Clinical Data Standards and Governance

October 31, 2018

Agenda

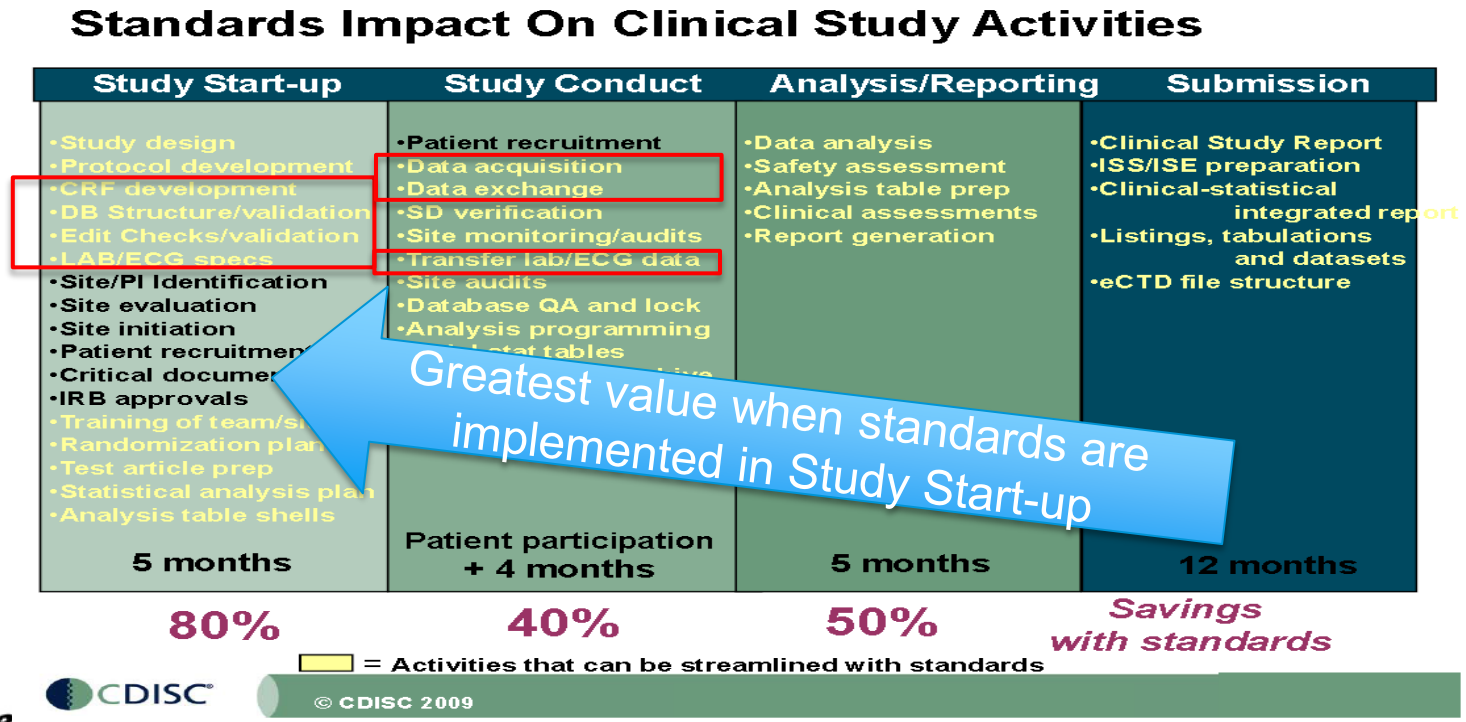
- The Need for Standard CRFs
- Approach for Creating Standard CRFs
- Implementing Standard CRFs in TrialMaster
- Governance of Standard CRFs

Regulatory Guidance

- ICH E6 2.10: All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification
- FDA Guidance: In 2014, FDA issued a binding guidance requiring the submission of data in a standardized format for any study starting after December 2016.
  - *"When planning a study (including the design of case report forms, data management systems, and statistical analysis plans), the sponsor or applicant must determine which FDA-supported standards to use"*
  - *"…establishing traceability is one of the most problematic issues… [and] can be enhanced when studies are prospectively designed to collect data using a standardized CRF, e.g., CDASH"*
- Data quality issues can be hidden, persistent: In 2016, 61% FDA Warning Letters focused on data integrity issues

Benefits of Data Standards

- Using standards can save significant time and cost, especially when implemented in the early stages of the study (case report forms, protocol)

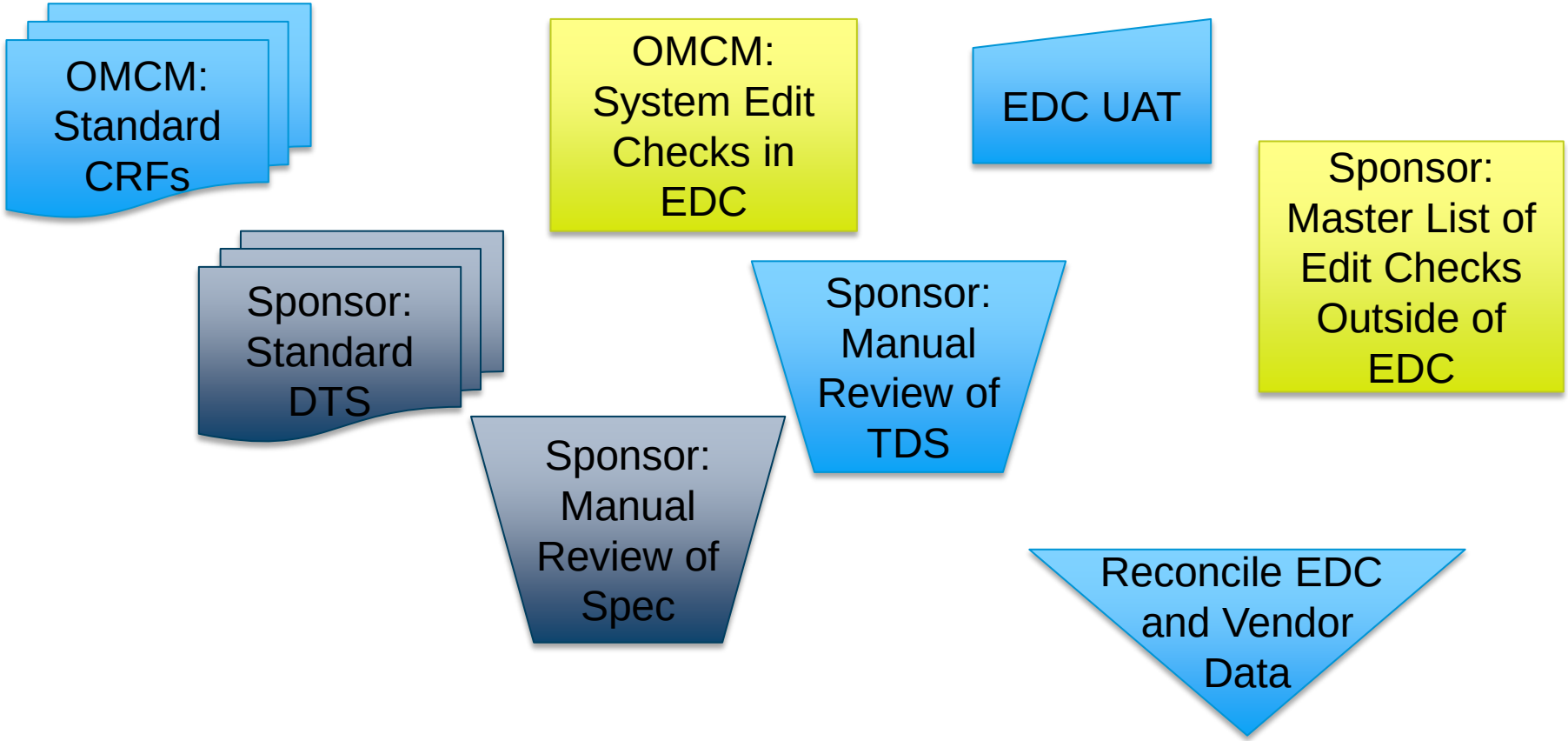


Efficiencies

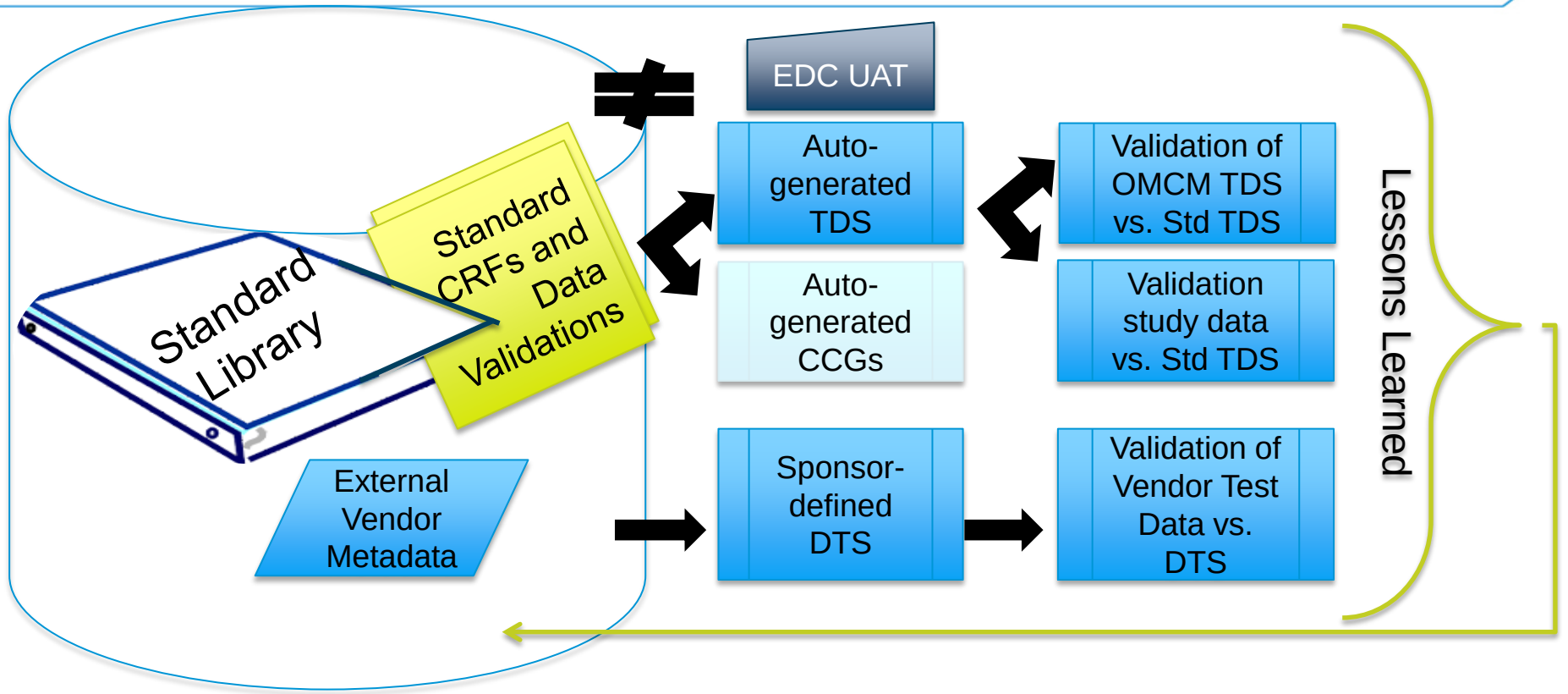
- Time
  - Quicker database set-up
  - Shorter UAT time
- Quality
  - Allow for electronic checks to quickly assess data conformance
  - Allow for software tools that aid in the evaluation of efficacy and safety
  - Sites and monitors become familiar with CRFs – fewer data entry issues
- Cost
  - Less time for database set-up = ↓$
  - Training can be abbreviated
  - Reduced monitoring
  - Fewer queries

Approach for Creating Standard CRFs

Current Standards Landscape



Future Standards Landscape



CRF Review Strategy – Inventory of Commonly Used Forms

			Program 1										Program 2		**Program 3**	Program 4		
		Review Batch	Study 1	Study 2	Study 3	Study 4	Study 5	Study 6	Study 7	Study 8	Study 9	Study 10	Study 1	Study 2	Study 1	Study 1	Study 2	Study 3
Alcohol Breath Test [AB]	Core	Batch 3											x	x	x			
ADT Compliance [AC]	Program													x				
Anti Depressant Therapy [ADT]	Program												x					
Adverse Event [AE]	Core, Safety	Batch 2	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse Events [AEYN]	Core, Safety	Batch 2	x	x	x	x	x	x	x	x	x	x		x	x	x	x	x
Abnormal Involuntary Movement Scale (AIMS) [AIMS]	Core, QOL	QRS				x	x	x	x									
Barnes Akathisia Rating Scale (BARS) [BARS]	Core, QOL	QRS				x	x	x	x									
Body Composition [BC]	Non-Core									x								
Cognitive Assessments [CA]	Non-Core														x			
Connor-Davidson Resilience Scale 25 (CD-RISC-25) [CD]	Program													x				
Chemistry [CHEM]	Core, Safety	Batch 2				x	x	x	x				x	x	x		x	
Caregiver/Informant Intake Form [CF]	Non-Core																	
Prior and Concomitant Medications [CM]	Core, Safety	Batch 2	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Prior and Concomitant Medications [CMYN]	Core, Safety	Batch 2	x	x	x	x	x	x	x	x	x	x		x	x	x	x	x

Each CRF used in a study was evaluated for use as a standard

CRF Review Strategy - Review for Industry Standards

- Evaluate each CRF/data point to be standardized against industry standards
  1. Can SDTM be used directly for collecting data?
  2. Does CDASH have guidance for this data?
  3. Does sponsor have a standard?
  4. Should we develop a standard?

CRF Review Strategy – Other Considerations

- Consider other contributing standards at same time
  - Edit checks
  - Validations outside of EDC
  - Completion guidelines
  - Data Manager training
  - UAT plan

- Feedback loop between protocol and CRFs
  - CRF changes should be reflected in protocol
  - Protocol template changes should be reflected in CRFs

Case Studies

1. Addition of Gender to Demographics
   - Clinical need for gender in addition to sex
   - Legal concerns with collecting gender (GDPR)
   - No CDISC guidance; looked for other published standards/studies
   - Definition of gender vs. sex
   - Options for gender (transgender, non-binary, other)
2. Changes to questionnaires, ratings and scales
   - Reviewed each against CDISC QRS standards
   - Decision on including pre-defined fields for evaluation interval, evaluator, etc.
3. How to collect adverse events and concomitant medications for extension studies

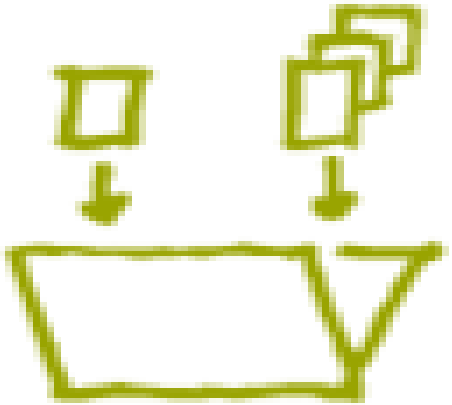
   Additional fields and categories for events and medications being carried over from previous study

   Defined processes and protocol language for handling prior events and meds

Implementing Standard Library in TrialMaster

Strategy in TrialMaster

- After several studies have been conducted



  - Gather all forms into one TrialGroup
  - Place the forms into separate folders/patient types based on category (e.g. QOLs, Safety, Efficacy, Other)
  - Conduct a thorough form review meeting
    - to initially review fields that are captured within each form
    - *discuss behavior and CDISC standards that can be* applied

- Consider each “folder” as a batch
- Create and maintain Timelines for each batch
- Each batch should follow the full study build SDLC

Focusing the Review Sessions

- Max length of all **specify textboxes**
- Format and max lengths for all **result fields**
- Max lengths for **dates**
- Accept **partial dates/future dates**?
- **Attributes that can be set at the item level** (will not change from study to study or visit to visit) such as read only, hidden
- **Codelists, displayed and stored values:** Ensure all confirm to CDISC if possible
- **SAS variables**
- **SAS labels:** Both SAS transport versions 5 & 8 will truncate labels to <=40
  - Alkermes determined the best way to abbreviate on a case by case basis

Focusing the Review Sessions

- **Scales:** If listed in CDISC standards, compare and ensure the correct SAS variables, labels, and codelist options are used.
- **Safety and Efficacy Batches:**
  - Design CRFs in such a way that can be easily used across studies.
  - If the same type of form changes slightly across study drug programs, consider creating several versions so that can easily be pulled into a new study without having to make changes
    - (e.g. adverse event, study drug admin, vital signs, etc)

Using the Standard Library for a New Study

Alkermes provides a list of forms to use from Standards

OMCM creates Casebook

- Using the selected standard forms
- Update standards, as necessary
- Add additional forms per protocol

Alkermes approves the casebook

OmniComm creates Specifications

- Copy standard edits specs
- Specify non-standard edit specs

Program non-standard edits

Test non-standard edits

Governance of Clinical Data Standards

What is Governance?

- Organization and framework for the establishment of strategy, objectives and policy of standards and implementation
- Continuous monitoring of proper implementation in order to ensure regulatory compliance
- Manage changes to standards in a traceable way
- Communication and dissemination of standards through membership

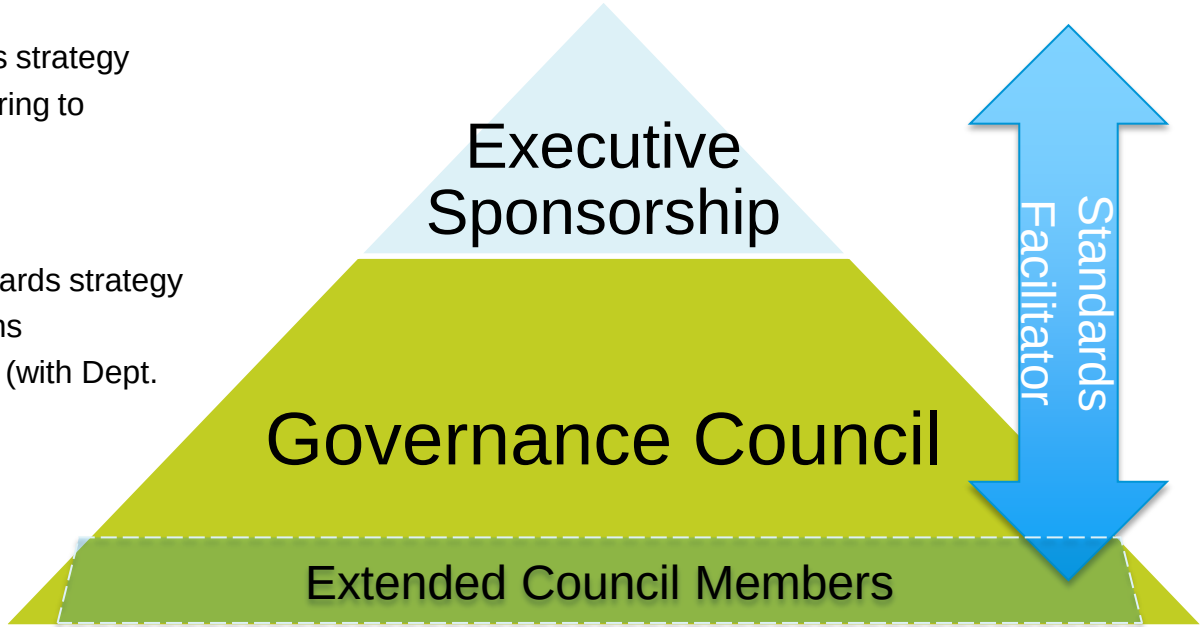
Alkermes

Clinical Data Standards Governance Structure

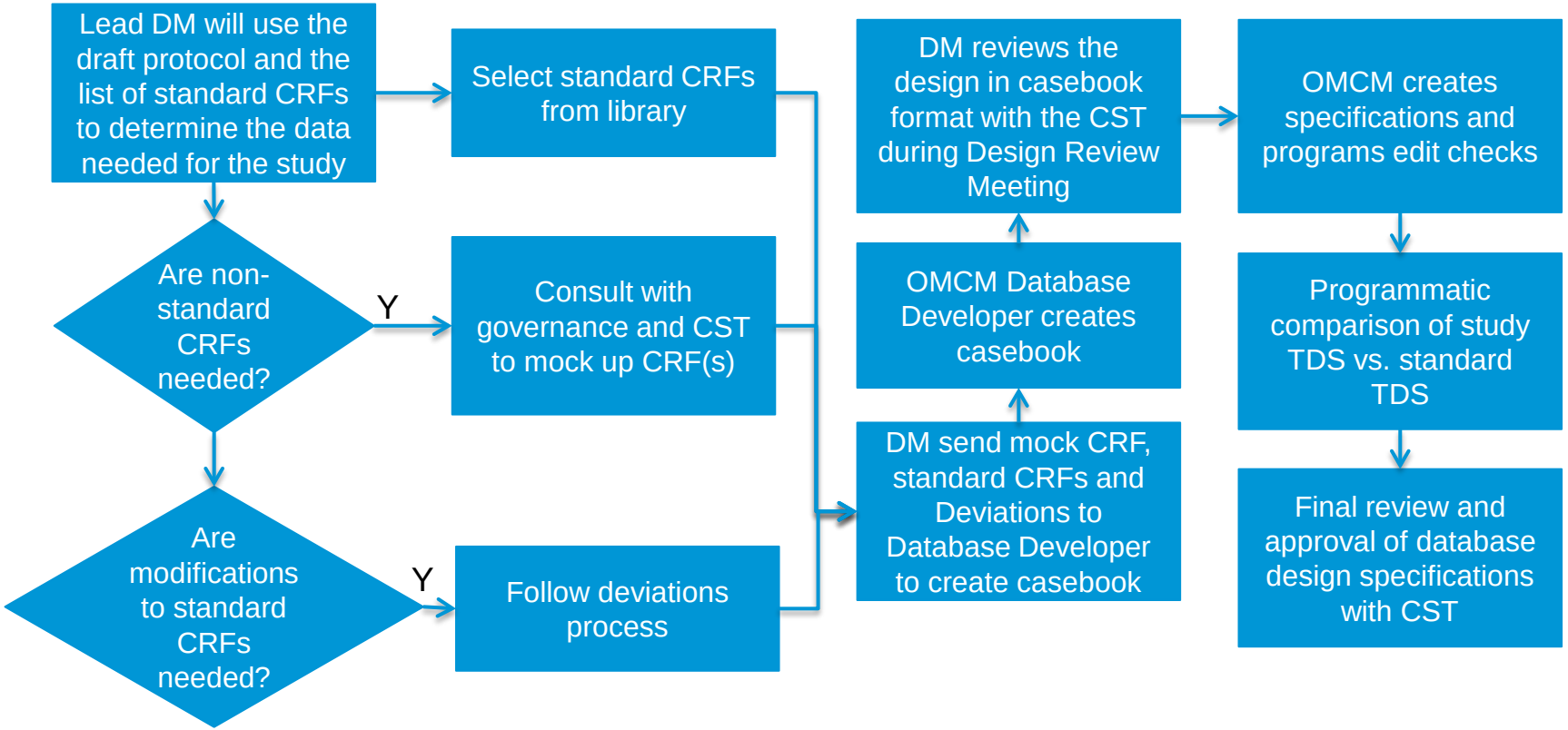
- Provides overall corporate standards strategy
- Holds function accountable for adhering to standards
- Adjudicates decisions, if needed

- Determines implementation of standards strategy
- Communicates standards to functions
- Approves deviations from standards (with Dept. Heads as needed)

- Provide guidance for their areas as needed

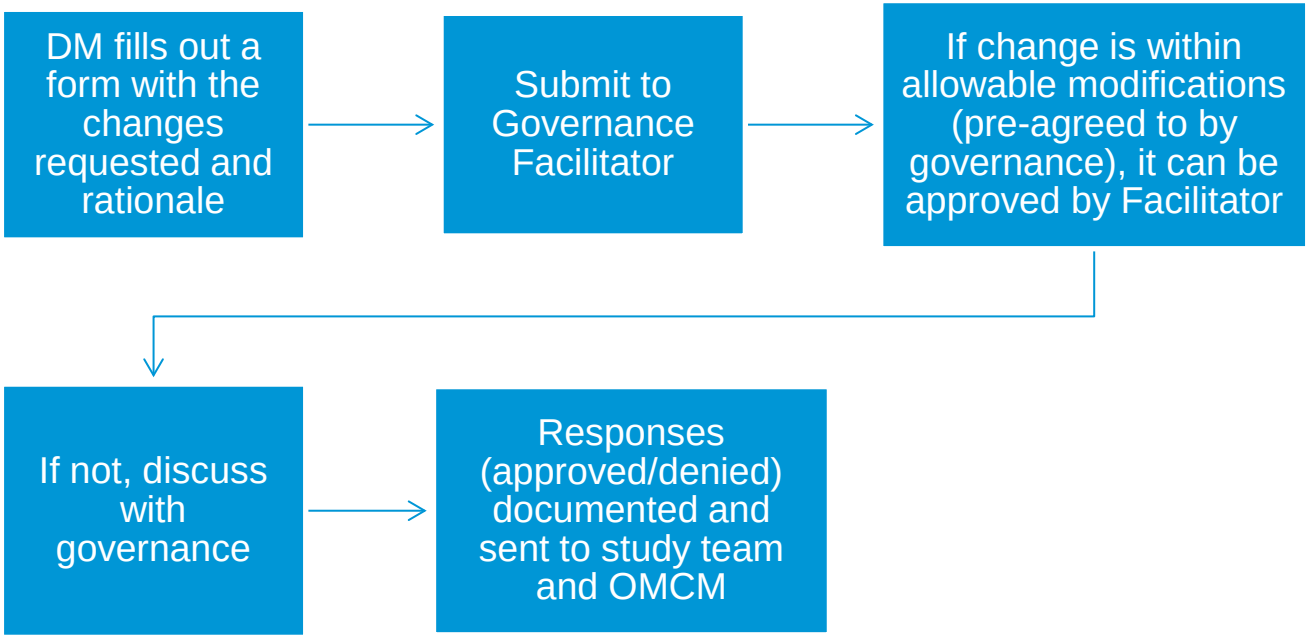


Clinical Data Standards Process



Process for Deviating from Standards

- If a study team does not want to use the standard CRFs for a topic covered by standards (Core and QRS)



Questions

Key Takeaways

- Best practice is to have standards for data collection as well as submission and analysis data
- Easier to convert existing CRFs into standards and review holistically
- TrialBuilder will copy entire CRF from standard ‘study’ into individual studies
- Cross-functional governance is needed for review, acceptance and adherence