THINK THEOREM

ACHIEVING CLARITY THROUGH PROPER STUDY DOCUMENTATION: AN INTRODUCTION TO THE STUDY DATA REVIEWER'S GUIDE (SDRG)

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AGENDA STUDY DATA REVIEWER GUIDE (SDRG)

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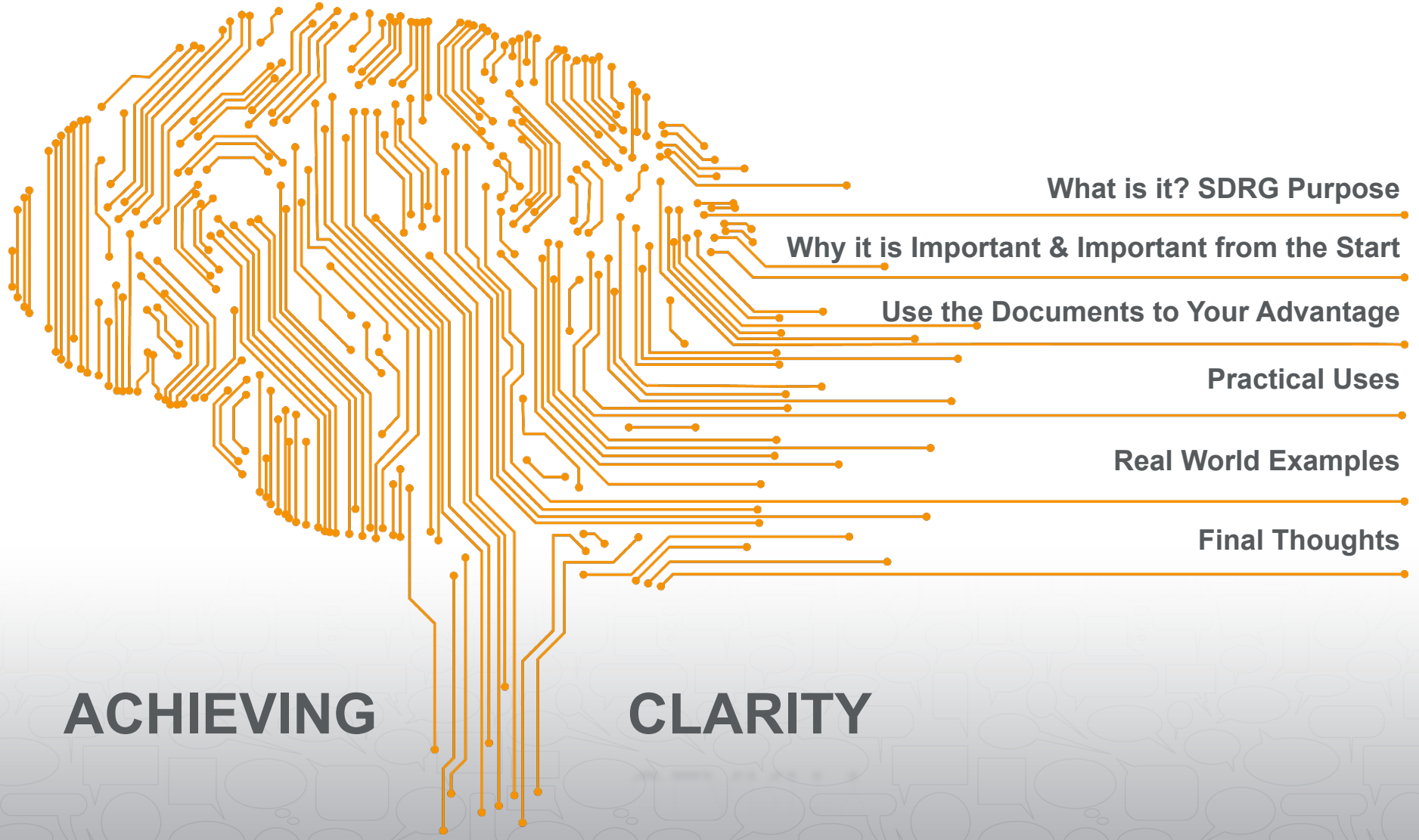

- What is it? SDRG Purpose
- Why it is Important & Important from the Start
- Use the Documents to Your Advantage
- Practical Uses
- Real World Examples
- Final Thoughts

ACHIEVING CLARITY

WHAT IS IT? SDRG PURPOSE

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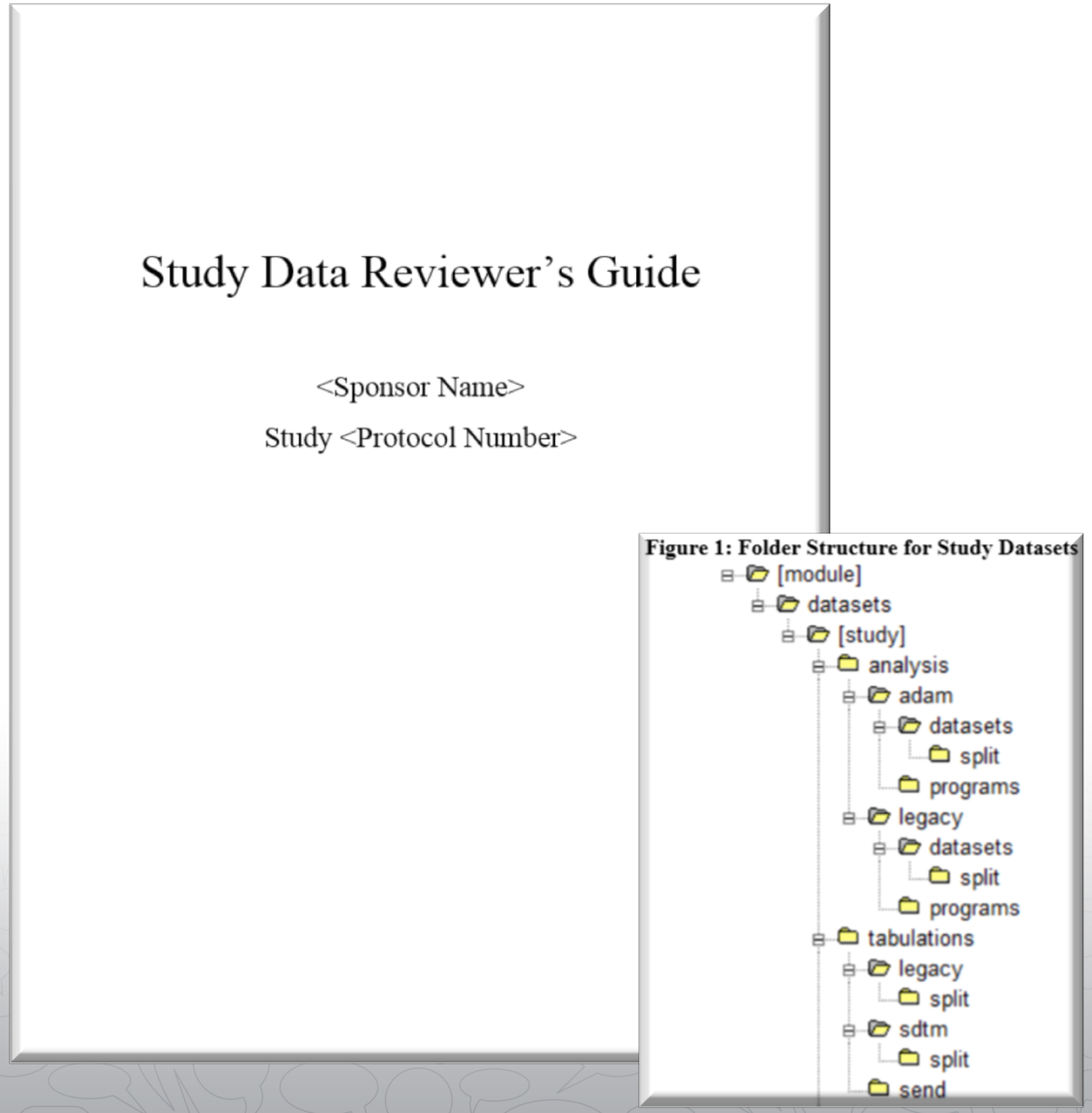
- Provides FDA Reviewers with additional context for SDTM datasets received as part of a regulatory submission.
- Per the completion guidelines, intended to describe SDTM data submitted for an individual study in the Module 5 clinical section of the eCTD (*also Module 4*)
- Purposefully duplicates information found in other submission documentation (e.g. the protocol, clinical study report, define.xml, etc.) to provide FDA Reviewers a single point of orientation
- Highlights SDTM version, Special/Custom Domains, Controlled Terminology, Define version, Dictionary versions, Data Conformance issues
- Developed to complement the define.xml to enable the reviewers to understand the data representations included in a submission
- ***A Living Document!***



WHY IMPORTANT & IMPORTANT FROM START

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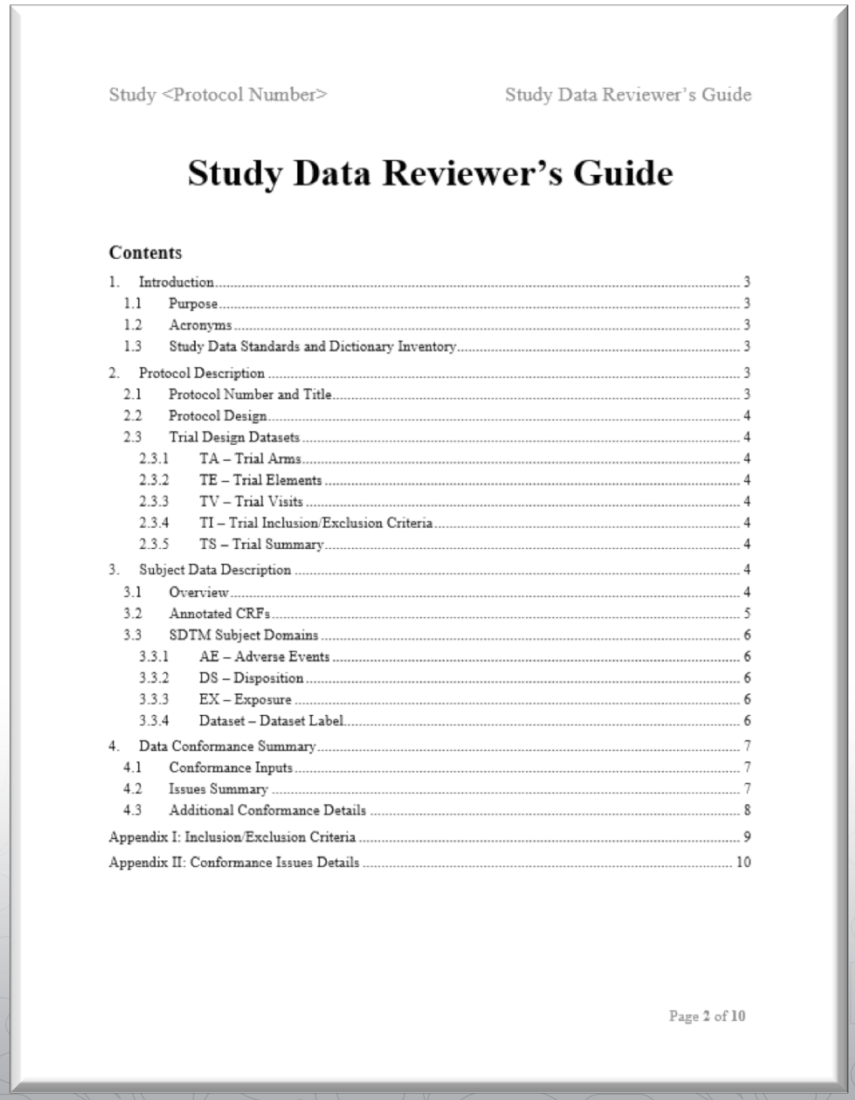
- Per the FDA's Study Data Technical Conformance Guide the SDRG is recommended as an integral part of a standards-compliant data submission
- Attention from the start ensures that all critical information is captured
- Maintains all relevant study information in one place which provides a central location to communicate decisions made throughout the course of a study to a regulatory body
  e.g. SDTM mapping decisions
- Creates transparency for the reviewer, team and sponsor
- SDRG's use in explaining data beyond what can easily be described in define
- ***Achieves Clarity*** between all documents and data where gaps currently exist



Study <Protocol Number> Study Data Reviewer's Guide

Study Data Reviewer's Guide

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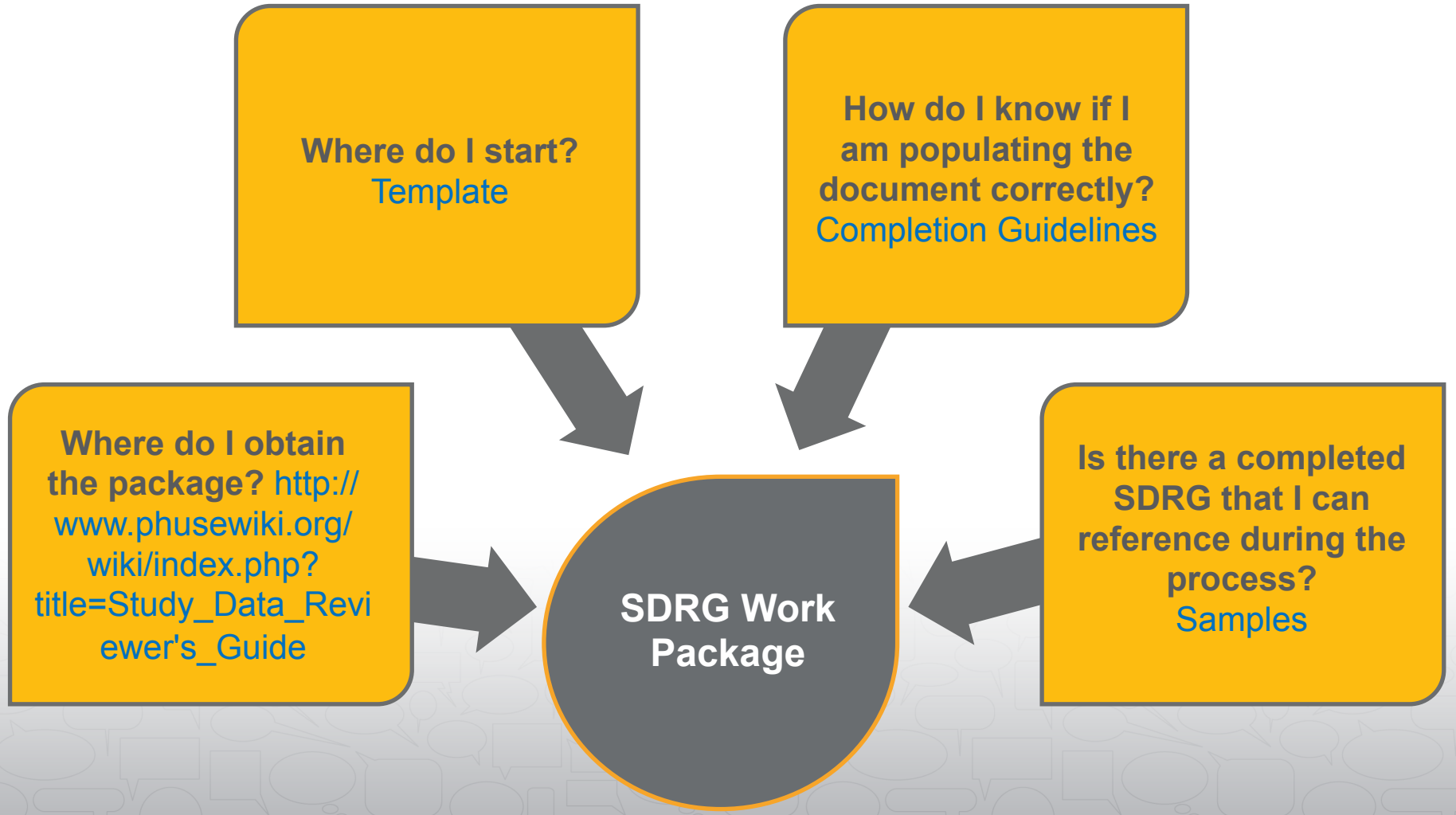
USE THE DOCUMENT TO YOUR ADVANTAGE



SDRG TEMPLATE HIGH LEVEL OVERVIEW (MAIN)

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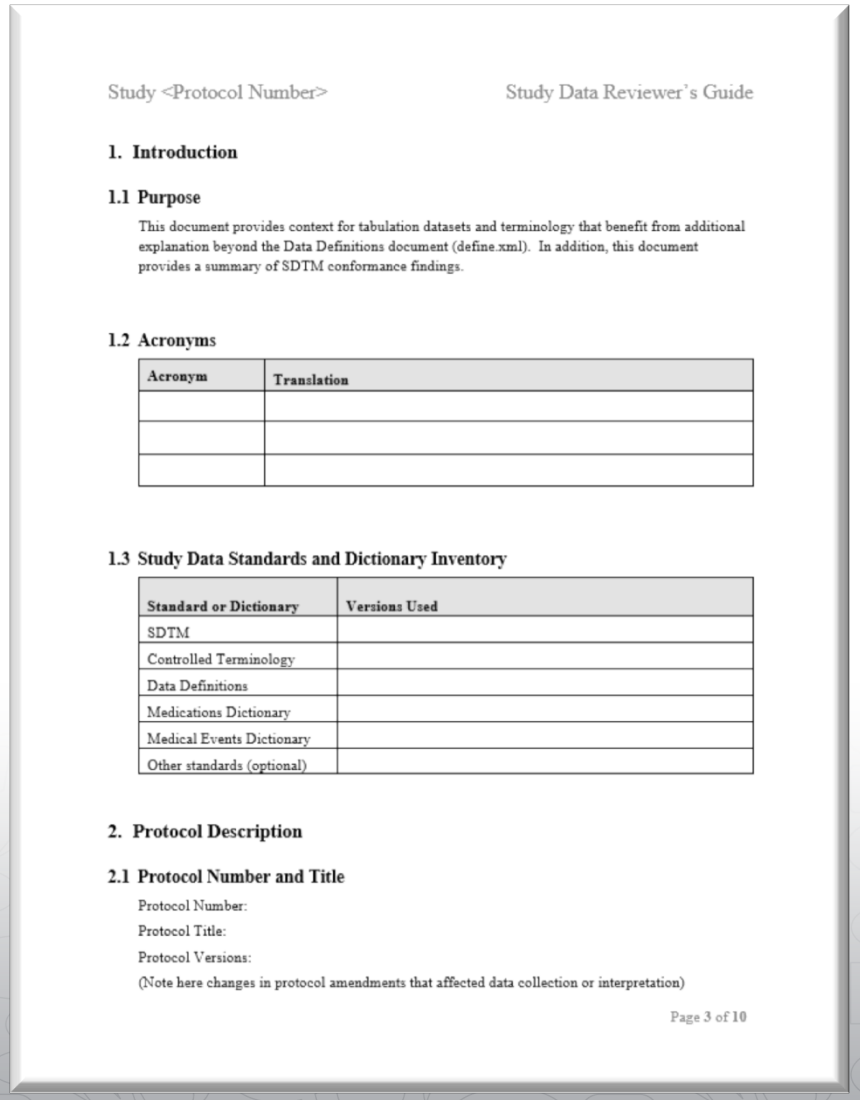
- Contains 4 Main Sections (Text from SDRG Completion Guidelines)
  - Introduction: Provides an overview and inventory of standards used on the study.
  - Protocol Description: Provides a brief orientation to the study and, if necessary, provides additional context about the Trial Design Datasets.
  - Subject Data Descriptions: Provides additional context for subject-level SDTM domains that are not adequately documented in define.xml or the SDTM Implementation Guide and its supplements.
  - Data Conformance Summary: Documents the validation inputs used to evaluate SDTM conformance and summarizes conformance findings ("Issue Summary" Worksheet in OpenCDISC Report).



Study <Protocol Number> Study Data Reviewer's Guide

1. Introduction

1.1 Purpose

This document provides context for tabulation datasets and terminology that benefit from additional explanation beyond the Data Definitions document (define.xml). In addition, this document provides a summary of SDTM conformance findings.

1.2 Acronyms

Acronym	Translation

1.3 Study Data Standards and Dictionary Inventory

Standard or Dictionary	Versions Used
SDTM	
Controlled Terminology	
Data Definitions	
Medications Dictionary	
Medical Events Dictionary	
Other standards (optional)	

2. Protocol Description

2.1 Protocol Number and Title

Protocol Number:

Protocol Title:

Protocol Versions:

(Note here changes in protocol amendments that affected data collection or interpretation)

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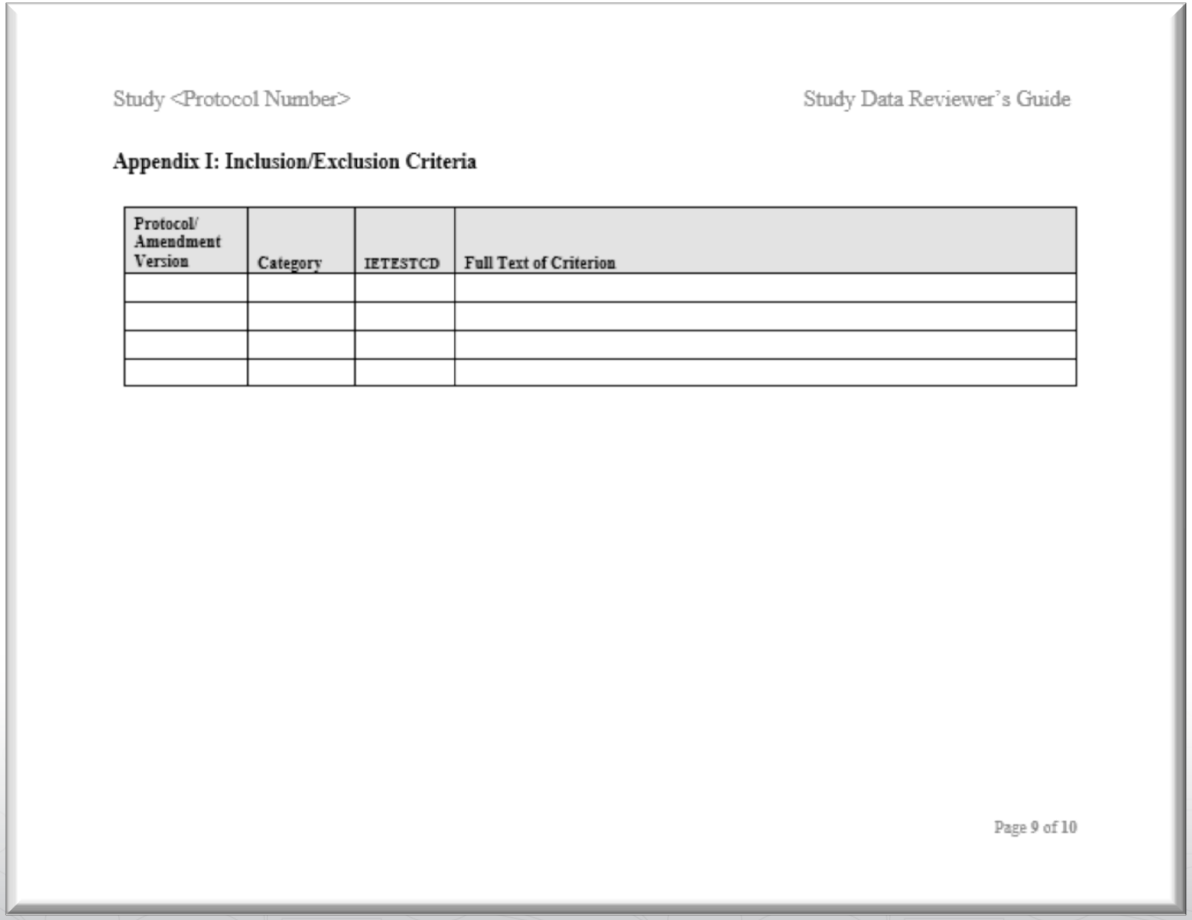
SDRG TEMPLATE HIGH LEVEL OVERVIEW (OPTIONAL)

- Contains 2 Optional Appendices (Text from SDRG Completion Guideline)
  - Appendix I: Inclusion/Exclusion Criteria: If the inclusion/exclusion criteria cannot be fully documented in the Trial Inclusion/Exclusion Criteria (TI) dataset due to SAS v5 limitations, the criteria can either be provided in Appendix I, or as a hyperlink to the full criteria in an annotated CRF.
  - Appendix II: Conformance Issues Details: A detailed record-level description of conformance issues may be included in Appendix II ("Details" Worksheet in OpenCDISC Report). Sponsors are strongly discouraged from including Appendix II due to its limited usefulness for FDA Reviewers.



Study <Protocol Number> Study Data Reviewer's Guide

Appendix I: Inclusion/Exclusion Criteria

Protocol/ Amendment Version	Category	IETESTCD	Full Text of Criterion

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SDRG: FLEXIBILITY AND CUSTOMIZABILITY

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study-data-reviewers-guide-example-001a-2014-08-06.doc

DON'T SEE A SECTION FOR IT? ADD IT.

- Template is a starting point

SECTION NOT NECESSARY? REMOVE IT.

- Not all sections in Template are required

Additional Content of Interest

Key analysis data points include:

- Spirometry endponts: LB domain where LBCAT = SPIROMETRY and LBNAM = SPIRO-GRAPH
- Asthma exacerbation endpoints: ZA domain where ZACAT = ASTHMA EXACERBATIONS and QS domain where QSTESTCD = QS12379A
- Safety analysis: AE domain
- Subject deaths: AE domain where AEOUT = FATAL, DS domain where DSSCAT = STUDY DISCONTINUATION and DSDECOD = DEATH

Screening failures are included in the SDTM datasets if the subject experienced an adverse event during the protocol-defined run-in period (see Section 2.2).

Reference start date was assigned as the date of randomization and will be missing for screening failures.

A CRF collected pregnancy event information; however, no pregnancy events were reported.

SDRG: SECTIONS WITH ADDITIONAL CONTENT

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- Sections with additional content added include…
  - Section 2.3 Trial Design Datasets
    - Additional context for the Trial Design datasets is necessary for both simple and complex protocol designs that are not adequately documented in define.xml or self-evident in the Trial Design Dataset content.
  - Section 3.1 Overview
    - Provide key information describing datasets containing subject data
  - Section 3.3.X Dataset – Dataset Label
    - Provide explanations beyond what is documented in define.xml or the SDTM Implementation Guide and its supplements

SDRG: SECTIONS SUBJECT TO REMOVAL

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- Optional Sections Include...
  - Section 1.2 Acronyms
    - Can be removed if sponsor-specific or non-industry standard acronyms are not used in the SDRG
  - Section 2.2 Protocol Design
    - Can be removed if a visual representation or brief textual description of the protocol design is not necessary
  - Section 3.2 Annotated CRF's
    - Can be removed if there are no deviations from the Metadata Submission Guidelines for Annotating and Bookmarking CRFs
  - Section 4.3 Additional Conformance Details
    - Can be removed if summary findings from validation rules other than the ones reported by OpenCDISC, which in the sponsor's opinion merit explanation
  - Appendix I: Inclusion/Exclusion Criteria
    - Can be removed if the inclusion/exclusion criteria can be fully documented in the Trial Inclusion/ Exclusion Criteria (TI) dataset
  - Appendix II: Conformance Issues Details
    - Sponsors are strongly discouraged from including this appendix due to its limited utility for FDA Reviewers

SDRG: WHEN DO I START CREATING IT?

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The Earlier, The Better

- Populate corresponding sections as each step of the study is started
  - Protocol - Section 1: Introduction, Section 2: Protocol Description
  - CRF Annotations/SDTM mapping - Section 3: Subject Data Description
  - SDTM Programming - Section 4: Data Conformance Summary
- Living document throughout the life of the study
  - Add Complex Derivations and Key Additional Content as they are first discussed.
  - Reduce the risk of forgetting to add critical information
- ***Avoid Scrambling at the end of the study***

PRACTICAL USE: USING THE SDRG DYNAMICALLY

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This is where a reviewer is going to look for information. Why can't your team use it dynamically throughout the project?

Important decisions are constantly being made throughout the course of a project, and this is where they ultimately need to be presented. Build it from the beginning, not at the end.

PRACTICAL USE: USING THE SDRG DYNAMICALLY

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- **Keep a decision log**
  - A simple spreadsheet of decisions made gives you the answers to many of the questions that a reviewer is going to have.

Domain	Variable	Issue	Resolution
<Impacted domains>	<Impacted variables>	<Description of issue>	<Description of resolution>

- **You already have all of the answers**
  - The template is right there. Your team has the answers. Build it with your study.

- **You're going to have questions too!**
  - If a reviewer is going to benefit from having all of the information in one place, won't your team?

REAL EXAMPLES: MULTIPLE STUDIES IN ONE

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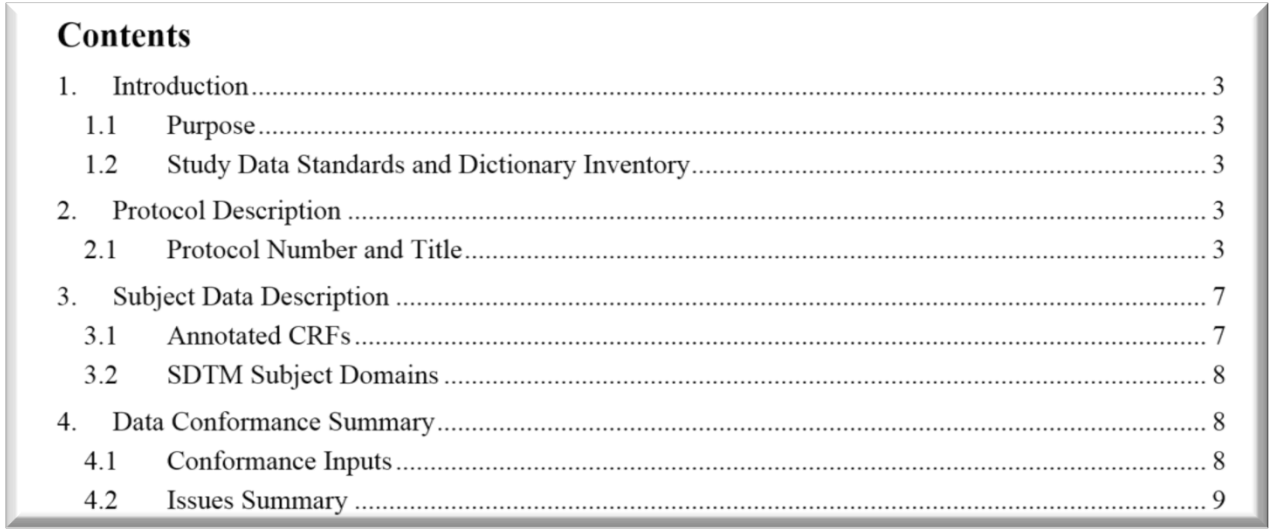
Not every project is for the submission of a single study. What if there are multiple studies being worked on at once?

The template is flexible. If a section is not relevant, it can simply be removed. This makes it very easy to summarize multiple studies within one document.

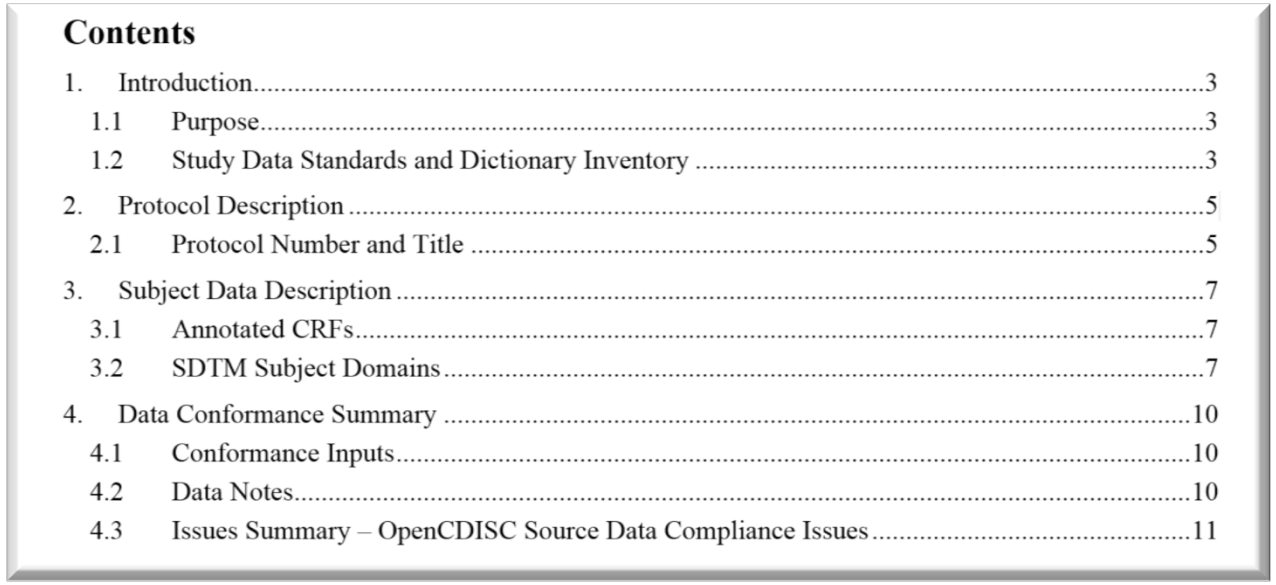
REAL EXAMPLES: MULTIPLE STUDIES IN ONE



Contents

- **Case 1:** ~50 protocols, standard set of domains within each study, no supplemental qualifier datasets
  - Lengthy Information that would need to be repeated for each protocol can be removed
    - Protocol design, trial design datasets, supplemental qualifier information, inclusion exclusion criteria, etc.
  - Most remaining information applies to all studies within the review guide

REAL EXAMPLES: MULTIPLE STUDIES IN ONE



Contents

- **Case 2:** 8 protocols, variety of domains and coding dictionaries used between studies
  - Some information needs to be expanded upon for each protocol, but other sections can be removed
    - Remove protocol design, trial design datasets, supplemental qualifier information, inclusion exclusion criteria, etc.
    - Expand on Study Data Standards and Dictionary Inventory and SDTM Subject domains

REAL EXAMPLES: MULTIPLE STUDIES IN ONE

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- **Study Data Standards and Dictionary Inventory**

Standard or Dictionary	Versions Used	
SDTM	Version 3.1.2 + Amendment 1, plus anything applicable from 3.2	
Controlled Terminology	SDTM Terminology 2013-06-28	
Data Definitions	Define.xml v1.0	
Medications Dictionary	STUDY A	WHODrug First Quarter, 2008
	STUDY B	WHODrug First Quarter, 2011
	STUDY C	WHODrug First Quarter, 2009
	STUDY D	WHODrug First Quarter, 2009
	STUDY E	WHODrug First Quarter, 2011
	STUDY F	WHODrug First Quarter, 2011
	STUDY G	WHODrug First Quarter, 2009
	STUDY H	WHODrug First Quarter, 2009
Medical Events Dictionary	STUDY A	MedDRA 10.0
	STUDY B	MedDRA 14.0
	STUDY C	MedDRA 12.0
	STUDY D	MedDRA 12.1
	STUDY E	MedDRA 14.0
	STUDY F	MedDRA 14.0
	STUDY G	MedDRA 12.0
	STUDY H	MedDRA 12.0

REAL EXAMPLES: MULTIPLE STUDIES IN ONE

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- **SDTM Subject Domains**

Dataset	Dataset Label	Class	Studies
AE	Adverse Events	Events	ALL
CE	Clinical Events	Events	ALL
CO	Comments	Special Purpose	STUDY A, STUDY C, STUDY F
CM	Concomitant Medications	Interventions	ALL
DA	Drug Accountability	Findings	STUDY G
DM	Demographics	Special Purpose	ALL
DS	Disposition	Events	ALL
EG	ECG Test Results	Findings	ALL
EX	Exposure	Interventions	ALL
FA	Findings About Events or Interventions	Findings About	ALL
IE	Inclusion/Exclusion Criterion Not Met	Findings	STUDY C, STUDY H
IS	Immunogenicity Specimen Assessment	Findings	STUDY E
LB	Laboratory Tests Results	Findings	ALL

REAL EXAMPLES: MULTIPLE STUDIES IN ONE

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- **Issues Summary**
  - Becomes an exceptional location to communicate decisions made throughout the course of a project

Study	Domain	Variable	Issue	Resolution
<Impacted protocols>	<Impacted domains>	<Impacted variables>	<Description of issue>	<Description of resolution>

  - Store all of your OpenCDISC findings and justifications in one document

Dataset	Diagnostic Message	Severity	Count	Explanation
STUDY A				
<DS>	<Message>	<Severity>	<Ct>	<Justification>
STUDY B				
<DS>	<Message>	<Severity>	<Ct>	<Justification>
STUDY C				
<DS>	<Message>	<Severity>	<Ct>	<Justification>

FINAL THOUGHTS

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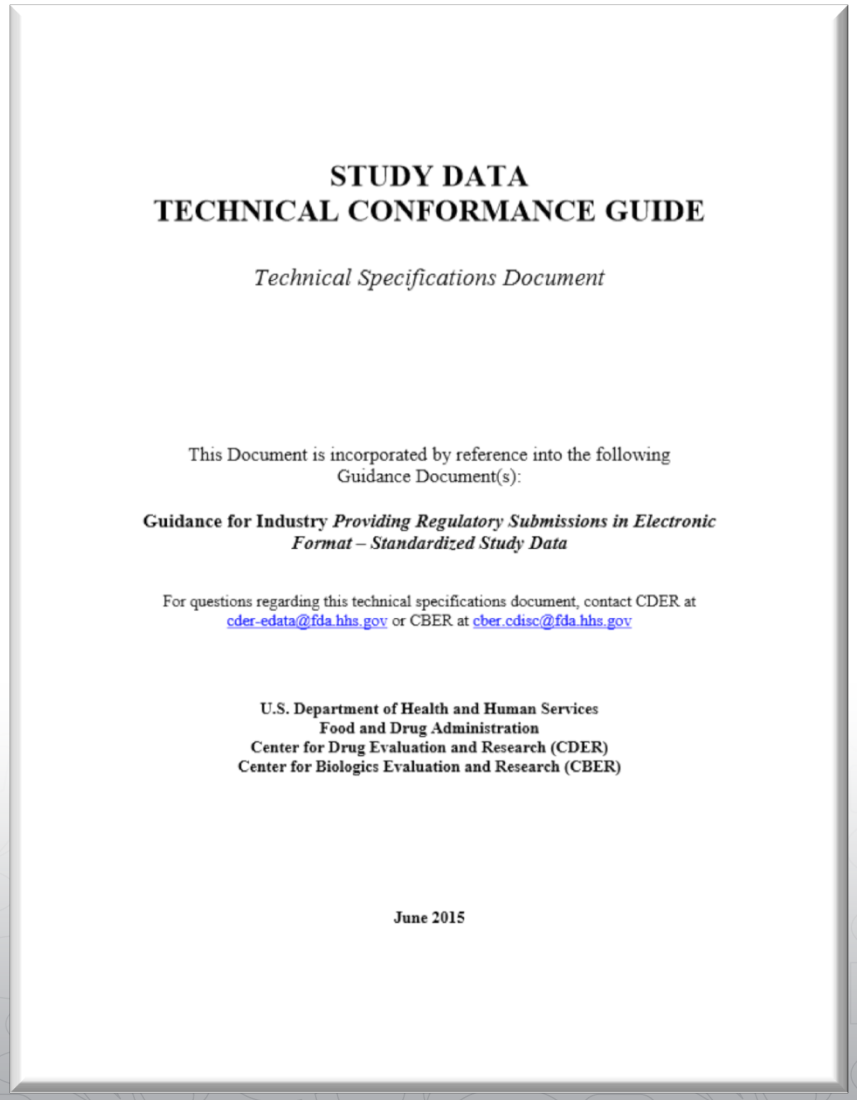
- Per the FDA's Study Data Technical Conformance Guide the SDRG is recommended as an integral part of a standards-compliant data submission.
- Per the Completion Guidelines, the document should be called the study-data-reviewers-guide.pdf and link to the blankcrf.pdf; however the FDA's Study Data Technical Conformance Guide now requests acrf.pdf instead of blankcrf.pdf.
- This document needs some minor updating
- Recommendation to standardize SDRG conformance issue explanation text on the Sponsor level where possible.
- Flexible, Customizable, Living document, start from the beginning of a project
- Creates transparency for the reviewer, team and sponsor
- ***Achieves Clarity!!***



STUDY DATA
TECHNICAL CONFORMANCE GUIDE

Technical Specifications Document

This Document is incorporated by reference into the following Guidance Document(s):

Guidance for Industry *Providing Regulatory Submissions in Electronic Format – Standardized Study Data*

For questions regarding this technical specifications document, contact CDER at cder-edata@fda.hhs.gov or CBER at cber.cdisc@fda.hhs.gov

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

June 2015

THANK YOU