WITH STANDARDS – UNLOCK THE POWER OF DATA

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2022
US
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26-27 OCTOBER | AUSTIN

CDISC's Activities on DDF, Benefits for the Community, and Looking Ahead

Presented by D Iberson-Hurst
Partner d4k & CDISC DDF Product Owner

Meet the Speaker

Dave Iberson-Hurst

Title: **Partner**

Organization: **d4k, Copenhagen**

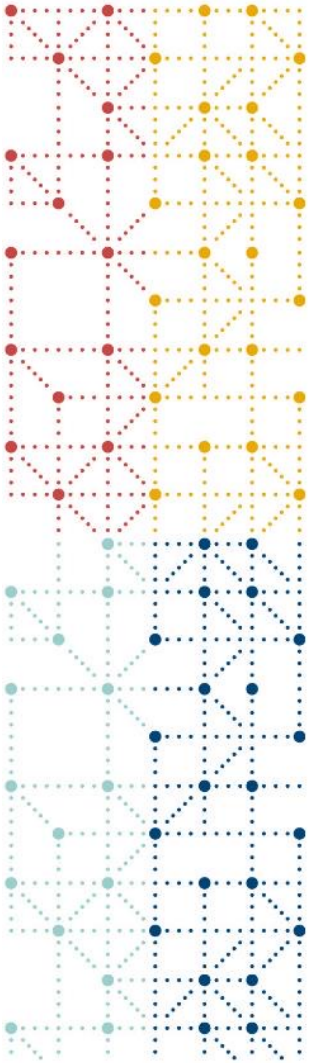
Dave has over 40 years' experience across several industries with the last 20 years spent in the pharmaceutical industry combining his technology and software development experience with clinical data standards.

During this time, he has worked on, and led, several CDISC teams, presented in many forums in Europe, the US, and elsewhere across the globe. He has worked closely with the FDA, EMA, HL7, ISO, and other standards organizations and was was a member of CDISC's Blue Ribbon commission.

He is a partner at data4knoweldge in Copenhagen and is focused on getting greater value and utility from clinical trial data.

Disclaimer and Disclosures

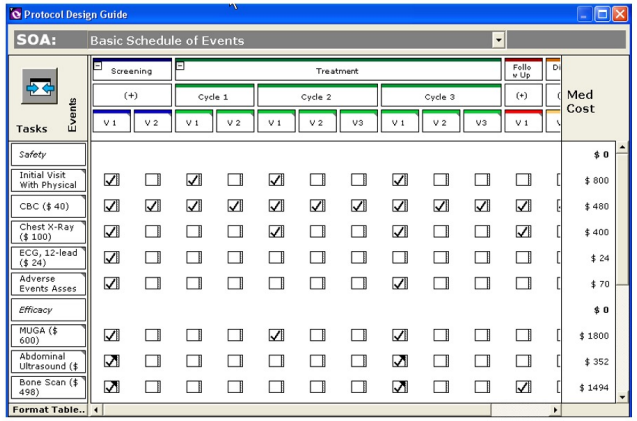
- *The views and opinions expressed in this presentation are those of the author(s) and do not necessarily reflect the official policy or position of CDISC.*
- *On contract to CDISC for the DDF work*



Agenda

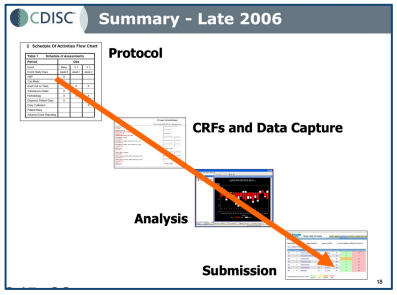
1. Introduction
2. DDF - The Project
3. The Challenges
4. Benefits and Use Cases
5. Looking Forward
6. Summary

Montreux, 2007



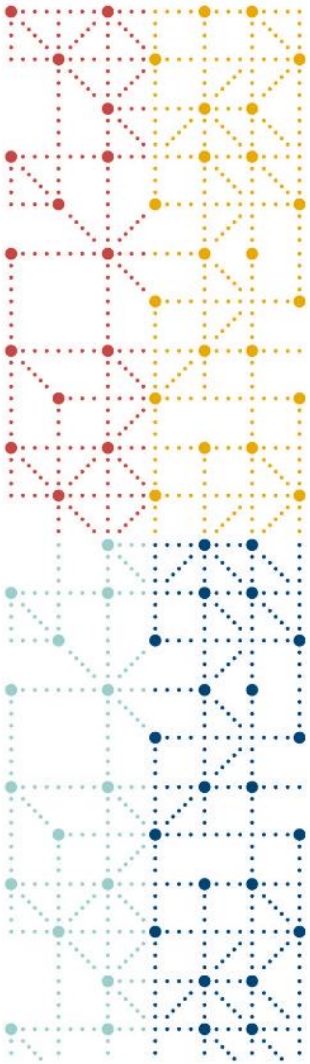
Generating the Schedule of Activities and study schema in TSD generates data reusable by clinical trial execution systems. For example: the structure and timing of periods, sub-periods, and visits.

borative environment for study design and protocol authoring environment



– Word based environment that collects Deep Structured Trial Design Information in XML

– Most relevant to this discussion…
  - Planned Interventions and Procedures
  - Clinical variables mapped to Procedures
  - Schedule of Activities
    – What activities at which events
    – Events built into superstructure of elements and arms
    – Formal Designs: Crossover, Titration, Adaptive
    – Conditionality: go here if...., do this if…
    – Iterations: cycles...
    – Continuous events... diary, concomitant meds
    – Unplanned events... SAE



Digital Data Flow - The Project

CDISC DDF Phase One

July, 2021 – July 2022

Unified Study Definitions Model (USDM) Class Diagram
The UML class diagram (normative) as well as SQL Data Dictionary, Entity Relationship Diagram and example JSON output (informative)

Application Programming Interface (API) Specification
The API definition (normative) in JSON and HTML forms

CDISC Controlled Terminology
The controlled terminology (normative) developed for the project. Provided in an Excel format so as to be easily searched and filtered.

Reference Architecture Conformance Tests
Provided by the functionality provided by tools such as SwaggerHub and Postman

Essential Users Stories
The User Stories. PDF document

Architecture Principles
The architectural principles developed by the project. PDF Document

Supporting Materials
A set of informational materials in PDF format to help understand the deliverables being reviewed. PDF documents or references.

V1.0 Provisional
https://www.cdisc.org/ddf

CDISC DDF Phase Two

Oct, 2022 – June 2023

Unified Study Definitions Model (USDM) Class Diagram
The UML class diagram (normative) as well as SQL Data Dictionary, Entity Relationship Diagram and example JSON output (informative)

Application Programming Interface (API) Specification
The API definition (normative) in JSON and HTML forms

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The controlled terminology (normative) developed for the project. Provided in an Excel format so as to be easily searched and filtered.

Test Files
Examples of USDM JSON files

Implementation Guide
Improved explanation of the model and its use, examples etc

Unified Study Definitions Model (USDM) Class Diagram

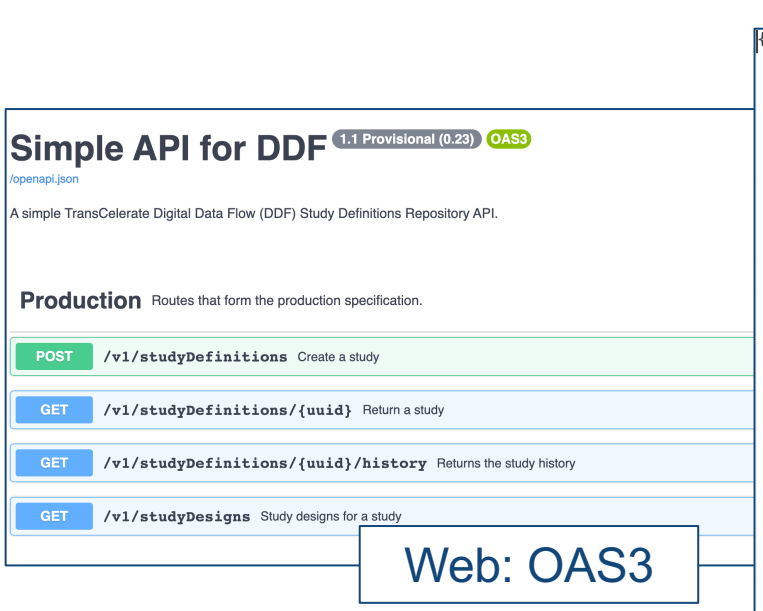
The UML class diagram (normative) as well as SQL Data Dictionary, Entity Relationship Diagram and example JSON output (informative)

UML

Screen shots are illustrative and from earlier versions and may have changed for the public review

Application Programming Interface (API) Specification

The API definition (normative) in JSON and HTML forms



Web: OAS3

JSON


```
{
  "openapi": "3.0.0",
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    "title": "Simple API for DDF",
    "description": "This is a sample API for the DDF project - including sectioning (Acc
    "license": {
      "name": "MIT",
      "url": "https://opensource.org/licenses/MIT"
    },
    "version": "1.2.6"
  },
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    }
  ],
  "paths": {
    "/studydefinitionrepository/v1/{study}": {
      "get": {
        "tags": [
          "default"
        ],
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        "description": "Get Study Build  Sections",
        "operationId": "get.studydesignrepository.sections",
        "parameters": [
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            "in": "path",
            "description": "Study Builder Study",
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            "style": "simple",
            "explode": false,
            "schema": {
              "type": "string",
              "example": "ACME001"
            }
```

CDISC Controlled Terminology

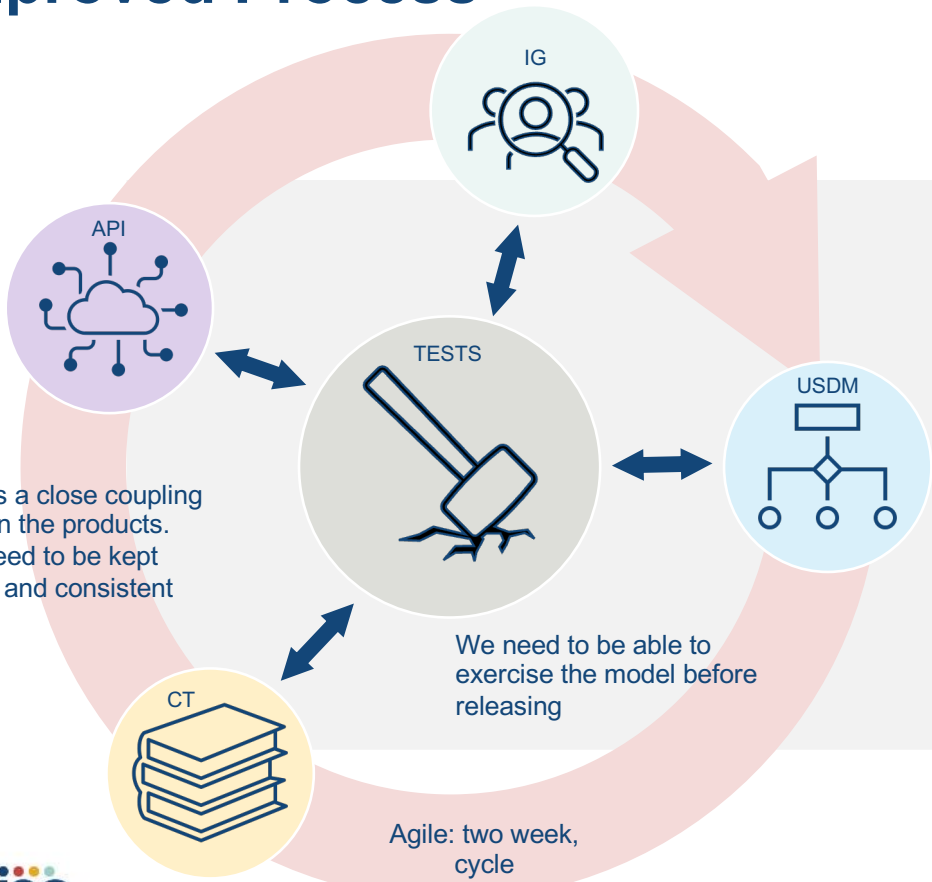
The controlled terminology (normative) developed for the project. Provided in an Excel format so as to be easily searched and filtered.

Row #	UML Class Name	UML Item Name	Role	NCI C-code	CT Item Preferred Name	Synonym(s)	Definition	Has Value List
1	STUDY	STUDY	Entity	C15206	Clinical Study		A clinical study involves research using human volunteers (also called participants) that is intended to add to medical knowledge. There are two main types of clinical studies: clinical trials (also called interventional studies) and observational studies. [[http://ClinicalTrials.gov]](CDISC Glossary)	N
2	STUDY	study_title	Attribute	C49802	Study Title	Trial Title; Official Study Title; Study Title	The sponsor-defined name of the clinical study.	N
3	STUDY	study_version	Attribute	C93490	Study Protocol Version		A plan at a particular point in time for a formal investigation to assess the utility, impact, pharmacological, physiological, and/or psychological effects of a particular treatment, procedure, drug, device, biologic, food product, cosmetic, care plan, or subject characteristic. (BRIDG)	N
4	STUDY	study_status	Attribute	CNEW	Protocol Status		A condition of the protocol at a point in time with respect to its state of readiness for implementation.	Y (CNEW Protocol Status Response)
5	STUDY	study_protocol_version	Attribute	C93490	Study Protocol Version		A plan at a particular point in time for a formal investigation to assess the utility, impact, pharmacological, physiological, and/or psychological effects of a particular treatment, procedure, drug, device, biologic, food product, cosmetic, care plan, or subject characteristic. (BRIDG)	N
6	STUDY_TYPE	STUDY_TYPE	Entity	C142175	Study Type	Study Type; Study Type Classification	The nature of the investigation for which study information is being collected. (After clinicaltrials.gov)	N
7	STUDY_TYPE	study_type_desc	Attribute	C142175	Study Type Classification	Study Type; Study Type Classification	The nature of the investigation for which study information is being collected. (After clinicaltrials.gov)	Y (C99077 STYPE)
8	STUDY_PHASE	STUDY_PHASE	Entity	C48281	Trial Phase	Trial Phase; Trial Phase Classification	A step in the clinical research and development of a therapy from initial clinical trials to post-approval studies. NOTE: Clinical trials are generally categorized into four (sometimes five) phases. A therapeutic intervention may be evaluated in two or more phases simultaneously in different trials, and some trials may overlap two different phases. [21 CFR section 312.21; After ICH Topic E8 NOTE FOR GUIDANCE ON GENERAL CONSIDERATIONS FOR CLINICAL TRIALS, CPMP/ICH/291/95 March 1998]	N
9	STUDY_PHASE	study_phase_desc	Attribute	C48281	Trial Phase Classification	Trial Phase; Trial Phase Classification	A step in the clinical research and development of a therapy from initial clinical trials to post-approval studies. NOTE: Clinical trials are generally categorized into four (sometimes five) phases. A therapeutic intervention may be evaluated in two or more phases simultaneously in different trials, and some trials may overlap two different phases. [21 CFR section 312.21; After ICH Topic E8 NOTE FOR GUIDANCE ON GENERAL CONSIDERATIONS FOR CLINICAL TRIALS, CPMP/ICH/291/95 March 1998]	Y (C66737 TPHASE)
10	STUDY_IDENTIFIER	STUDY_IDENTIFIER	Entity	C83082	Study Identifier		A sequence of characters used to identify, name, or characterize the study.	N
11	STUDY_IDENTIFIER	org_code	Attribute	CNEW	Study Identifier Organization Code		A coded value specifying the organization that creates and/or assigns the study identifier.	N
12	STUDY_IDENTIFIER		Attribute	CNEW	Study Identifier Name		The literal identifier (i.e., distinctive designation) of the sequence	

DDF Entities&Attributes | DDF Valid Value Sets

EXCEL

Improved Process



There is a close coupling between the products. They need to be kept aligned and consistent

We need to be able to exercise the model before releasing

Agile: two week, cycle

Deliver regular and consistent USDM, CT and API increments every two weeks* with associated test materials of API examples.

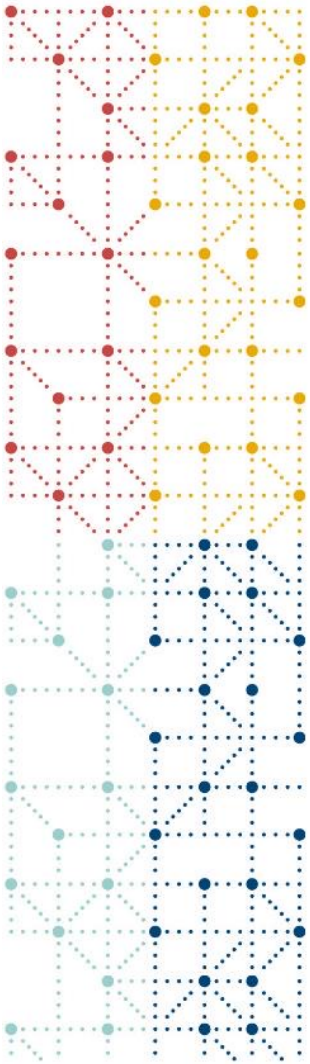
Be able to regression test the model and build a library of USDM study designs.

Doing this as part of model development de-risks the ACCN & TCB programmes

** May be adjusted to reflect next work item*

TCB, ACCN

CDISC Community



The Challenges

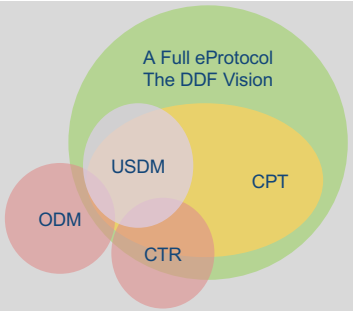
Challenges and Choices …

- Choices
  - Recreate the current world or look for something better?
  - How radical do we wish to be?
  - Don't just want to recreate the "paper world"
- DDF is not a "normal" CDISC project, it has technical and content aspects
- Scope and perspective of the participants
- The project exposes the complexity of our world

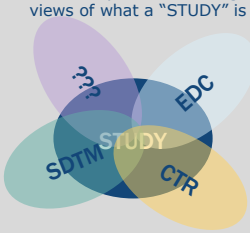
Challenges and Standards

CT standards may also inform the process. SNOMED, MedDRA, LOINC all have "models" behind their content

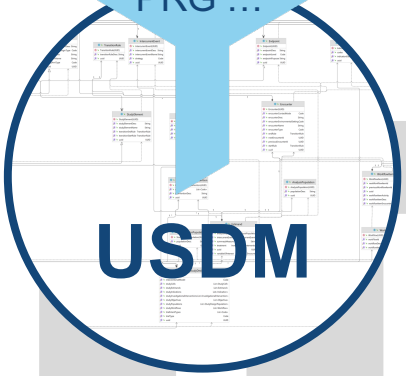
Every standard has something to say about some USDM related information



"Semantics"
An example, the differing views of what a "STUDY" is



SDTM, BRIDG, ICH M11, PRG …



The important "human readable" form.

Key question: Should USDM support the whole eProtocol … AND / OR … Should SDR being able to generate the complete protocol?

XML standards are about getting information from A to B, from system to system. But, they define content, semantics, definitions etc.

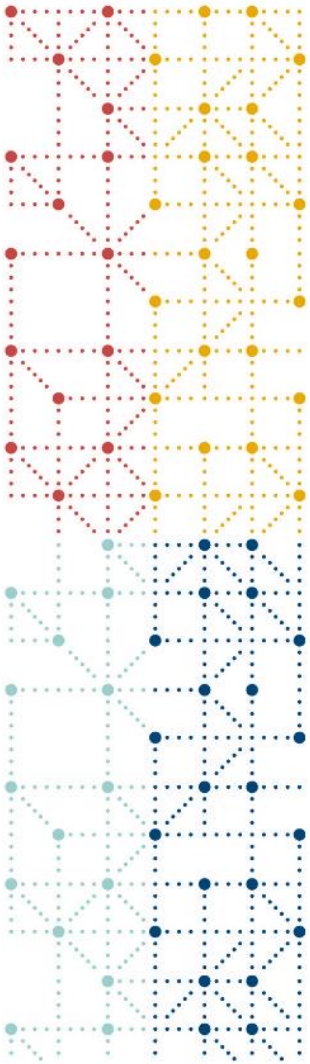
Other standards define models and content, controlled terms etc.

But these overlap.

BRIDG has Inclusion / Exclusion criteria models. So does CTR, so does SDTM, all subtly different.

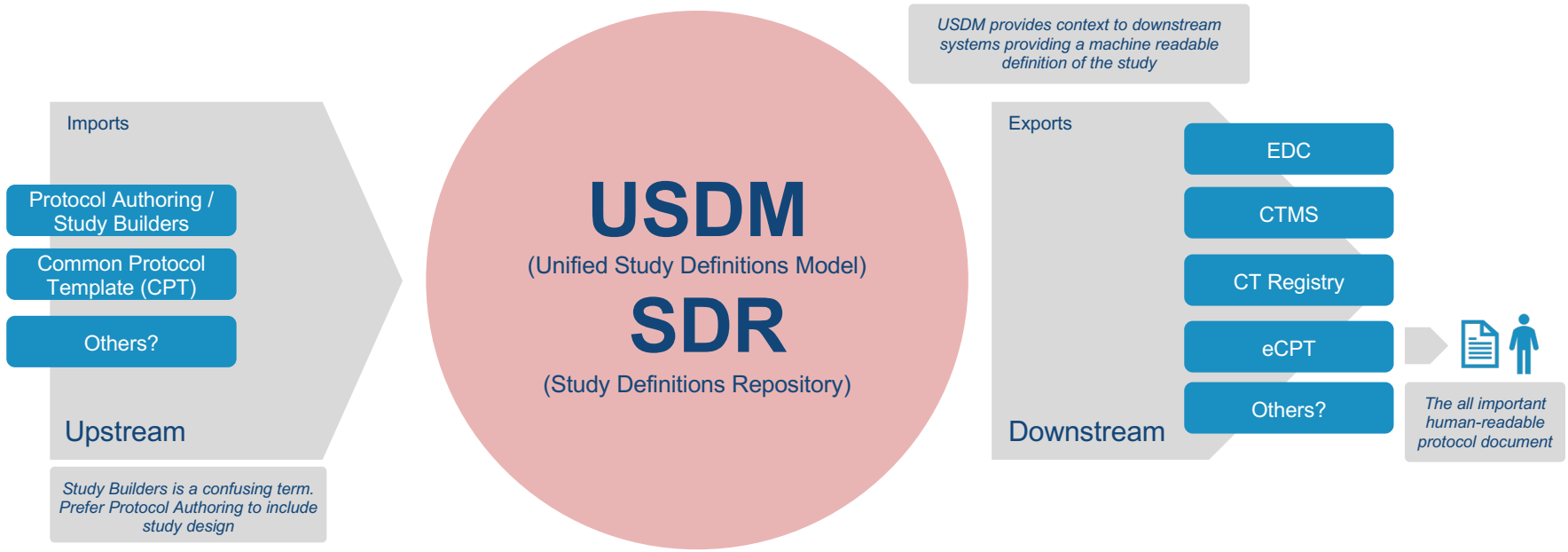
CPT XML, Rest API, CTR XML …

ODM, Rest API, ALS, CTR XML, HL7 Vulcan SoA, CPT XML …



Benefits and Use Cases

Overview and Benefits



- Speed of execution, stems from the automation which comes from a common understanding
- Data Quality resulting from better context and consistency
- Data Utility, the ability to reuse data when the context is available
- APIs will facilitate building of systems and eco systems
- A single source [of truth] for the protocol

Example Use Cases … There Are Many

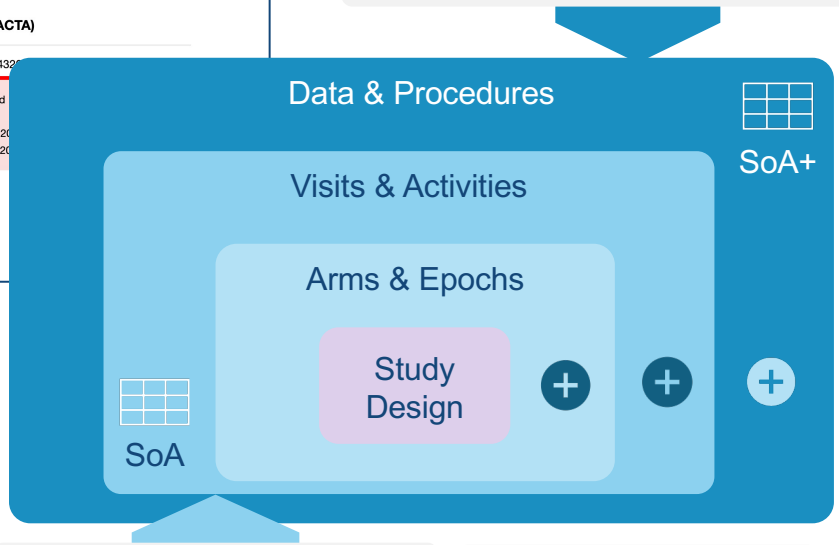
USDM
(Unified Study Definitions Model)
SDR
(Study Definitions Repository)

Data Capture	*Setup of data capture systems with sufficient information to automate the process as much as possible incl. RWE*
CTMS / TMF	*The provision of protocol information to down stream systems needing "study" information*
CT Registry	*The provision of study information to a CT registry*
Common Protocol Template (CPT)	*Generation of the CPT from a study design* 
Data Decay	*Re-import data using the USDM as a framework to rebuild a study design based on the SDTM Trial Design Domains*
Scoring	*The "scoring" of a study for such purposes as site impact, subject impact, environmental impact etc.*
Feasibility	*The use of the design to determine study feasibility including subject recruitment.*
FAIR Data	*The use of the design to aid Findability, Accessibility, Interoperability, and Reusability*

The Data Capture Use Case (EDC)

Increasing Detail

Provide precision on the data to be captured to the capture systems in a generic manner to facilitate automation. The data precision has not, typically, been in the "paper" protocol. It is SoA "plus", SoA+



Current "Limit"

SoA is where we are today with associated footnotes and free text. Activities sit at a CRF form "level"

Technology Independent

Definition should be independent of any capture technology

Capability Level Approach

1. PDF of protocol. Manual copy/creation of EDC forms.
2. SoA can be taken from SDR. Forms names can be matched to Activity names.
3. Level Two plus employ StudyData (observation) names to inform a better form search.
4. Level Three plus StudyData crfLink can be employed to link to EDC resources.
5. Level Four plus introduce BCs and use a mix of levels two, three and four alongside BCs.
6. Level Five plus maximise the use of BCs with EDC libraries migrating to BC based composition

Increasing Detail – SoA

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				
		x			
Demographic data	x				
		x			
Medical history		x			

Study Tocilizumab in Patients With Severe COVID-19 Pneumonia - WA42380

Owner: , Version: 0.1.0

	Screening	Treatment	Treatment	Treatment	Treatment	Treatment	Treatment	Treatment
	Screening	Baseline	Day 1	Day 2A	Day 2B	Day 3	Day 4	Day 5
Informed consent	X							
Inclusion/exclusion criteria	X	X						
Demographics	X							

Increasing Detail – Observations

Appendix 1
Schedule of Activities: Days 1 and 2

	Screening[a, b]	Baseline			
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Informed consent	x				
		x			
Demographic data	x				
		x			
Medical history		x			

4.5.2 Medical History, Baseline Conditions, Concomitant Medication, and Demographic Data

Medical history, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, home oxygen use, will be recorded at baseline. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient within 7 days prior to first dose of study drug will be recorded. At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded.

Demographic data will include age, sex, and self-reported race/ethnicity.

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	Screening	Baseline	Day 1	Day 2A	Day 2B	Day 3	Day 4	Day 5
Informed consent	X							
Inclusion/exclusion criteria	X	X						
Demographics	X							

Demographics X

Race

Sex

Age

Increasing Detail – Observation Detail

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Schedule of Activities: Days 1 and 2

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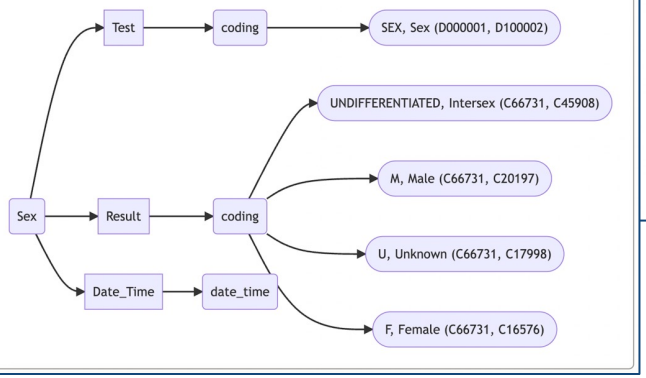
	Screening	Baseline	Day 1	Day 2A	Day 2B	Day 3	Day 4	Day 5
Informed consent	X							
Inclusion/exclusion criteria	X	X						
Demogr								X

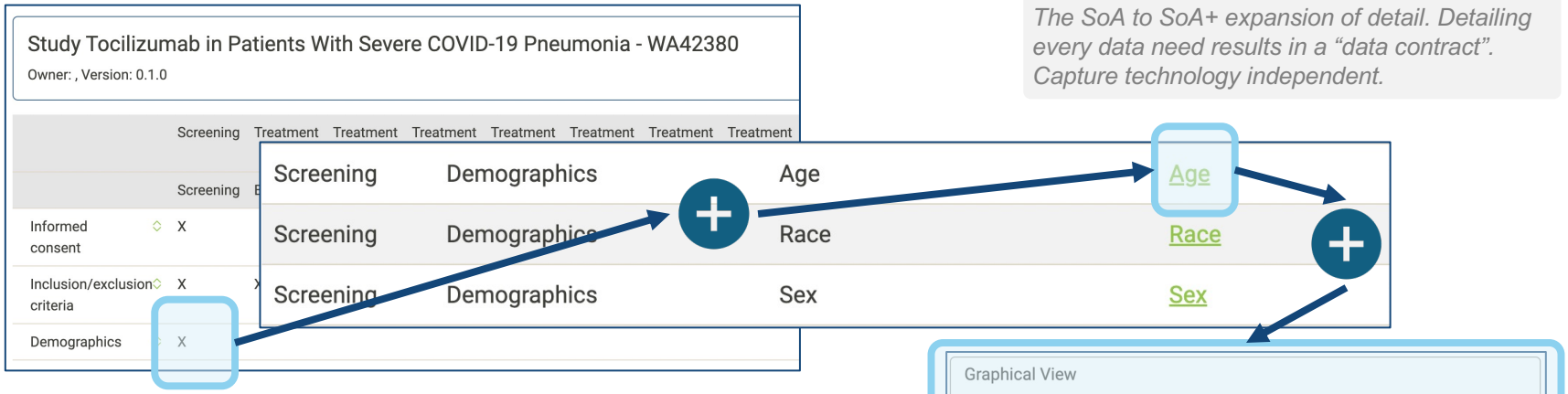
Graphical View



Increasing Detail – Data Contract

Increasing Detail

The SoA to SoA+ expansion of detail. Detailing every data need results in a "data contract". Capture technology independent.



Form Recommendation

Systems can use the richness of definition to suggest forms for data capture builds

Demographics	Age, Race, Sex	Demographics_2: *Enrollment, Ethnicity, Sex, Age [0.6666666666666666]* Demographics: *Enrollment, Sex, Age [0.6666666666666666]*

Capability Level Approach

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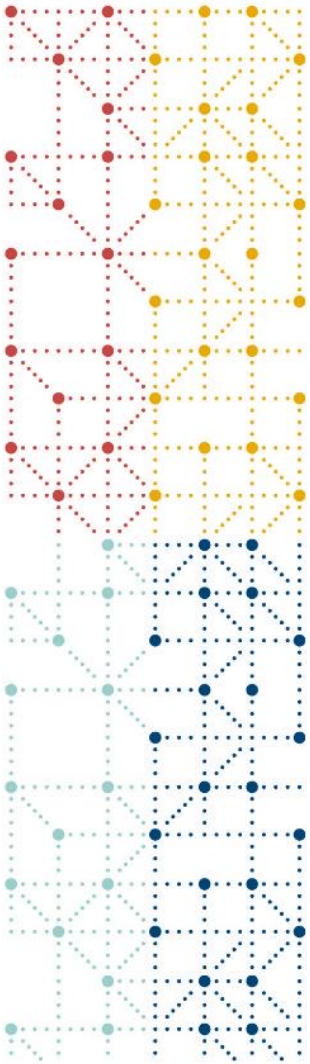
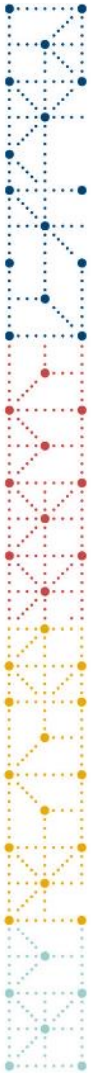


Looking Forward



DDF 1

The first step in a journey. The base model providing an initial capability. Industry already pushing the boundaries of the model and using for a varied use cases

DDF 2

DDF 2 just starting. Focused on two major use cases: EDC and CPT but the model will be expanded in other areas.

Tipping Point?

When does the community recognise the benefits of an "electronic" study design / protocol? The "what is in it for me" question. There is a change management issue.

Short Term Gains

Where is the win? The tangible, short term, gains … CTMS, CT registries (e.g. CT.gov) and others

Longer Term Challenge

An eco-system of tools, APIs available off-the-shelf (the protocol API, the CTMS API …) supported by well-understood model(s).

Implications for the CDISC products driving the need for "integrated", "consistent" and "aligned" standards

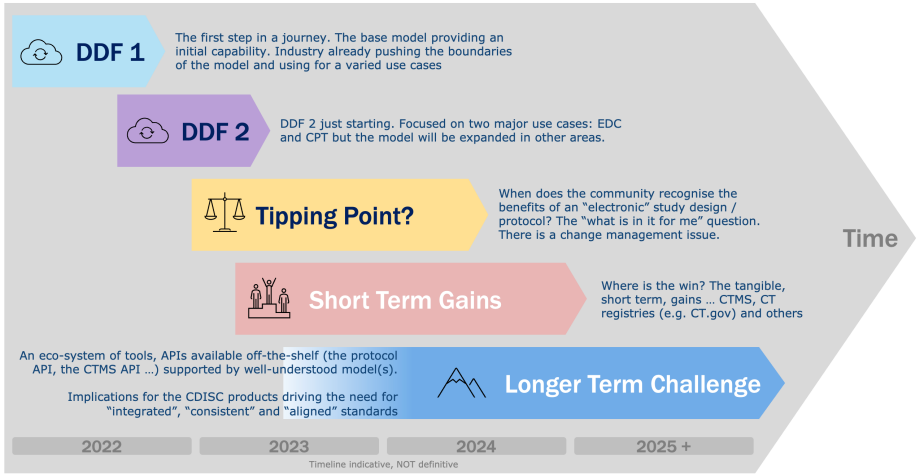
Time

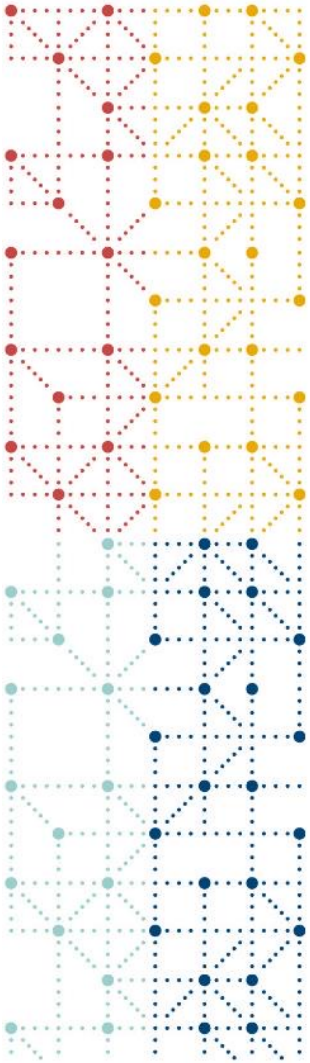
2022 | 2023 | 2024 | 2025 +

Timeline indicative, NOT definitive

Summary

- DDF fills an important gap
- It is complex and that complexity becomes visible
- A single source of truth
- An opportunity to improve
  - Speed of study execution
  - Data quality
  - Data utility
  - FAIR data
  - Capture independent





Thank You

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