Clinical Protocol Metadata – From Concept to Conclusion

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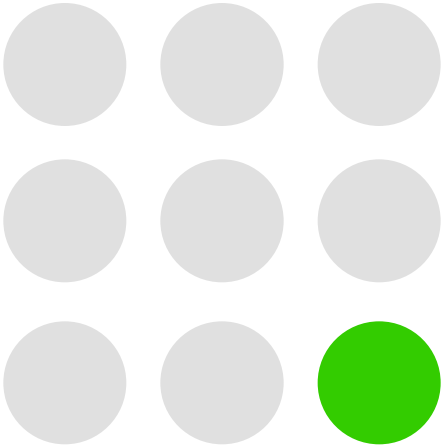
VP, Implementation Services



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Trends in Study Design

Annual Trend[1]
(from 1999 – 2005)

- # of unique procedures: ↑ 6.5%
- Frequency of procedures per protocol: ↑ 8.7%
- Site work burden to administer each protocol: ↑ 10.5%

Major Contributor…

- Duration of trial time: ↑ 74%
- Patient enrollment cycle time: ↑ 65%
- Number of amendments ($250~450K to implement one amendment[1])
- Length of CRF: ↑ 270%

Implications for…

- Study results quality
- Scientific value of study[2]
- Operational efficiencies[3]
- Time to market
- Cost of development

1 Assessing the impact of protocol design changes on clinical trial performance, Tufts Center for the Study of Drug Development, Tufts University, Boston, MA

2 Tufts CSDD Impact Report Volume 10, No. 1 January/February 2008; Science Magazine Volume 322, 210-213 October 10, 2008;

3 American Journal of Therapeutics Volume 15 No. 5, 1075-2765 September/October 2008

Controlling bloat and complexity in study design can impact millions of dollars in study budget

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Why Study Design and Protocol?

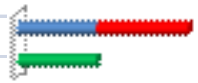
- Complex protocols have on average one amendment more than simple protocols[1]
- Nearly 40% of amendments occur before first subject first dose[2]
- Protocol Design flaws responsible for 11.3% of amendments[2]
- 34% of all amendments are partially or completely avoidable[2]
- 15-30% data never used in NDA[1]
  - Simply ensuring the purpose for conducting a procedure is known will reduce cost

1 2008 study by Tufts Center for the Study of Drug Development
2 Applied Clinical Trials: Protocol Amendments: A costly solution, By Ken Getz, 01 May 2011

1 Tufts Center for Drug Development: Assessing the down stream impact of protocol design complexity

Impact of Protocol and Study Design

Clinical Study Analysis (ANTI-INFECTIVE)
Sponsor vs Industry Median (indications, phase and year)

Complexity - Study Work Effort	Sponsor	80.57		224% higher
	Industry	36.05		
Total Procedures	Sponsor	254.27		217% higher
	Industry	117.25		
Unique Procedures	Sponsor	31.69		149% higher
	Industry	21.27		
Total Study Visits	Sponsor	10.94		128% higher
	Industry	8.58		
Patients per site	Sponsor	15.40		160% higher
	Industry	9.63		
Cost Per Patient	Sponsor	$13,810		171% higher
	Industry	$8,083		
Benefit Per Study (Potential)				
Sponsor spend compared to Industry	Avg/study	$69,205	Avg of individual study details	

Analysis includes 32 sponsor studies – Medidata PICAS and CROCAS data

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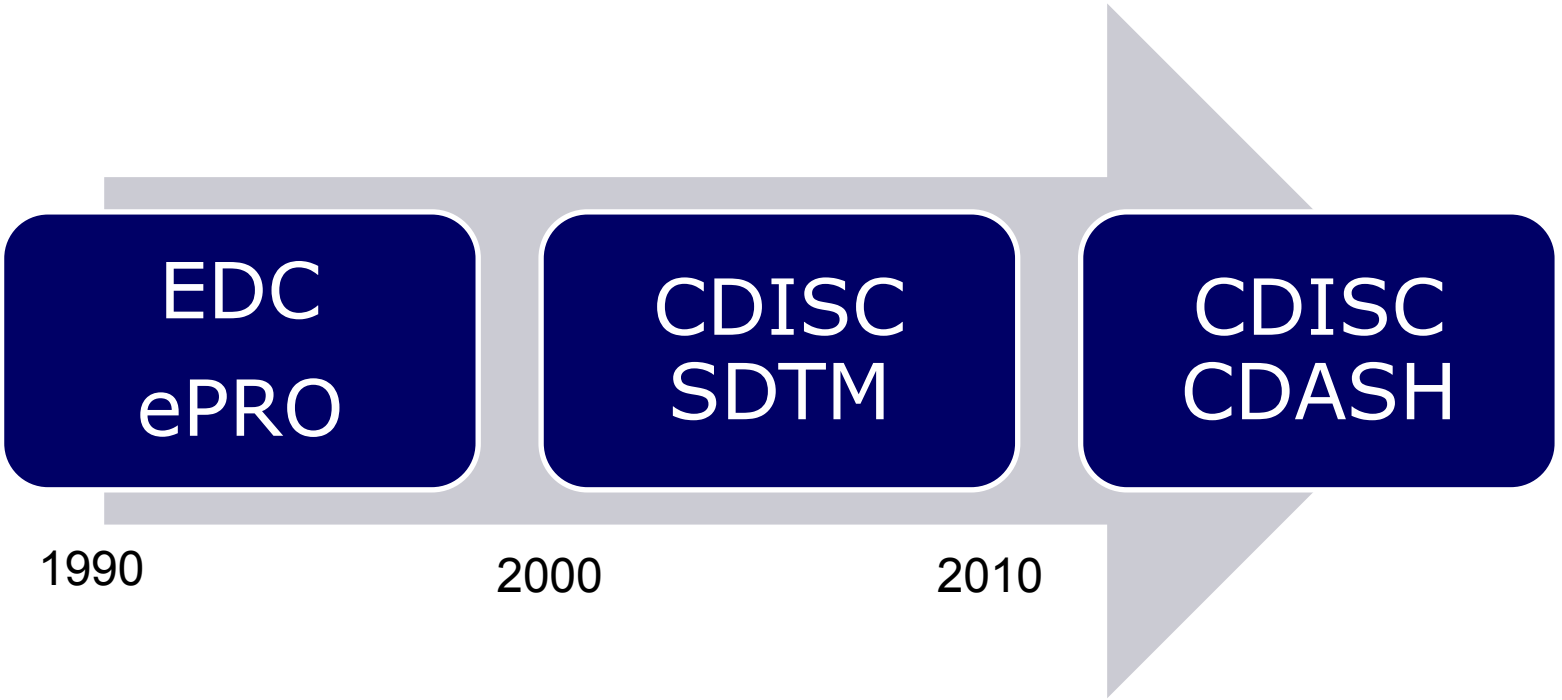
Study Design Remains Document Centric

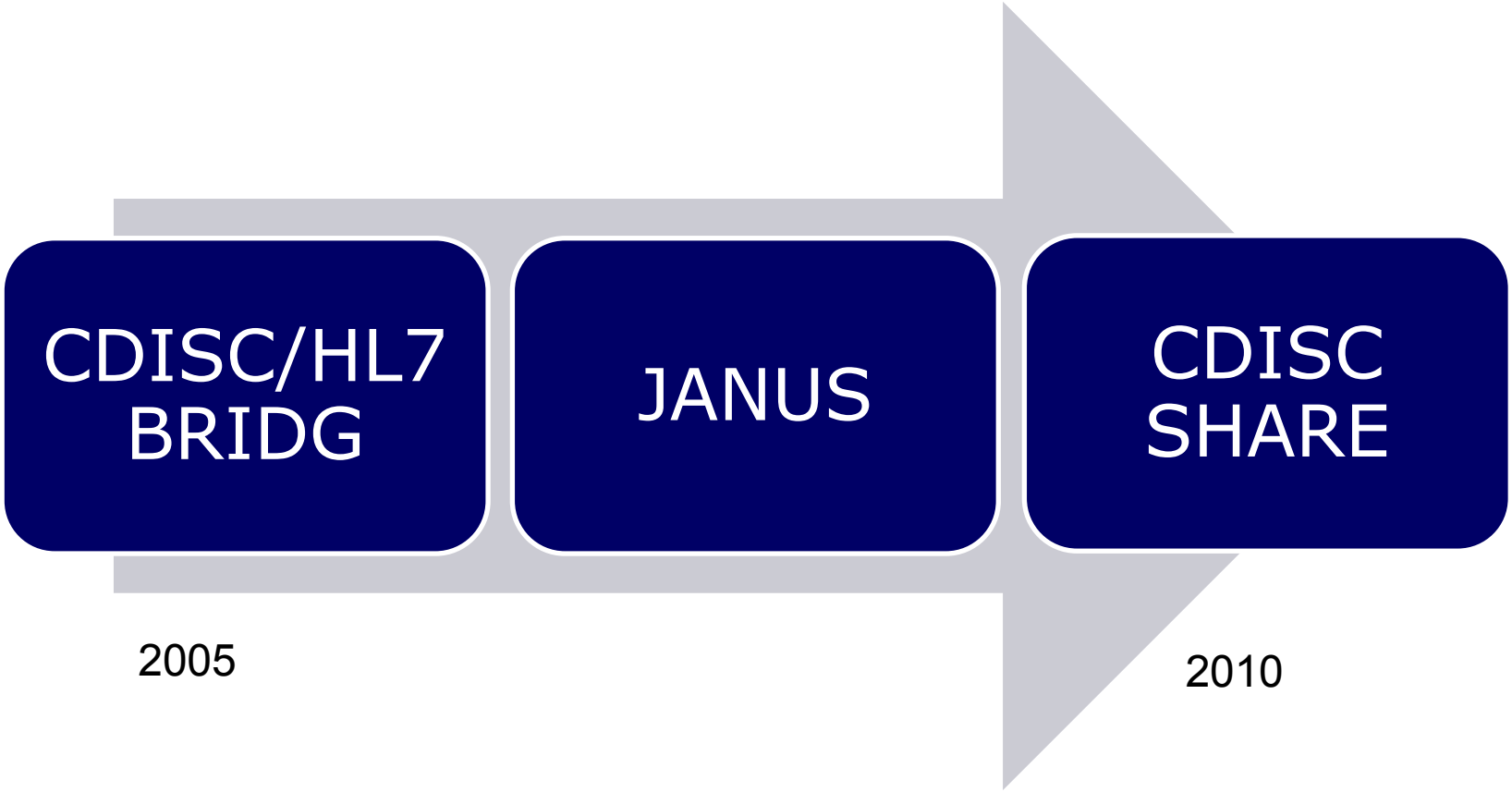
Industry Approach

- Early focus on data collection and submission



Recent Shift in Focus

- Latest focus on consistency of data and metadata throughout lifecycle



Metadata and Study Design

Complexity

- Standard CRF's mapped directly to clinical procedures
- Align Schedule of Activities with anticipated Statiscal Analyses

Consistency

- Linking of data within study design (e.g Objectives, Endpoints, Procedures)
- Metadata definition consistent across systems

Reuse

- Up to 80% of study design is not unique to a given study
- Standardized content in study design drive standardized downstream activities (e.g. CDASH CRF's mapped to Clinical Procedures)

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From Protocol to Submission

- Make submission metadata available to Clinicians and Writers during study design and protocol creation process and persist through submission

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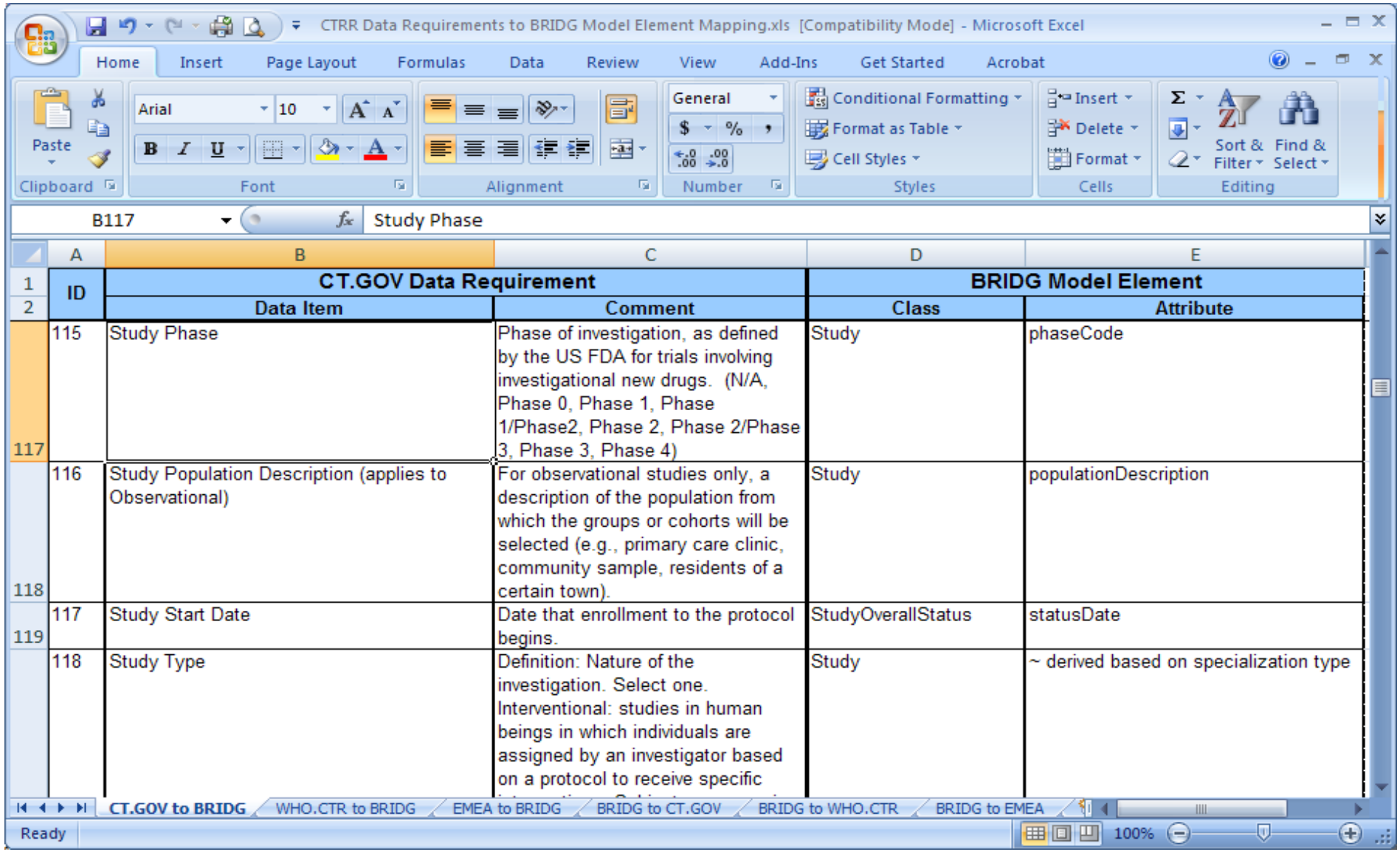
Need for Standard Metadata: Phase of Study

Registry requirement	Data element	Data element definition
Clinicaltrials.gov	Study Phase	Phase of investigation, as defined by the US FDA for trials involving investigational new drugs. (N/A, Phase 0, Phase 1, Phase 1/Phase2, Phase 2, Phase 2/Phase 3, Phase 3, Phase 4)
EudraCT v8	Trial Type	Eight different elements: ▪Trial type human pharmacology (phase I) ▪Trial type First Administration to Humans ▪Trial type Bioequivalence Study ▪Trial type Other ▪Trial type Other specification ▪Trial Type Therapeutic Exploratory (Phase II) ▪Trial type Therapeutic Confirmatory (Phase III) ▪Trial Type Therapeutic Use (Phase IV)
WHO	Study Type - Phase	Phase of investigation, as defined by the US FDA for trials involving investigational new drugs. (N/A, Phase 0, Phase 1, Phase 1/Phase2, Phase 2, Phase 2/Phase 3, Phase 3, Phase 4)

Need for Mappings Does Not Go Away



	ID	CT.GOV Data Requirement		BRIDG Model Element	
		Data Item	Comment	Class	Attribute
117	115	Study Phase	Phase of investigation, as defined by the US FDA for trials involving investigational new drugs. (N/A, Phase 0, Phase 1, Phase 1/Phase2, Phase 2, Phase 2/Phase 3, Phase 3, Phase 4)	Study	phaseCode
118	116	Study Population Description (applies to Observational)	For observational studies only, a description of the population from which the groups or cohorts will be selected (e.g., primary care clinic, community sample, residents of a certain town).	Study	populationDescription
119	117	Study Start Date	Date that enrollment to the protocol begins.	StudyOverallStatus	statusDate
	118	Study Type	Definition: Nature of the investigation. Select one. Interventional: studies in human beings in which individuals are assigned by an investigator based on a protocol to receive specific	Study	~ derived based on specialization type

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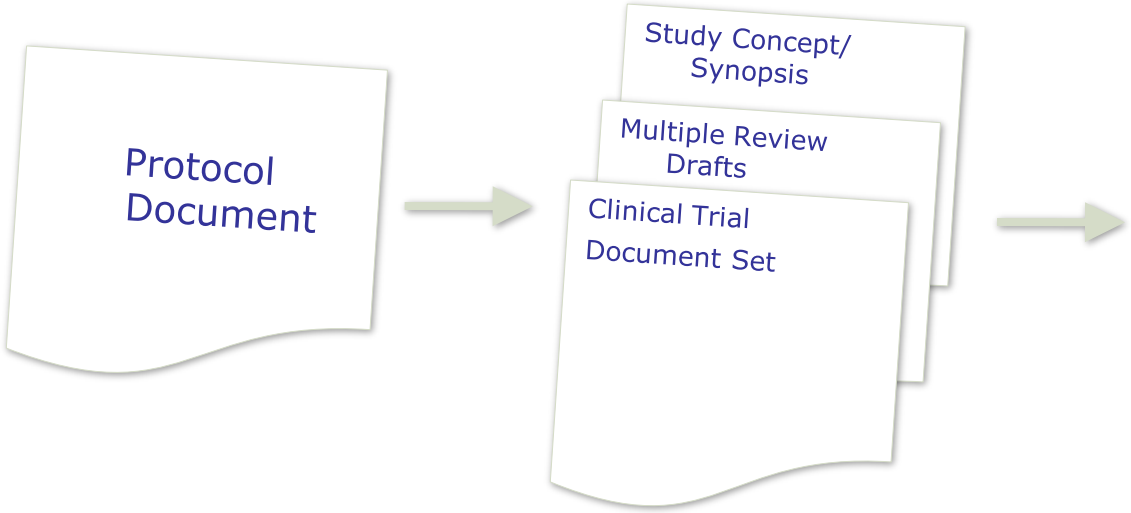
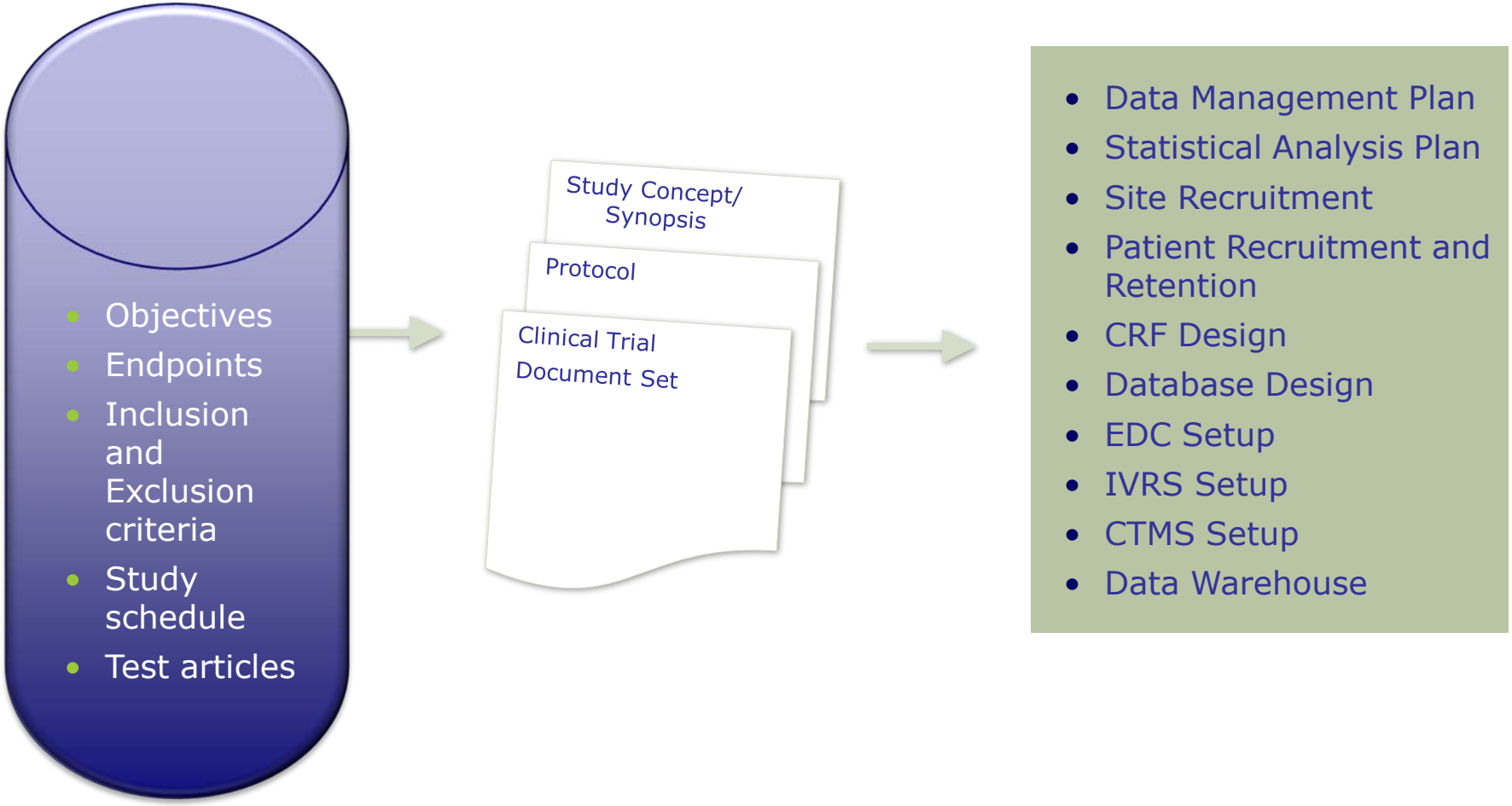
Current Document Evolution



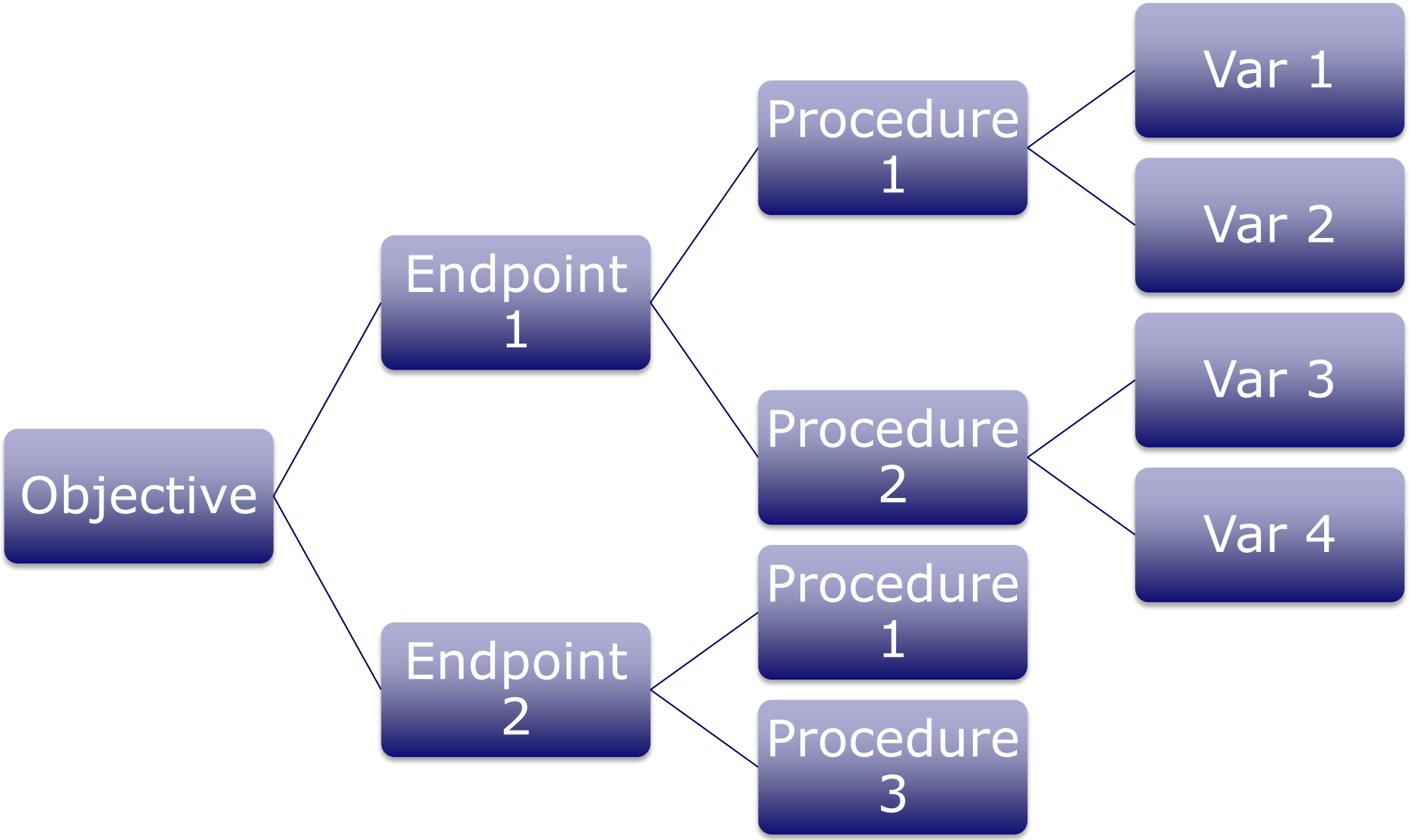
- Data Management Plan
- Statistical Analysis Plan
- Site Recruitment
- Patient Recruitment and Retention
- CRF Design
- Database Design
- EDC Setup
- IVRS Setup
- CTMS Setup
- Data Warehouse

All clinical and operational activities conducted as part of the trial are derived from the protocol

Solution: Real World Design Centric Thinking



Metadata Relationships



Protocol vs CRF Data Organization

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- Structured protocol information
  - Visits, procedures, variable information
- Requires information on variable attributes and procedure to variable mappings

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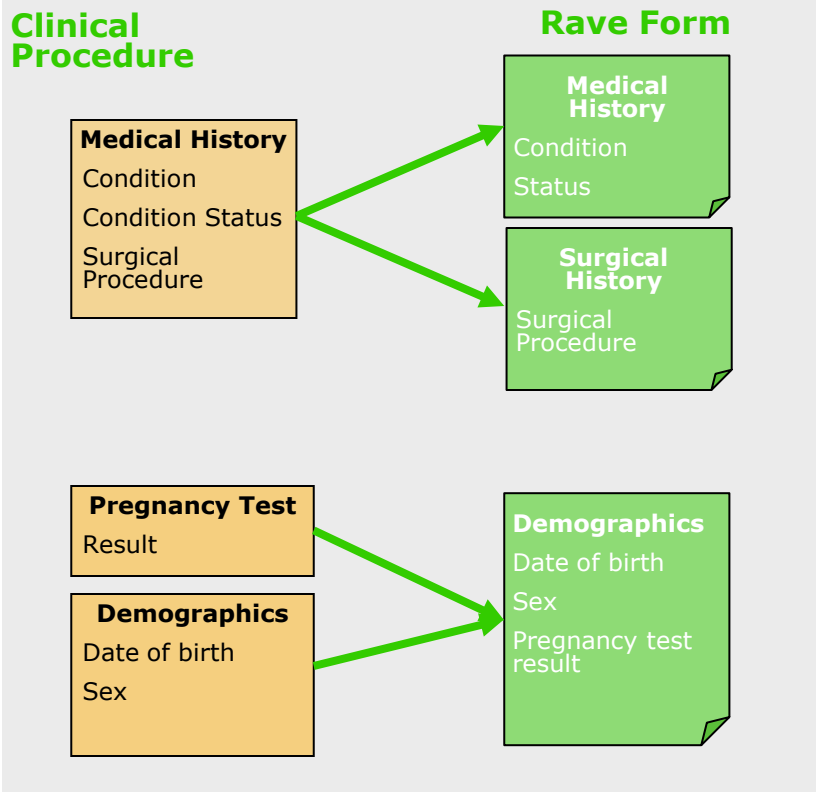
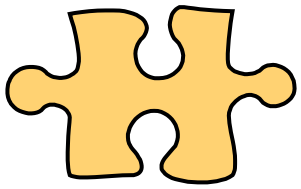
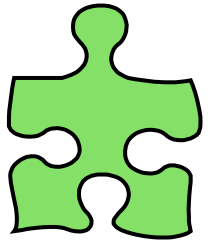
- Libraries of CRF standards
  - Data standards, variable attribute information
- Requires configuration based on protocol structure







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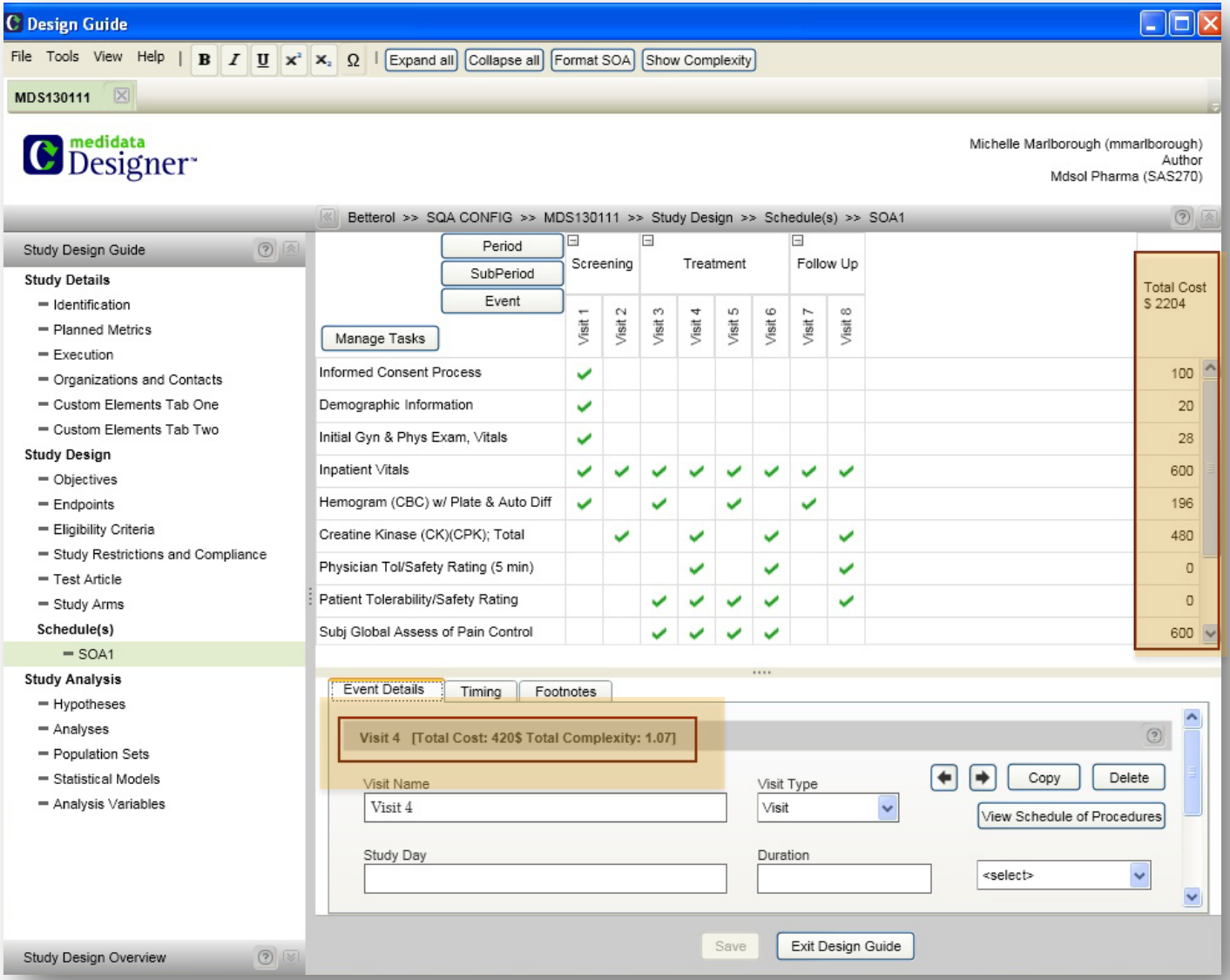
Accessing Average Procedure Costs



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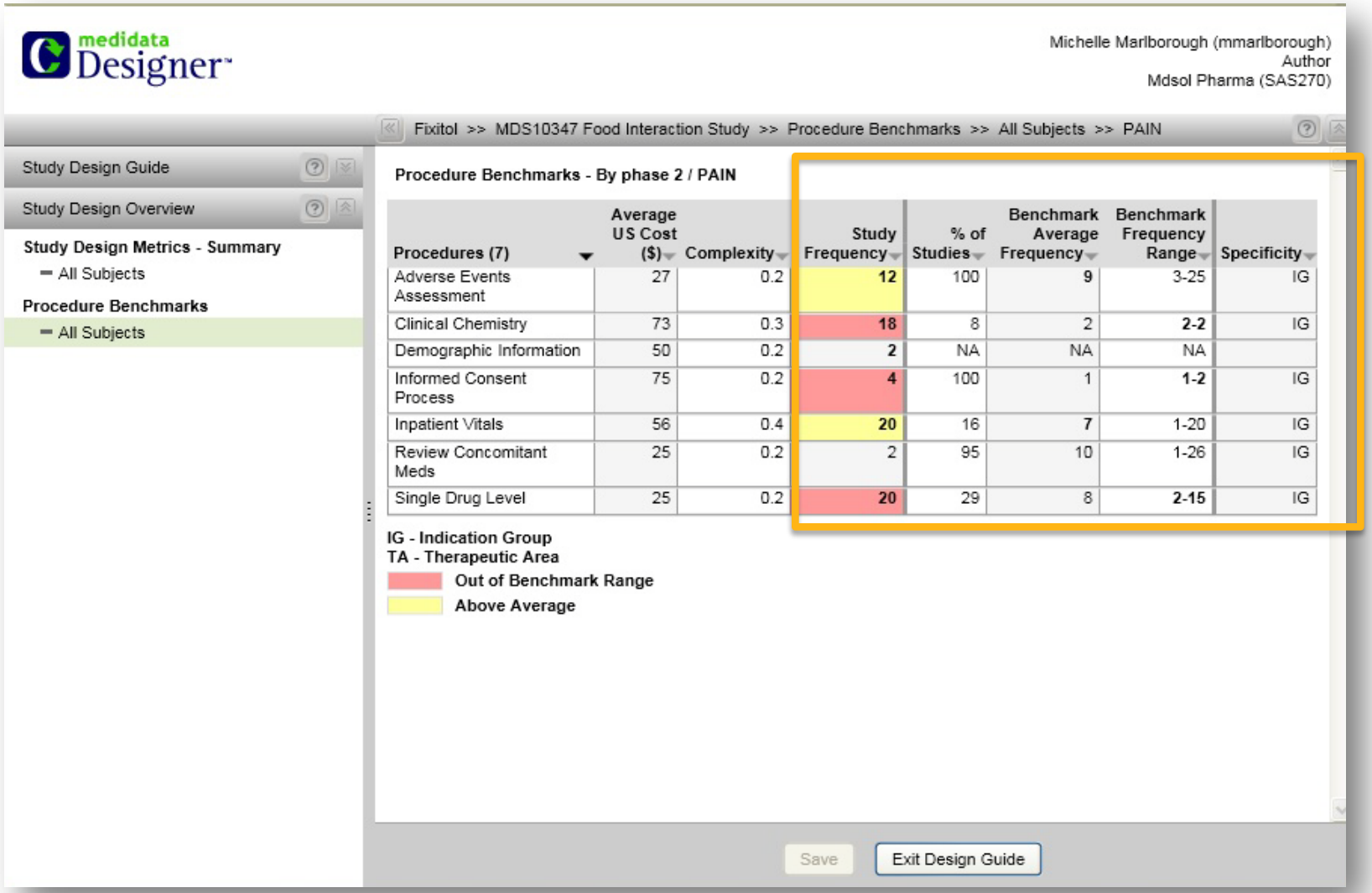
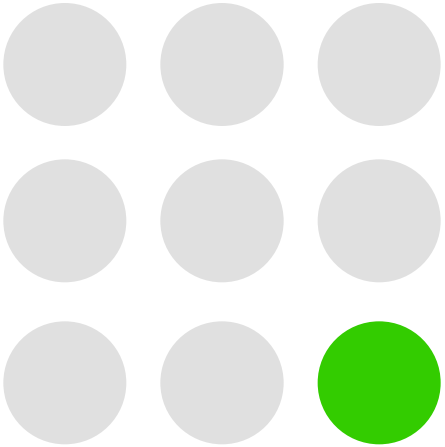
Accessing Protocol Design Benchmarks



Questions?



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