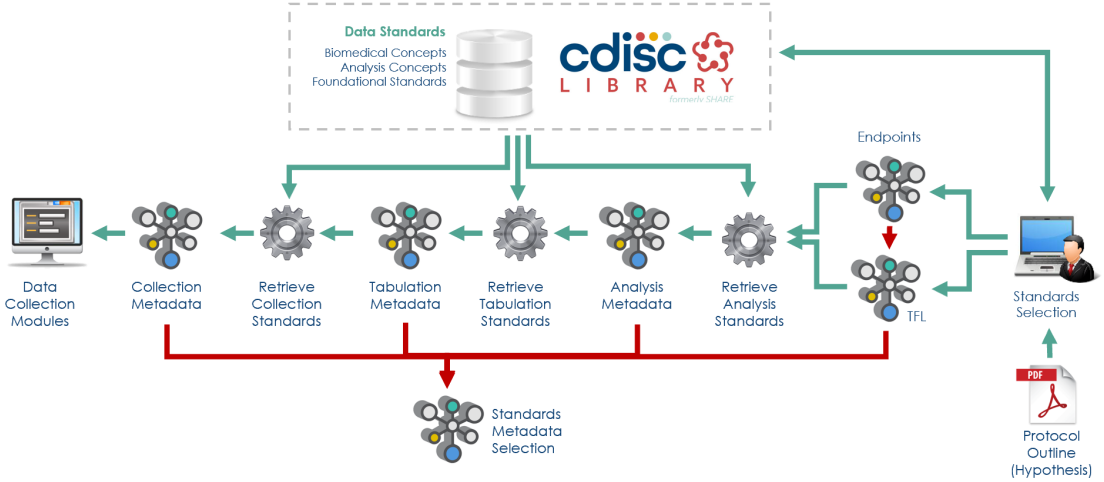
The Problem with This Approach

- Labor-intensive; requires extensive knowledge of standards documents
- Subject to interpretation (and therefore, *mis*interpretation)
- Can result in inconsistent implementation

The intense effort required is a barrier to standards adoption

How We Evolve: CDISC Library

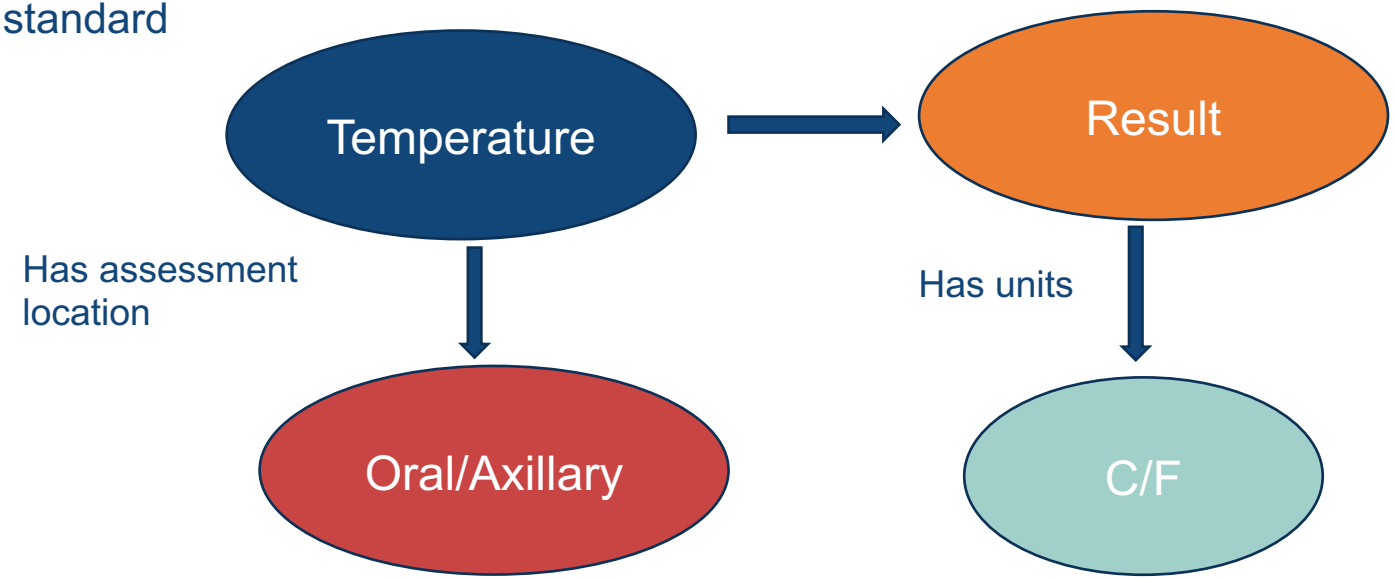
- Electronically publish data standards as groups of linked metadata
- Define relationships between variables, associated terminology codelists, and linkages across standards
- ***CDISC 360 Piloted development of linked biomedical concept metadata to enable end to end automation***



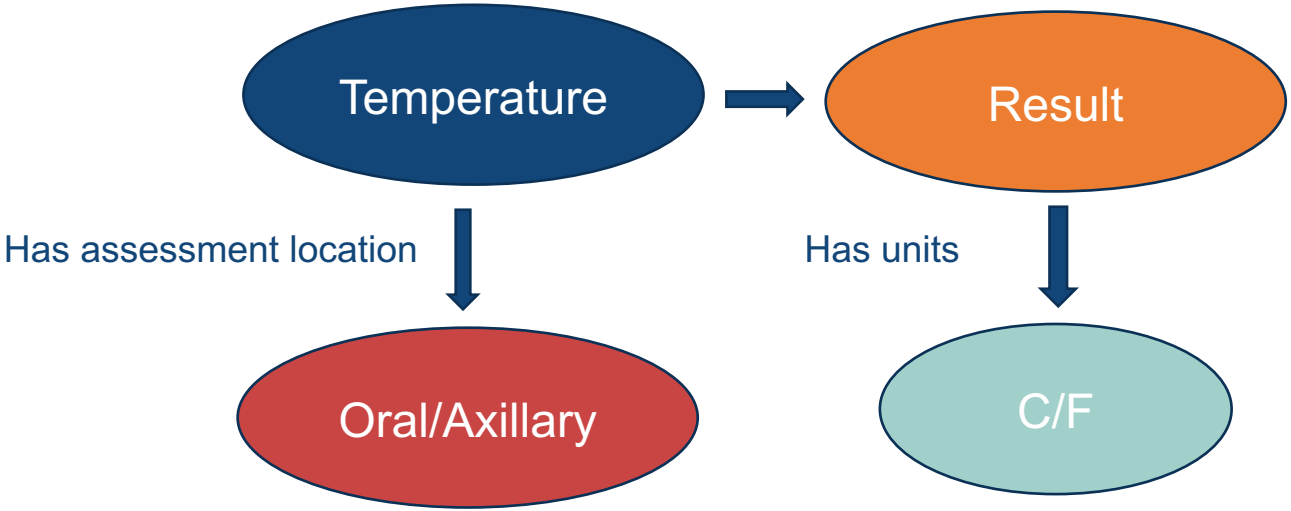
What is a Biomedical Concept (BC)?

ISO 11179 Definition: *A unit of knowledge created by a unique combination of characteristics*

- Independent of study
- Independent of a representation in any standard, but can be tethered to a standard



What Is a Biomedical Concept (BC)?



Conceptual Layer

VSTEST	VSTESTCD	VSORRES	VSUNIT	VSLOC
Temperature	TEMP	101.3	F	ORAL

Implementation Layer

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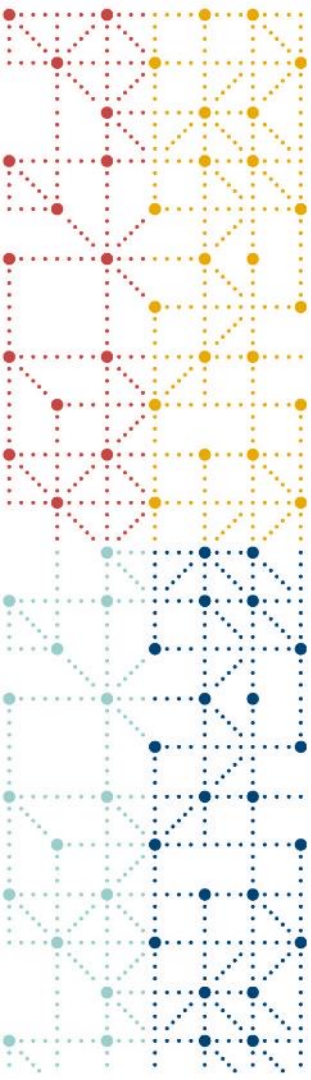

CDISC Biomedical Concepts

What are CDISC Biomedical Concepts?

A pragmatic, iterative approach to creating biomedical concepts with a focus on providing tangible value for the CDISC community

Key Objectives:

- Reduce barriers to operational implementation
- Reduce variability in standards implementations
- Increase metadata-driven automation

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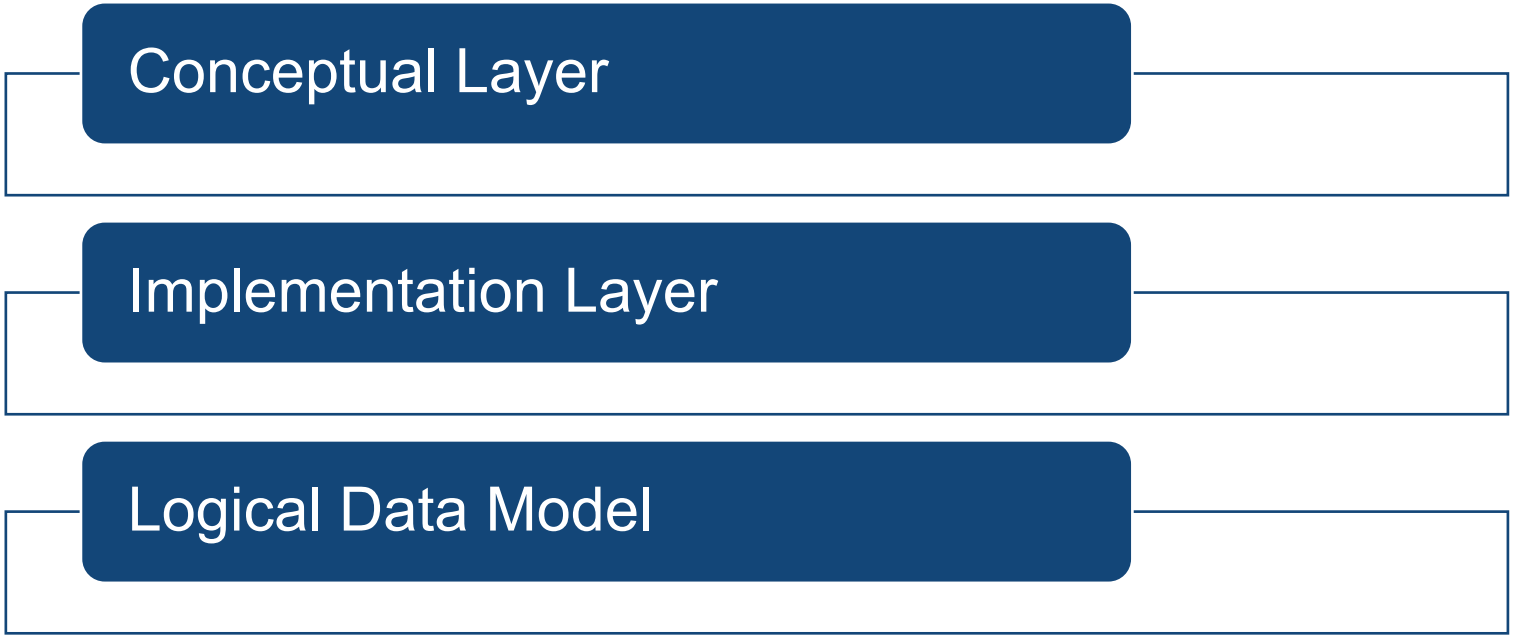
Key Components of CDISC BCs



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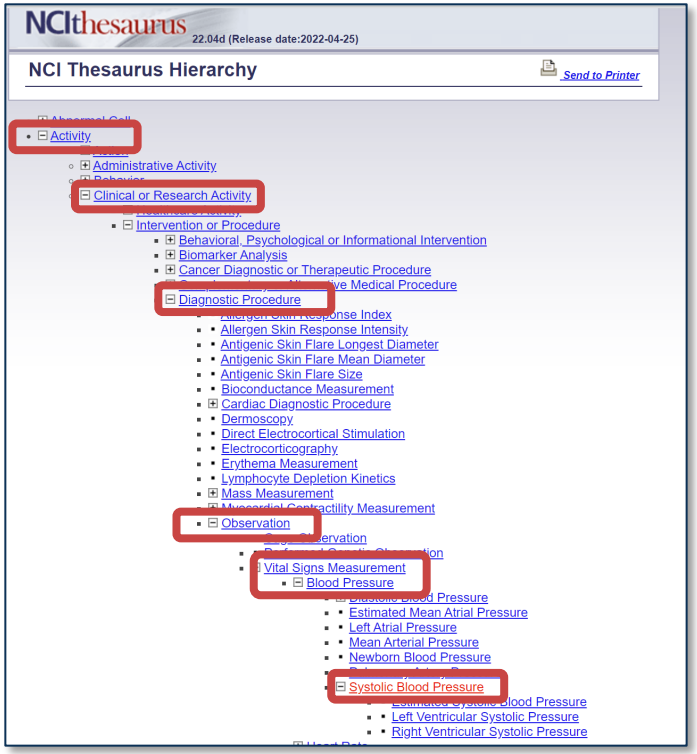
Conceptual Layer

- Rooted in NCI Hierarchy
- Consistent reference definitions provide consistent meaning across studies, all phases of development
- Data standard agnostic
- All indexed by C-Codes
- Provides for consistency in standards implementation



BC Curation Template (Conceptual Layer)

package_date	bc_categories	bc_id	ncit_code	parent_bc_id	short_name	synonyms	result_scales	definition	system	system_name	code	dec_id	ncit_dec_code	dec_label	data_type	example_set
2022-10-26	Vital Signs; Body Measurements	C164634	C164634		Body Height	Height	Quantitative	The vertical measurement or distance from the base to the top of a subject or participant.	http://loinc.org/	LOINC	8302-2					
2022-10-26	Vital Signs; Body Measurements	C164634	C164634		Body Height							C173522	C173522	Vital Signs Result	decimal	
2022-10-26	Vital Signs; Body Measurements	C164634	C164634		Body Height							C168688	C168688	Unit of Height	string	Centimeter; Inch; Millimeter; Meter
2022-10-26	Vital Signs; Body Measurements	C81328	C81328		Body Weight	Weight	Quantitative	The weight of a subject.	http://loinc.org/	LOINC	29463-7					
2022-10-26	Vital Signs; Body Measurements	C81328	C81328		Body Weight							C173522	C173522	Vital Signs Result	decimal	
2022-10-26	Vital Signs; Body Measurements	C81328	C81328		Body Weight							C48208	C48208	Unit of Weight	string	Kilogram; Gram; Pound

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SDTM BC Curation Template (Implementation Layer)

(a subset of model attributes shown)

package_date	bc_id	dec_id	sdtmig_start_version	sdtmig_end_version	domain	vlm_source	vlm_group_id	short_name	sdtm_variable	codelist	codelist_submision_value	value_list	assigned_term	assigned_value
2022-10-26	C164634		3-2		VS	VS.VSTESTCD	HEIGHT	Height	VSTESTCD	C66741	VSTESTCD		C25347	HEIGHT
2022-10-26	C164634		3-2		VS	VS.VSTESTCD	HEIGHT	Height	VSTEST	C67153	VSTEST		C25347	Height
2022-10-26	C164634	C173522	3-2		VS	VS.VSTESTCD	HEIGHT	Height	VSORRES					
2022-10-26	C164634	C168688	3-2		VS	VS.VSTESTCD	HEIGHT	Height	VSORRESU	C66770	VSRESU	in; cm; m		
2022-10-26	C164634	C173522	3-2		VS	VS.VSTESTCD	HEIGHT	Height	VSSTRESC					
2022-10-26	C164634	C173522	3-2		VS	VS.VSTESTCD	HEIGHT	Height	VSSTRESN					
2022-10-26	C164634	C168688	3-2		VS	VS.VSTESTCD	HEIGHT	Height	VSSTRESU	C66770	VSRESU			
2022-10-26	C81328		3-2		VS	VS.VSTESTCD	WEIGHT	Weight	VSTESTCD	C66741	VSTESTCD		C25208	WEIGHT
2022-10-26	C81328		3-2		VS	VS.VSTESTCD	WEIGHT	Weight	VSTEST	C67153	VSTEST		C25208	Weight
2022-10-26	C81328	C173522	3-2		VS	VS.VSTESTCD	WEIGHT	Weight	VSORRES					
2022-10-26	C81328	C48208	3-2		VS	VS.VSTESTCD	WEIGHT	Weight	VSORRESU	C66770	VSRESU	kg; LB; g		
2022-10-26	C81328	C173522	3-2		VS	VS.VSTESTCD	WEIGHT	Weight	VSSTRESC					
2022-10-26	C81328	C173522	3-2		VS	VS.VSTESTCD	WEIGHT	Weight	VSSTRESN					
2022-10-26	C81328	C48208	3-2		VS	VS.VSTESTCD	WEIGHT	Weight	VSSTRESU	C66770	VSRESU			

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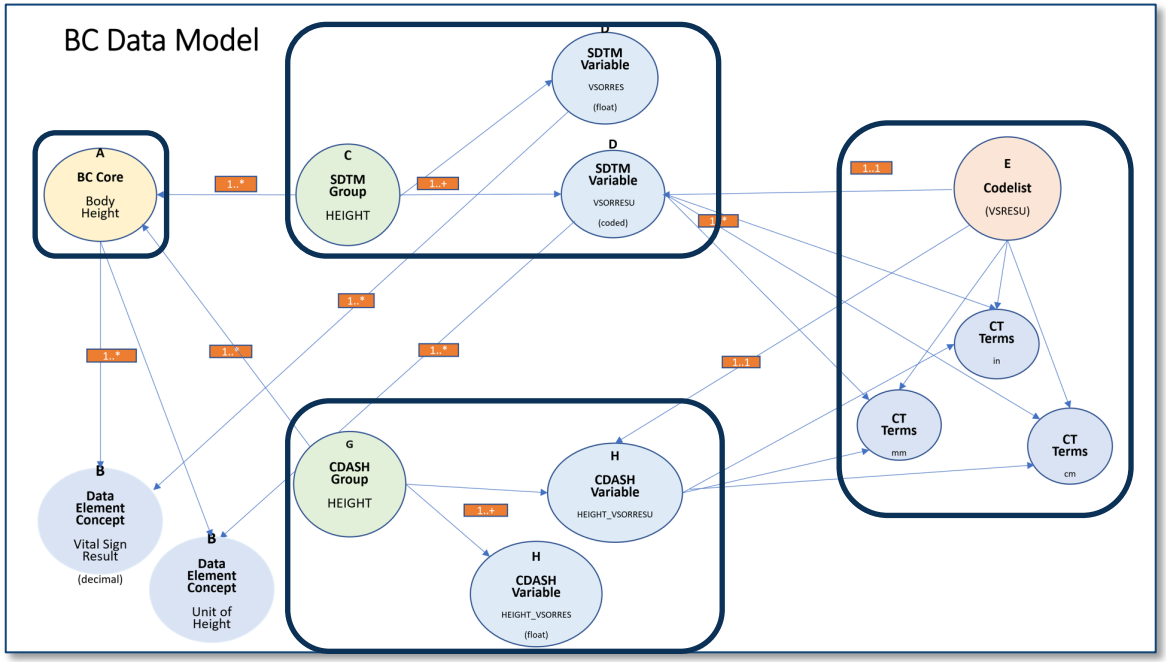
Logical Data Model

- Concept specific value level metadata
- Add explicit relationships between variables
- Additional operational metadata, e.g., data type, format, etc.
- Creation of structured machine-readable YAML files validated with conformance rules
- Searchable and retrievable via CDISC Library APIs



Focus on your data. Let the standards come to YOU

Your data
"shopping list"

CDISC
Library

Retrieve your BCs as
machine-readable files

vs.xpt

Row	STUDYID	DOMAIN	USUBJID	VSSEQ	VSTESTCD	VSTEST	VSPOS	VSORRES	VSORRESU	VSSTRESC	VSSTRESN	VSSTRESU	VSSTAT	VSREASND	VSLOC	VSLOBXFL	VISITNUM	VISIT	VISITDY	VSDTC	VSDY
1	ABC	VS	ABC-001-001	1	SYSBP	Systolic Blood Pressure	SITTING	154	mmHg	154	154	mmHg			BRACHIAL ARTERY	Y	1	Baseline	1	2022-06-19T08:45	1
2	ABC	VS	ABC-001-001	2	DIABP	Diastolic Blood Pressure	SITTING	44	mmHg	44	44	mmHg			BRACHIAL ARTERY	Y	1	Baseline	1	2022-06-19T08:45	1
3	ABC	VS	ABC-001-001	3	HEIGHT	Height		178	cm	178	178	cm				Y	1	Baseline	1	2022-06-19	1
4	ABC	VS	ABC-001-001	4	WEIGHT	Weight		90.5	kg	90.5	90.5	kg				Y	1	Baseline	1	2022-06-19	1
5	ABC	VS	ABC-001-001	5	PULSE	Pulse Rate		72	beats/min	72	72	beats/min			CAROTID ARTERY	Y	1	Baseline	1	2022-06-19	1
6	ABC	VS	ABC-001-001	6	RESP	Respiratory Rate		34	breaths/min	34	34	breaths/min				Y	1	Baseline	1	2022-06-19	1
7	ABC	VS	ABC-001-001	7	TEMP	Temperature		37.1	C	37.1	37.1	C			EAR	Y	1	Baseline	1	2022-06-19	1

You're most of the way there towards implementing CDISC for your data!

Initial Biomedical Concept Use Cases

Retrieve a List of Assessments for a Study

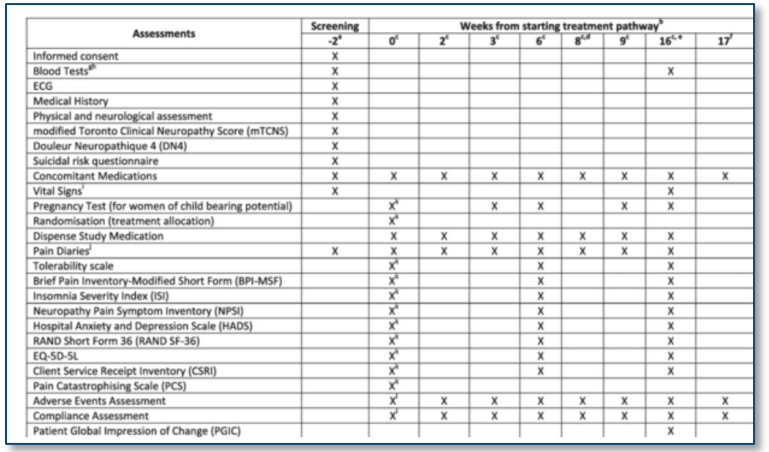
Publish BC content as Define-XML document including Value Level Metadata

Use Case 1: Support Study Design – Schedule of Assessments

Biomedical Concepts – Conceptual Layer for SOA

Current Way of Working and Issues

- Protocol isn't specific enough to facilitate data collection
- Translation to EDC setup requires further work
- Time and effort can be significant and costly
- Forms are used to attempt standardization but proliferate over time



Assessments	Screening	Weeks from starting treatment pathway[3]							
	-2[3]	0[c]	2[c]	3[c]	6[c]	8[c,d]	9[c]	16[c,e]	17[f]
Informed consent	X								
Blood Tests[gh]	X							X	
ECG	X								
Medical History	X								
Physical and neurological assessment	X								
modified Toronto Clinical Neuropathy Score (mTCNS)	X								
Douleur Neuropathique 4 (DN4)	X								
Suicidal risk questionnaire	X								
Concomitant Medications	X	X	X	X	X	X	X	X	X
Vital Signs[i]	X							X	
Pregnancy Test (for women of child bearing potential)		X[a]		X	X		X	X	
Randomisation (treatment allocation)		X[a]							
Dispense Study Medication		X	X	X	X	X	X	X	
Pain Diaries[j]	X	X	X	X	X	X	X	X	
Tolerability scale		X[a]			X			X	
Brief Pain Inventory-Modified Short Form (BPI-MSF)		X[a]			X			X	
Insomnia Severity Index (ISI)		X[a]			X			X	
Neuropathy Pain Symptom Inventory (NPSI)		X[a]			X			X	
Hospital Anxiety and Depression Scale (HADS)		X[a]			X			X	
RAND Short Form 36 (RAND SF-36)		X[a]			X			X	
EQ-5D-5L		X[a]			X			X	
Client Service Receipt Inventory (CSRI)		X[a]			X			X	
Pain Catastrophising Scale (PCS)		X[a]							
Adverse Events Assessment		X[l]	X	X	X	X	X	X	X
Compliance Assessment		X[l]	X	X	X	X	X	X	X
Patient Global Impression of Change (PGIC)								X	

Use Case 1

Support Study Design - SOA

Biomedical Concepts – Conceptual Layer for SOA

- BCs are retrievable standards agnostic assessments for a study SOA
- They include pointers to pre-configured SDTM and CDASH dataset specializations
- BC provide unambiguous information for EDC setup and dataset creation
- BCs are more than just a term, e.g., Heart Rate is collected as an integer and includes a term with allowable units, body positions, etc.
- Preconfigured BCs linked to CDASH and SDTM dataset specializations facilitate automation around study setup and SDTM delivery

Use Case 2: Define-XML – Value Level Metadata

Pre-configured Define-XML Building Blocks

- Practical implementation of BCs as at the SDTM implementation layer
- Pre-configured and ready to go value level metadata
- Templates to support consistent curation
- Fully opinionated and out of the box – allows for tweaks as needed
- Immediate benefit to data management and programming producing SDTM

VS (Vital Signs) - [SDTMIG 3.1.2]

Related Supplemental Qualifiers Dataset: SUPPVS (Supplemental Qualifiers for VS)

Variable	Where Condition	Label / Description	Type	Length or Display Format	Controlled Terms or ISO Format
VSORRES VLM		Result or Finding in Original Units	text	30	
	VSTESTCD = "DIABP" (Diastolic Blood Pressure)	Diastolic Blood Pressure in Orig U	integer	2	
	VSTESTCD = "FRMSIZE" (Body Frame Size)	Body Frame Size - Orig	text	6	Size • "SMALL" • "MEDIUM" • "LARGE"
	VSTESTCD = "HEIGHT" (Height)	Height in Orig U	float	5.1	


```
{
    "name": "VSTESTCD",
    "isNonStandard": false,
    "codelist": {…
    },
    "assignedTerm": {
        "conceptId": "C25347",
        "value": "HEIGHT"
    },
    "role": "Topic",
    "relationship": {
        "subject": "VSTESTCD",
        "linkingPhrase": "is decoded by the value in",
        "predicateTerm": "IS_DECODED_BY",
        "object": "VSTEST"
    },
    "comparator": "EQ",
```

BCs now available via CDISC Library API as JSON output

Biomedical Concepts (BC)

- GET /mdr/bc/packages
- GET /mdr/bc/packages/{package}/biomedicalconcepts
- GET /mdr/bc/packages/{package}/biomedicalconcepts/{biomedicalconcept}
- GET /mdr/bc/packages/{package}/biomedicalconcepts/{biomedicalconcept}/dataelementconcepts
- GET /mdr/bc/packages/{package}/biomedicalconcepts/{biomedicalconcept}/dataelementconcepts/{dataelementconcept}

Study Data Tabulation Model Dataset Specializations (SDTM)

- GET /mdr/specializations/sdtm/packages
- GET /mdr/specializations/sdtm/packages/{package}/datasetspecializations
- GET /mdr/specializations/sdtm/packages/{package}/datasetspecializations/{datasetspecialization}
- GET /mdr/specializations/sdtm/packages/{package}/datasetspecializations/{datasetspecialization}/variables
- GET /mdr/specializations/sdtm/packages/{package}/datasetspecializations/{datasetspecialization}/variables/{variable}

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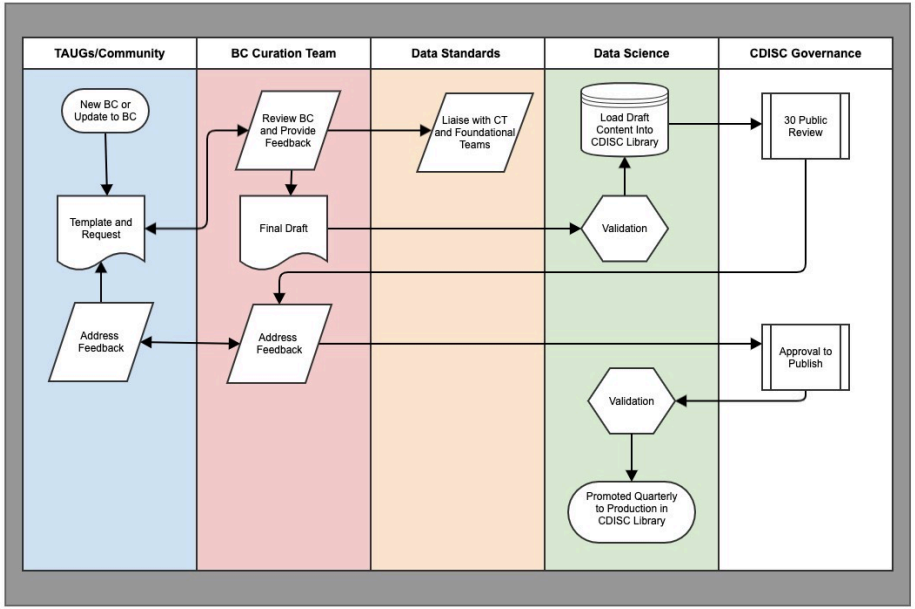
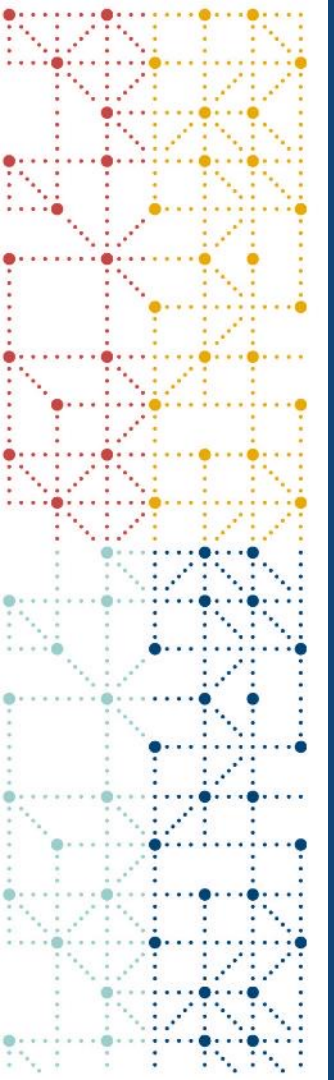
BC Governance

- Light-weight CDISC curation and governance process
- 30-day Public Review
- Published quarterly
- Mechanism for community change requests



Draft governance process



Looking Towards the Future

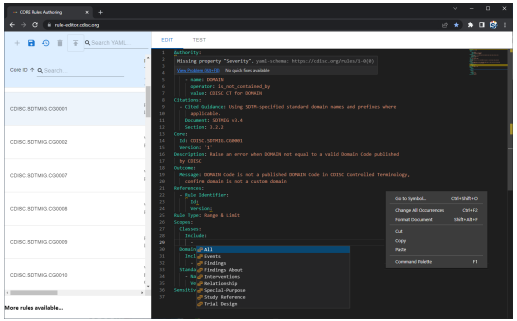
- Adding CDISC Library functionality
- Adding to conceptual and implementation layers

Adding Functionality to CDISC Library

- Searchable and Retrievable BCs via CDISC Library APIs and Data Standards Browser

cdisc LIBRARY Data Standards Browser

- Web-based editor for BC authoring



Adding to Conceptual and Implementation Layers

- End to end standardization
  - Addition of Collection and Analysis Concepts
  - Derivations and transformations
- Use by Digital Data Flow to generate schedule of assessments
- Development of BCs for all new standards
- Community collaboration through the donation and curation of BCs

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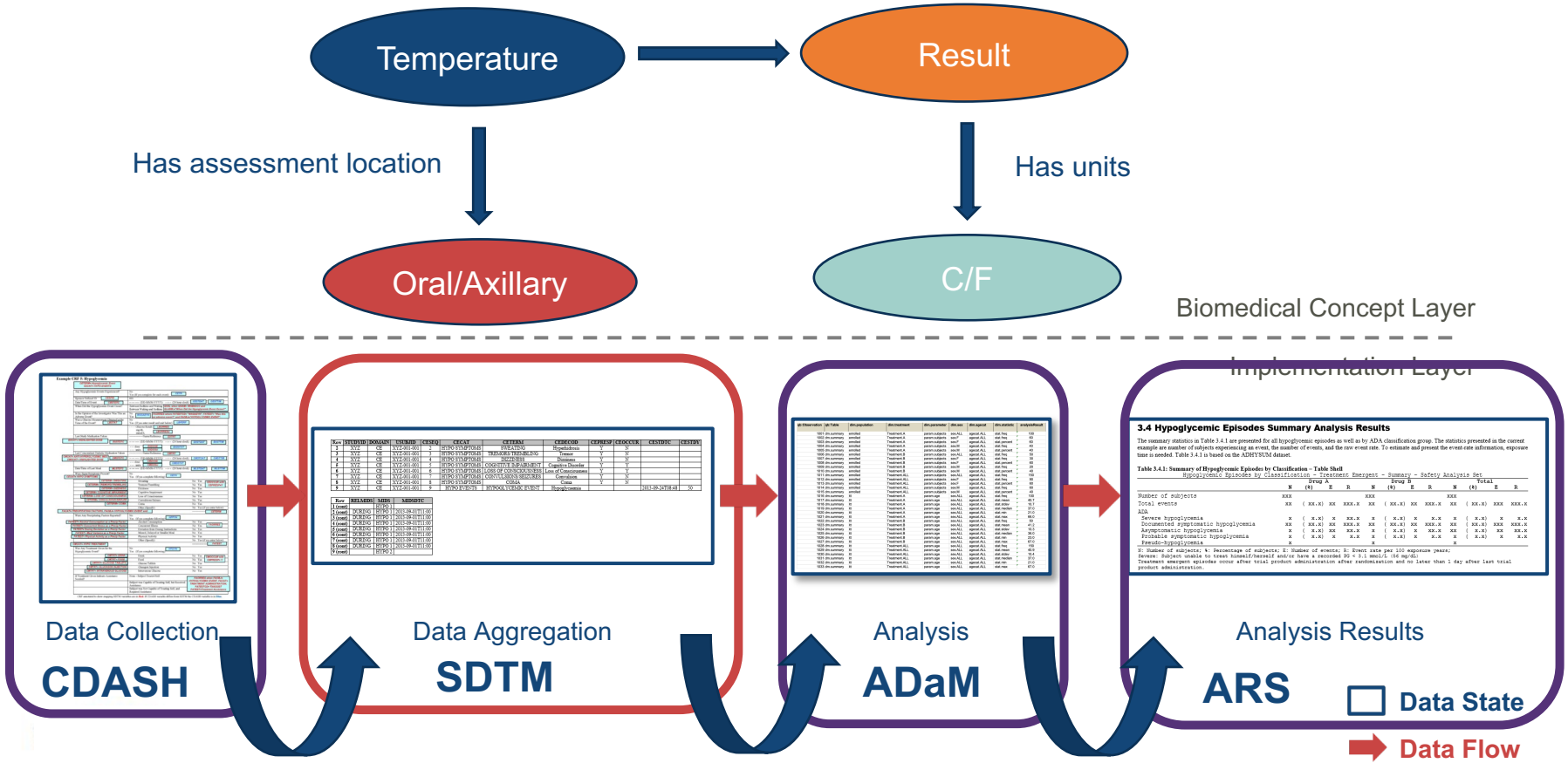
End to End Standardization: Expanding the Implementation Layer



Use of BCs in TransCelerate Digital Data Flow Initiative (DDF)

TransCelerate BIOPHARMA INC.

- The DDF initiative aims to modernize clinical trials by enabling a digital workflow to allow for the automated creation of study assets and configuration of study systems to support clinical trial execution.

- Use of BCs to support schedule of assessments: SEVERE COVID-19 PNEUMONIA (Roche)

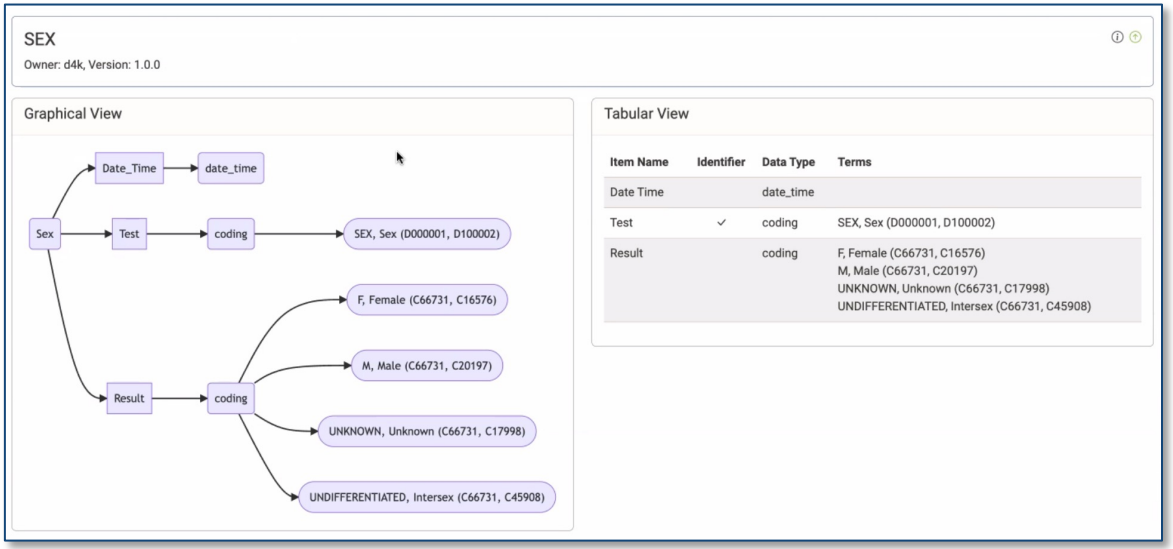
Appendix 1
Schedule of Activities: Days 1 and 2

	Screening [a, b]	Baseline			
Study Day	–2 to 0	1		2	
Time Post Initial Treatment (Assessment Window)		0 Pre-dose (–4 hrs)	15 min After end of infusion (+1 hr)	24 hrs (±4 hrs)	36 hrs (±4 hrs)
Informed consent	x				
Inclusion/exclusion criteria	x	x			
Demographic data	x				
Randomization		x			
Medical history		x			
Complete physical examination [c]	x				
Weight		x			
COVID-19 diagnosis [d]	x				
Chest X-ray/CT scan [e]	x				
ECG	x				
Pregnancy test [f]	x				
PaO_2/FiO_2 [g]	x	← Optional →			
SpO_2 [h]	x	x	x	x	x
Vital signs [h]	x	x	x	x	x
Ordinal scoring [i]		x		x	
Adverse events [j]		x		x	
Concomitant medications [k]		x		x	

Using BCs to Build Schedule of Assessments

- Schedule of assessments consists of groupings of biomedical concepts

- Demographics
  - Sex
  - Date of Birth
  - Age
  - Race
  - Ethnicity



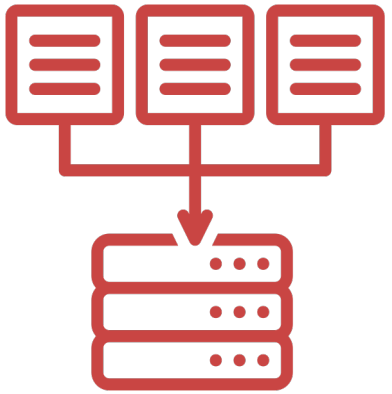
Development of BCs for Therapeutic Areas

- Oncology Team authoring BCs using CDISC framework for Disease Response Criterion standards

- Tobacco Implementation Guide (TIG)

Additional Sources of BCs

- Donation of company created BCs
- Mining datasets
- Code Table mapping files
- LOINC to LB mapping
- NCI Thesaurus



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Summary/Conclusions

- BCs provide consistent meaning around collected concepts
  - Everyone is speaking the same language
  - Conceptual layer details provide for easily browsable catalog to drill down into the data you need to collect
- BCs have the power to significantly lower barriers to implementation of standards
  - Start with the concepts. The standards implementation details come along with them
  - Sponsors no longer need to spend as much effort poring over documentation to match their data with implementation details
- BCs provide consistent implementation of standards

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Thank You!

A special thank you to Lex Jansen and Linda Lander