Steps and Slides of Implementing Global Standards – Producing High Quality Programming Outputs Edition

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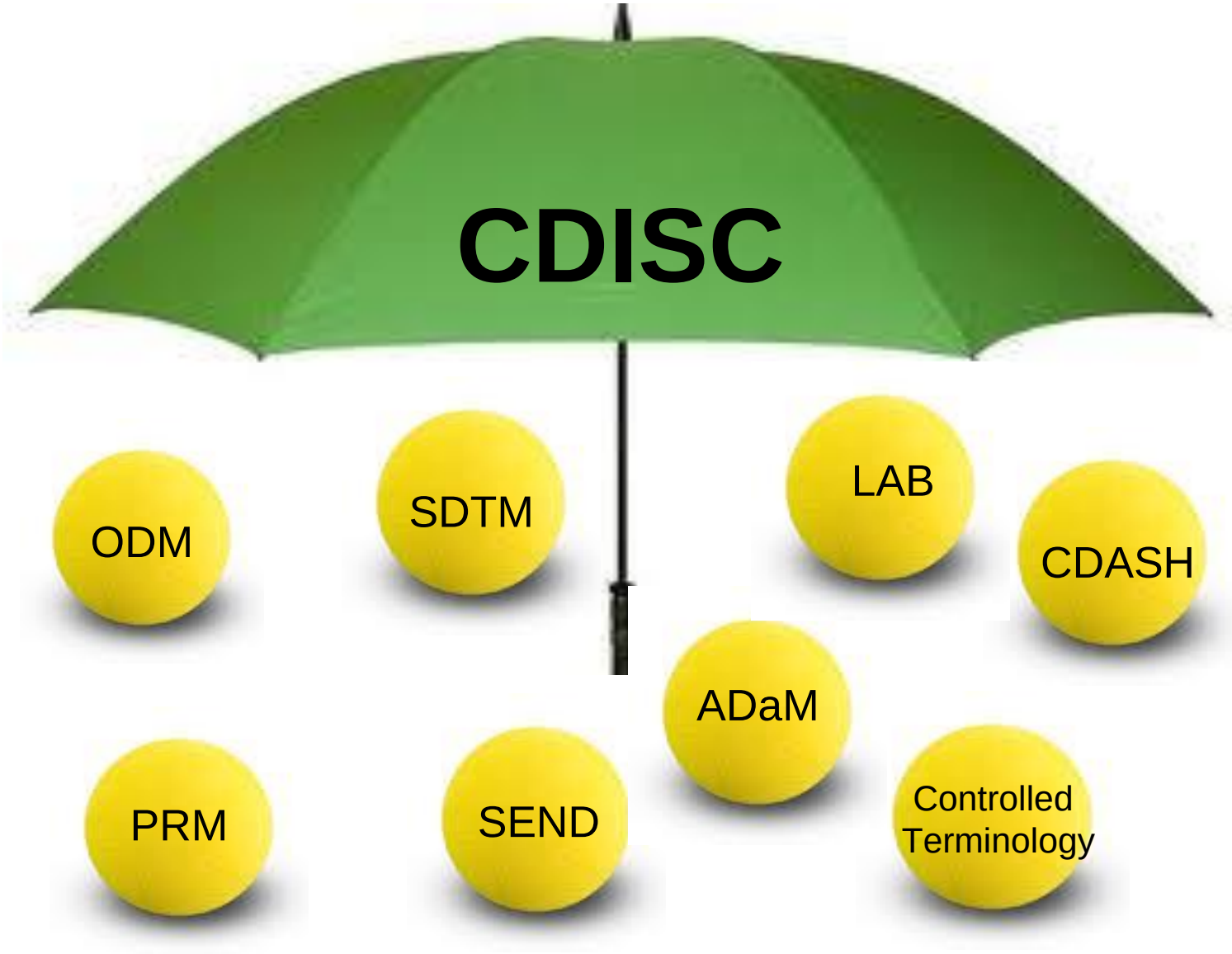
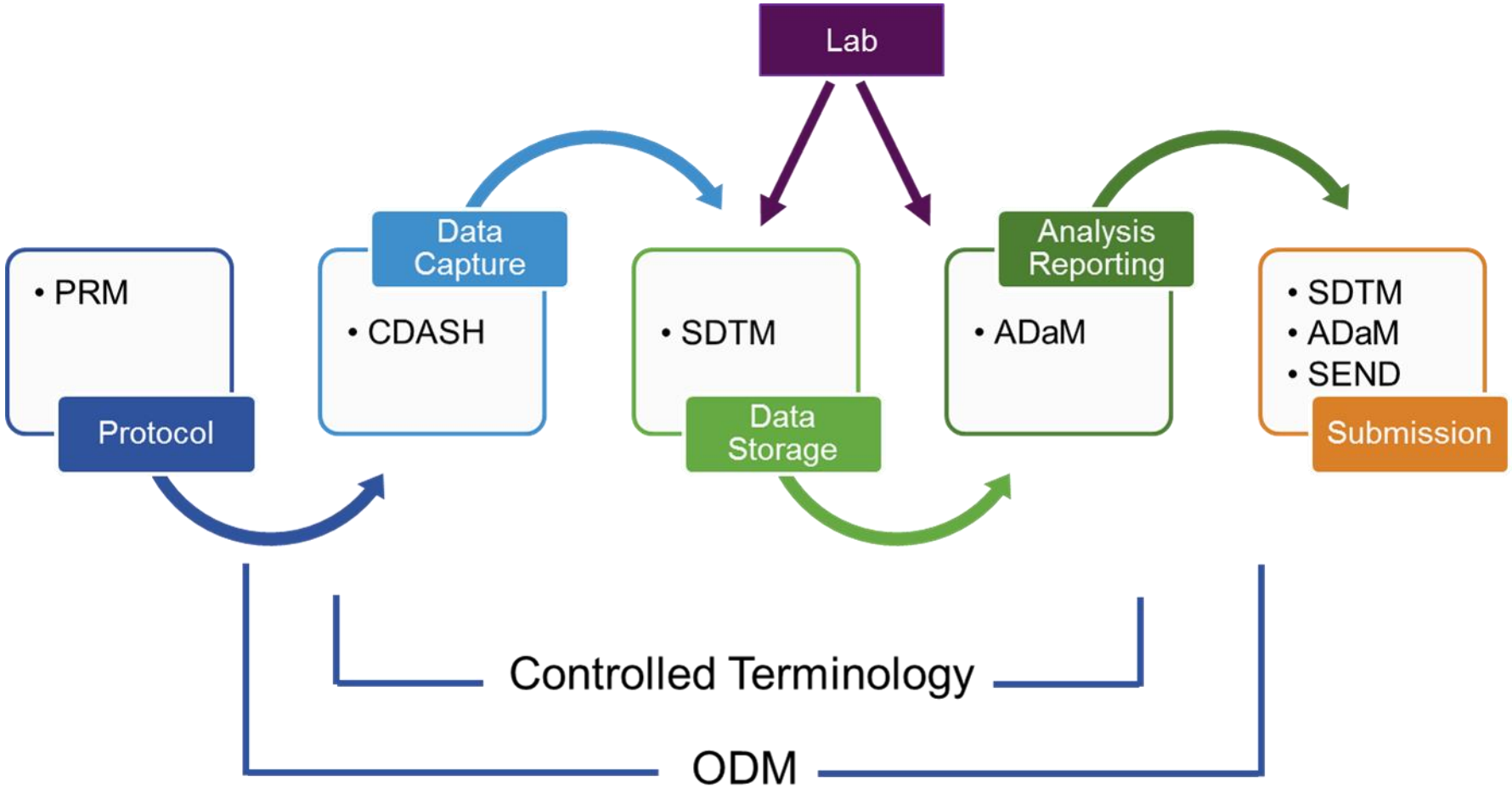


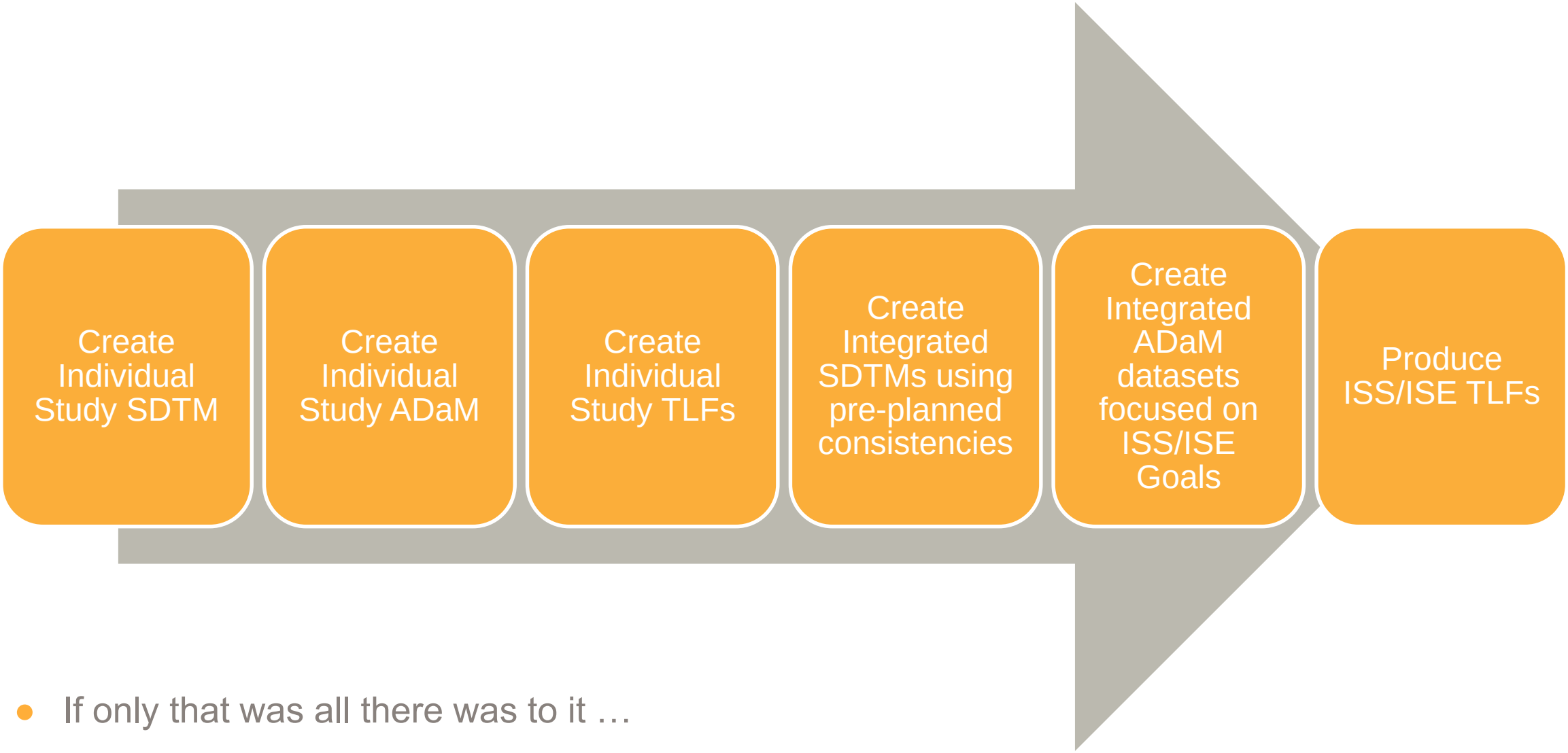
CDISC Acronyms - Decoded

- **CDISC** = Clinical Data Interchange Standards Consortium
- **SDTM** = Study Data Tabulation Model
- **ADaM** = Analysis Data Model
- **SEND** = Standard for the Exchange of Non-Clinical Data
- **CDASH** = Clinical Data Acquisition Standards Harmonization
- **ODM** = Operational Data Model
- **LAB** = Operational Data Model for Laboratory Data
- **PRM** = Protocol Representation Model
- **MSG** = Metadata Submissions Guideline
- **BRIDG** = Biomedical Research Integrated Domain Group
- **SHARE** = Shared Health and Clinical Research Electronic Library

CDISC Standards End to End

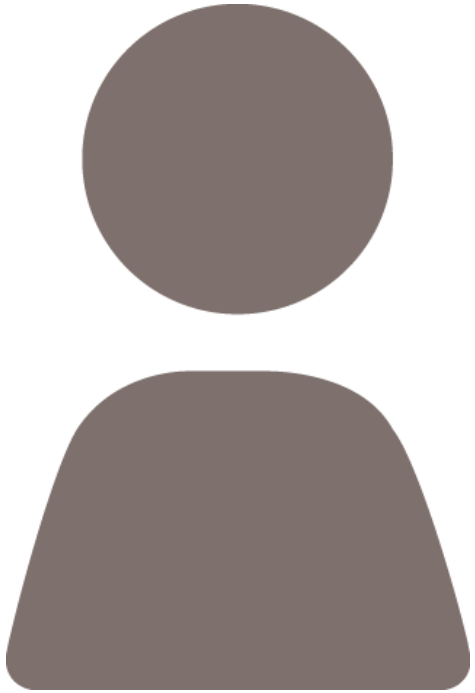


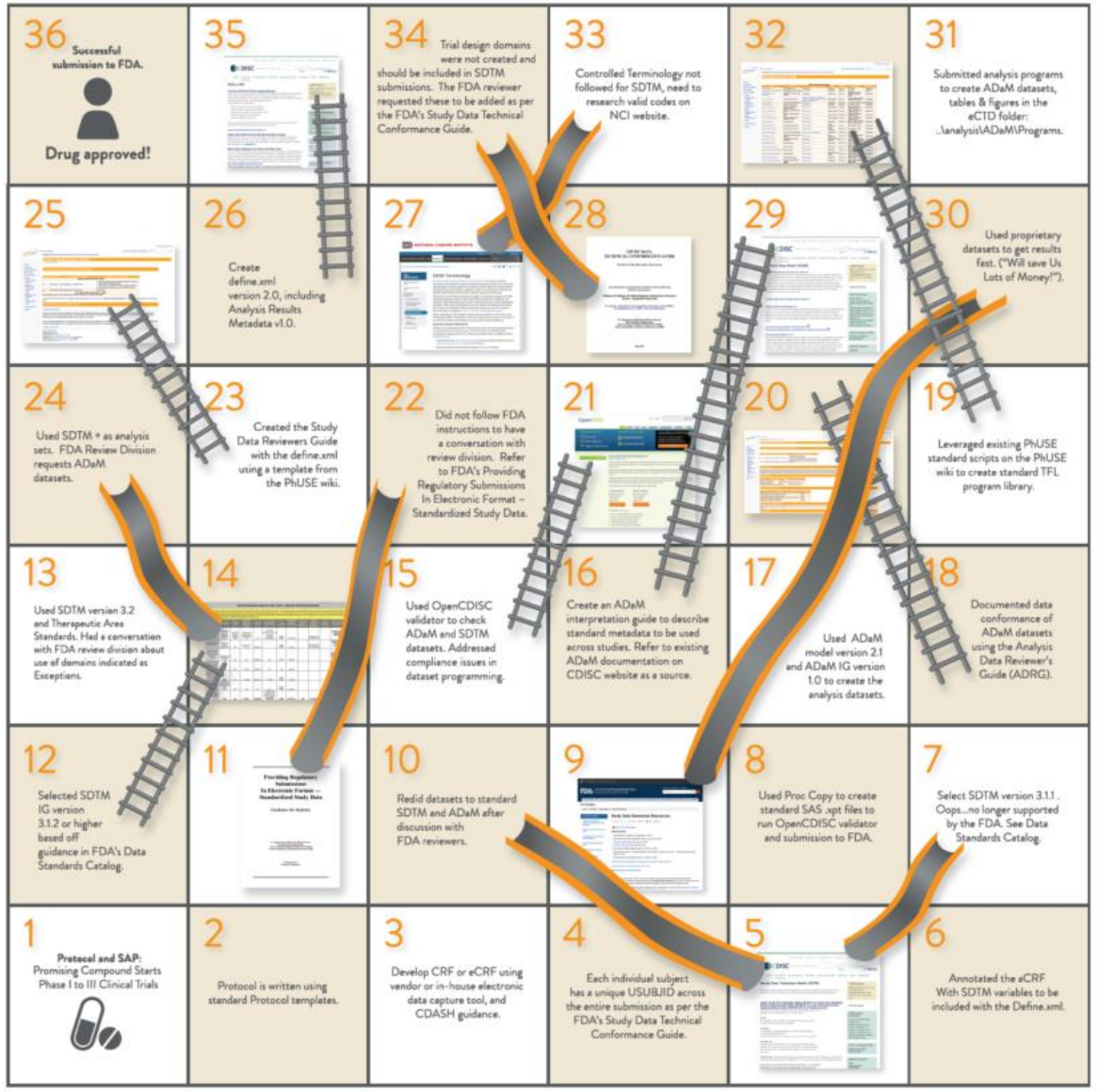
Typical Process Flow?



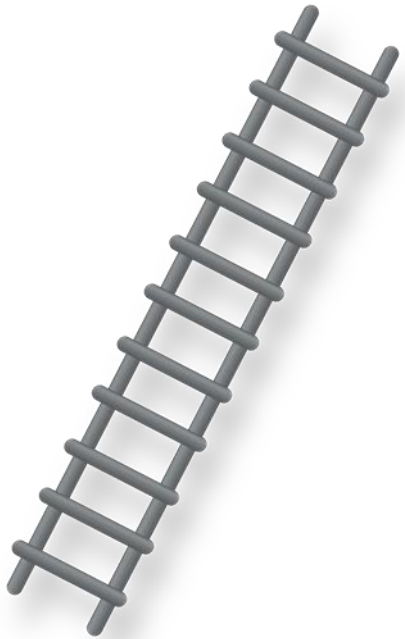
- If only that was all there was to it …

What Usually Happens



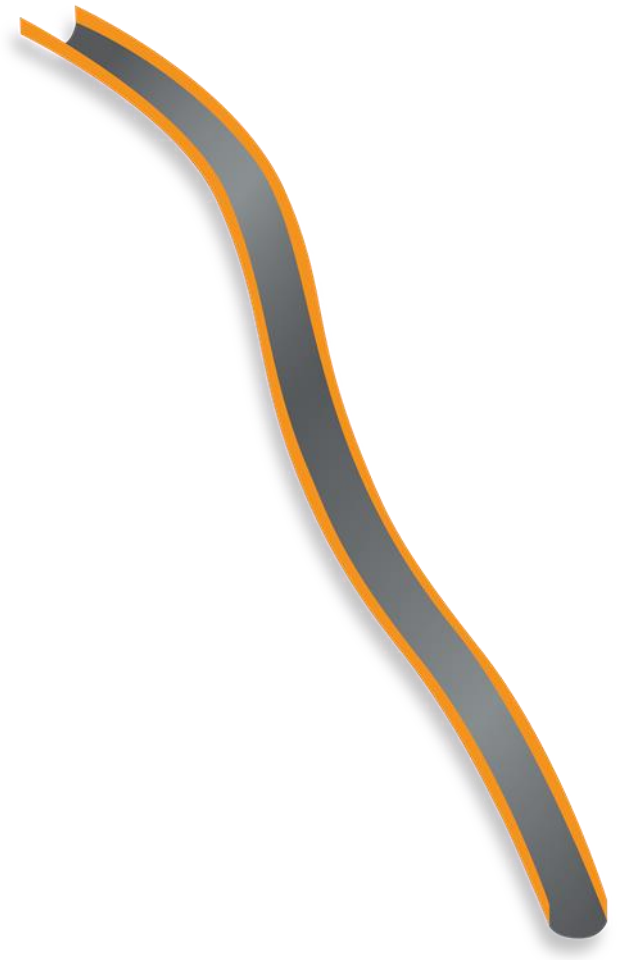


Steps and Slides



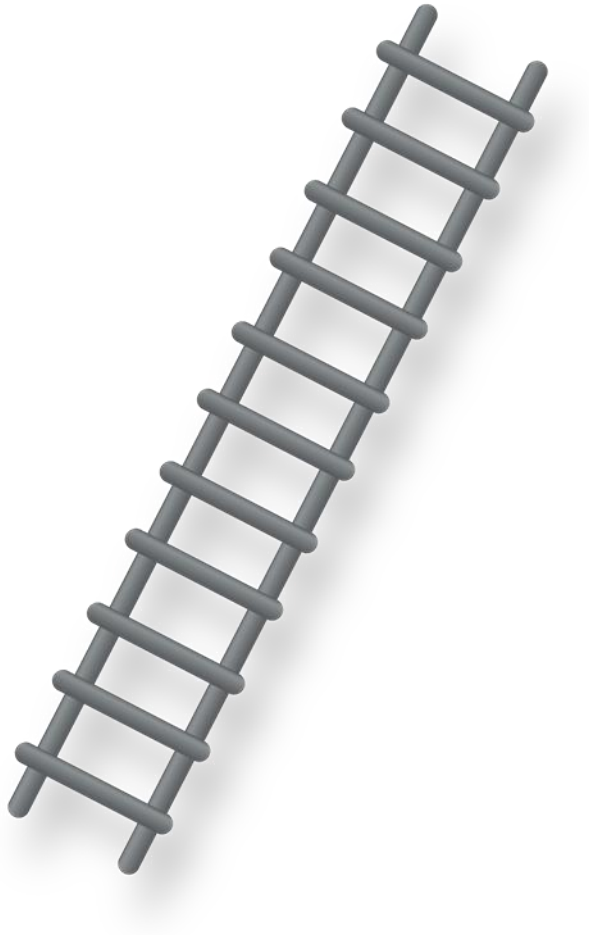
- Steps: Helpful strategies, documents, and plans with the endpoint of a successful submission
- Slides: Pitfalls in processes or resistance

Slides – A Few Examples



- Not following the FDA's Study Data Technical Conformance Guide
- Not having a conversation with the FDA review division until ready to submit
- Selecting non-supported versions of standards (e.g., SDTM IG 3.1.1)
- Not following standard controlled terminology
- Leaving conformance checks to the end
- Using proprietary analysis datasets

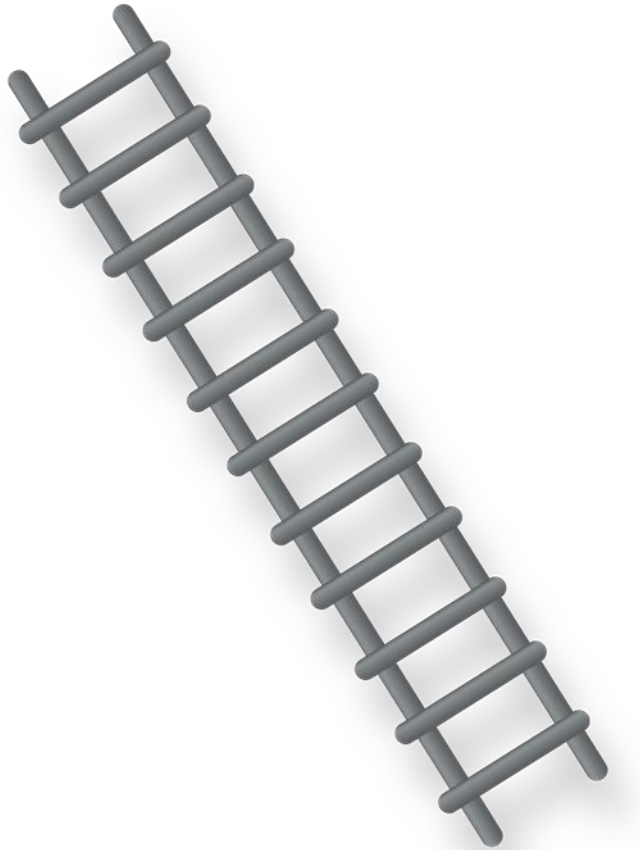
Steps



- Interpretation guides
- In Stream conformance checking
- Crosschecking macros
- Senior review
- Checklists
- Right tasks at the right time
- Automate completion of submission documents

Steps – Concrete Actions to Produce Quality Results

- Interpretation guides
  - Consistent results across studies
  - Considered decisions – not rash ones
- In-Stream conformance checking
  - Catch problems early – often during initial programming
  - Check items as they are updated – not once and done
- Crosschecking macros
  - Ensures deliverables are consistent with each other
- Senior review
  - A submission is not created in a vacuum – someone needs to look at the big picture
  - An expert is more likely to catch subtle errors



In-Stream Conformance Checking

Type	Macro Message
Parent Domain	
Compliance	Missing domain label
Compliance	The following variables are missing variable labels
Compliance	The following variables have labels with lengths greater the 40 characters
Quality	The following variables in <domain> are permissible in the <version> IG and null. Verify that these variables should be included in domain.
Quality	The following variables in <domain> are permissible in the <version> IG and null. Verify that these variables should be included in domain.
Quality	Variable label does not match <version> IG defined variable label in the <domain> template. Verify that variable label is accurate.
Quality	Variable is not defined in <version> IG <domain> template. Verify that variable should be included in domain.
Compliance	Check discrepancies for non-ascii characters. Non-ascii characters have been replaced with XX in COMPARE observations and control characters have been removed. Compare back with BASE to see where characters have been replaced. If it is not clear what is different, attempt viewing on unix to look for non-printable characters
Quality	Check ARM and ARMCD for accuracy and 1:1 relationship
Quality	Check ACTARM and ACTARMCD for accuracy and 1:1 relationship
Quality	Check EXTRT values for accuracy
Compliance	Both --DOSE and --DOSETXT populated for these subjects
Compliance	Negative values of --DOSE
Compliance	Missing --TRT for these subjects
Compliance	--OCCUR populated, but missing --PRESP for these subjects
Compliance	Missing --TERM for these subjects
Compliance	--TERM populated, but missing --DECOD
Compliance	Duplicating --SEQ values
Compliance	--STDY is greater than --ENDY. Confirm in raw data.
Compliance	SDTM cannot have study day values of 0. Make sure program is compensating for these values

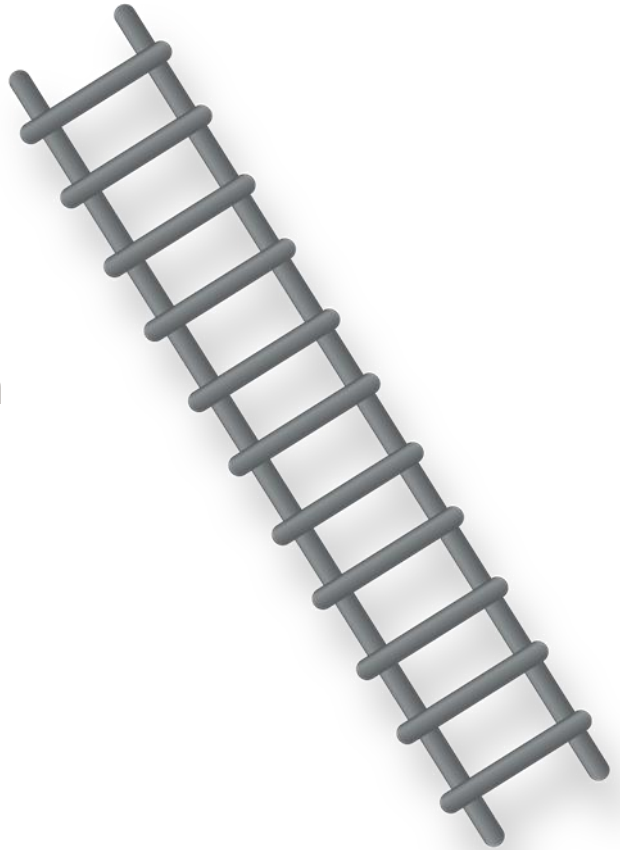
- Reduce the number of warnings and errors late in the process
- Can be customized to look for data quality items
- Should be seamless in the programming process
- Comprehensive, but not too much. Balanced

Steps – Concrete Actions to Produce Quality Results

- Checklists
  - Ensures none of the many, many steps are overlooked
  - Spreads expertise and provides roadmaps
  - Useful in project management and accountability

- Right tasks at the right time
  - A task is not complete until the deliverable is checked – don't move on to the next step of a process until you know you are on sound footing

- Automate completion of submission documents
  - In-house tools or using tools such as OpenCDISC/Pinnacle21
  - Enter data once – avoid cut and paste errors
  - Information only needs to be updated in a single location
  - Streamlines the process and reduces time and effort



Checklists, Checklists, Checklists

ADRG Review Checklist

Review of the Analysis Data Reviewer's Guide

Last updated:
12/18/2015

Section	Check
0.00	**General**
0.01	The audience for the ADRG is an external reviewer, and often, the FDA. Confirm verbiage: terms such as 'other Vendor', 'You', 'We', or 'I' should not be used. Full sentences should be used as much as possible.
0.02	Bulleted items should only have additional explanations if the response is 'Yes'
0.03	Confirm all sections are present. If optional sections have no applicable content, the sections should still appear in the ADRG and should be noted as not being applicable. Section 8 is an exception - if there is no content for this section, it should not be present.
1.00	**Section 1**
1.01	1.1 Purpose (required): Confirm section is completed with standard text from the ADRG template or other appropriate text.
1.02	1.2 Acronyms (optional): Confirm sponsor-specific or non-industry standard acronyms used elsewhere in the ADRG are documented in this section or confirm note stating section is not applicable is included.
1.03	1.3 Study Data Standards and Dictionary Inventory (required): Confirm values are consistent with other material included in the submission (such as the SDRG and define files).
1.04	1.4 Source Data Used for Analysis Dataset Creation (required): Confirm section is completed. If input data are not in SDTM format insure that corresponding adjustments are made to other sections as needed as the standard template assumes SDTM inputs.

- Ensure quality deliverables when tasks can be objectively confirmed as correct
- Makes sure none of the many, many steps required to generate a deliverable are overlooked
- Reminders for more experienced personnel – and roadmaps for the less experienced
- Promotes consistency across projects and submissions
- Provides accountability and aids in project management

Automate completion of submission documents: data definition file (define.xml)

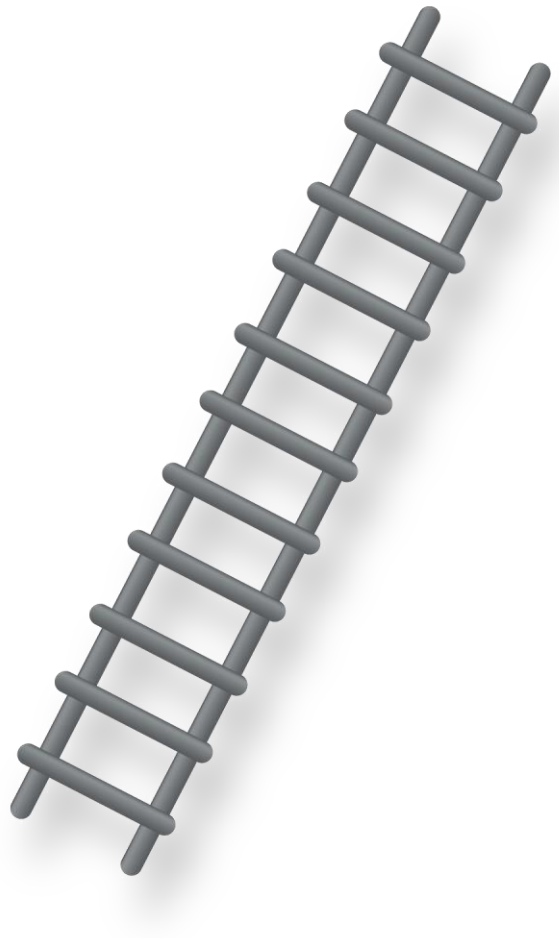
Disposition (DS) [Location: ds.xpt]

Variable	Label	Key	Type	Length	Controlled Terms or Format	Origin	Derivation/Comment
STUDYID	Study Identifier	1	text	7		Protocol	
DOMAIN	Domain Abbreviation		text	2	["DS" = "Disposition"] <Domain Abbreviation (DS)>	Assigned	
USUBJID	Unique Subject Identifier	2	text	14		Derived	Concatenation of STUDYID and SUBJID
DSSEQ	Sequence Number		integer	1		Derived	Sequential number identifying records within each USUBJID in the domain.
DSTERM	Reported Term for the Disposition Event		text	34	Reported Term for the Disposition Record	CRF Pages 6 16 18	
DSDECOD	Standardized Disposition Term	6	text	21	Completion/Reason for Non-Completion	CRF Pages 6 16 18	CRF controlled terminology was mapped to match CDISC controlled terminology.
DSCAT	Category for Disposition Event	5	text	18	["DISPOSITION EVENT" = "Disposition Event", "PROTOCOL MILESTONE" = "Protocol Milestone"] <Category for Disposition Event>	Assigned	
EPOCH	Epoch		text	9	["SCREEN", "TREATMENT"] <Epoch>	Assigned	
DSSTDTC	Start Date/Time of Disposition Event	4	date		ISO8601	CRF Pages 6 16 18	
DSSTDY	Study Day of Start of Disposition Event	3	integer	3		Derived	DSSTDY = DSSTDTC - RFSTDTC+1 if DSSTDTC is on or after RFSTDTC. DSSTDTC - RFSTDTC if DSSTDTC precedes RFSTDTC. Null if RFSTDTC is Null.

Go to the top of the define.xml

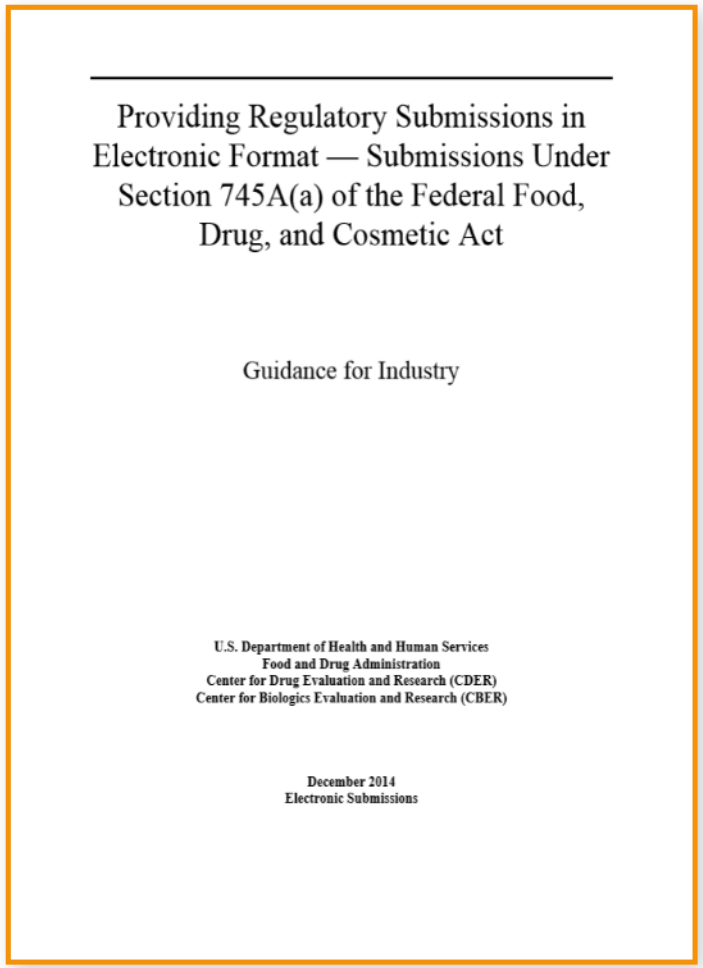
- Automating extraction of Page numbers on the define.xml from aCRFs for Origin column
- Move away from manual entry to increase quality
- Can be done via in-house macro(s)
- Tools may be purchase that automate

Building Steps to Avoid Slides



- Know the requirements
- Start with the end in mind
- Know the preferences
- Have a plan
- Develop consistent and thorough processes
- Build systems

Know the Requirements: FDA Guidance

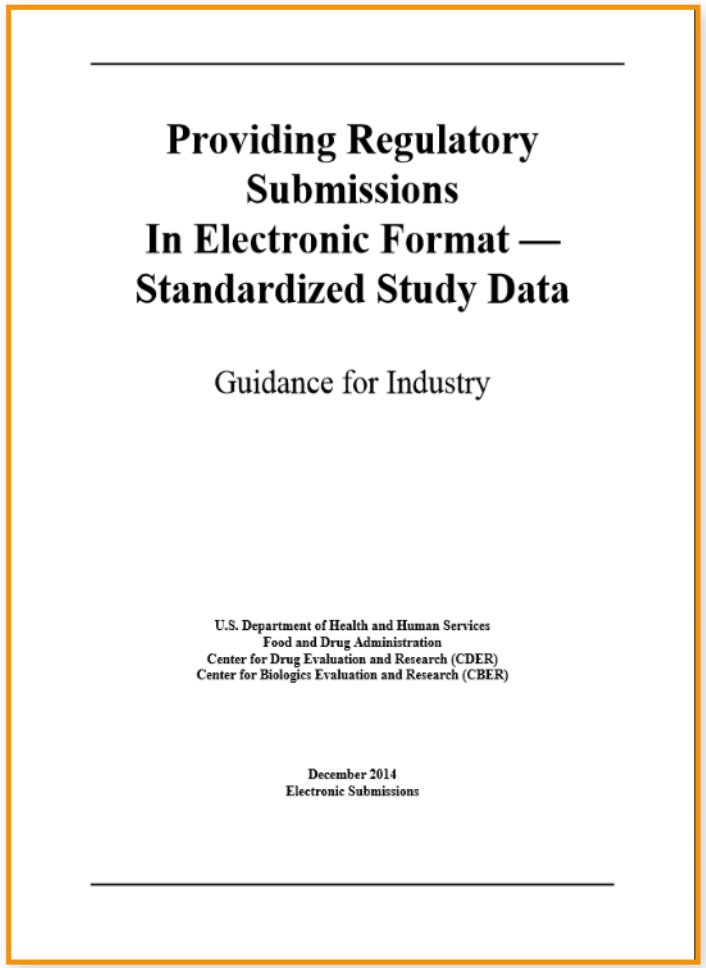


Providing Regulatory Submissions in Electronic Format — Submissions Under Section 745A(a) of the Federal Food, Drug, and Cosmetic Act

Guidance for Industry

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)

December 2014
Electronic Submissions

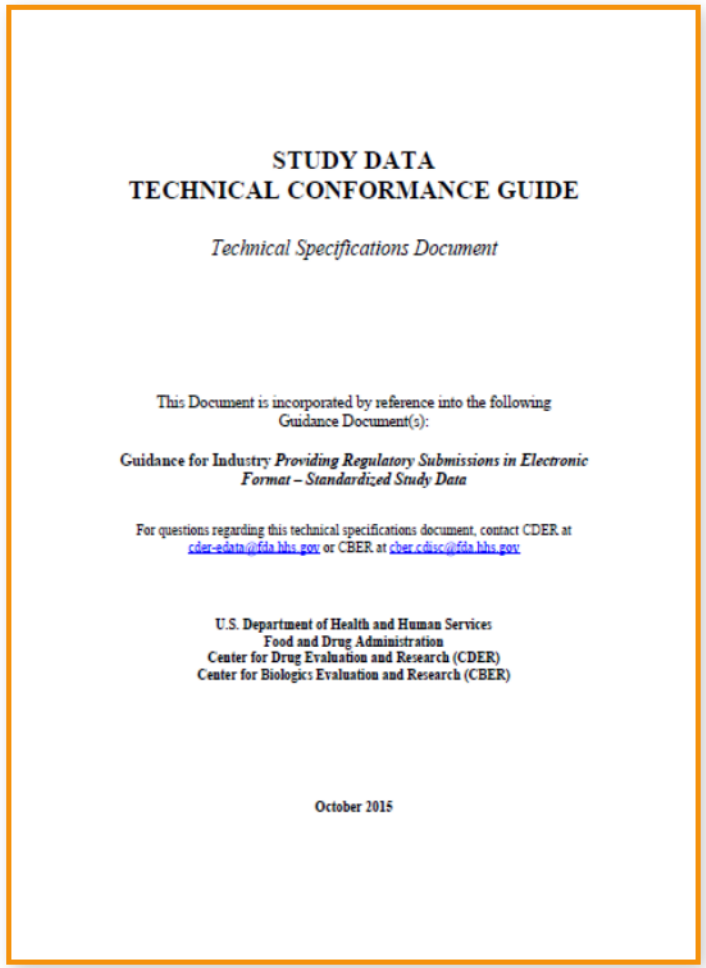


Providing Regulatory Submissions In Electronic Format — Standardized Study Data

Guidance for Industry

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)

December 2014
Electronic Submissions



STUDY DATA TECHNICAL CONFORMANCE GUIDE

Technical Specifications Document

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

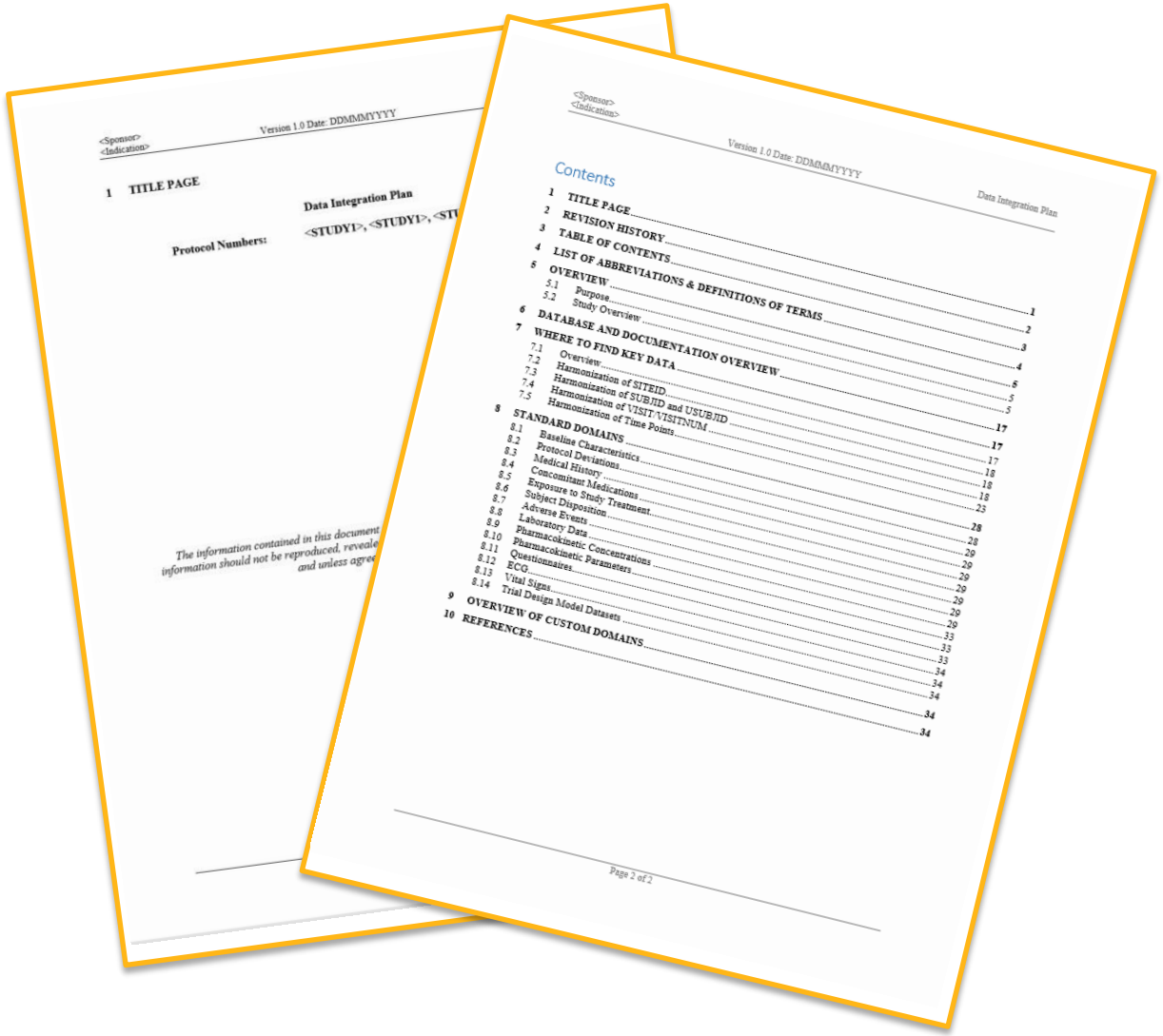
Guidance for Industry *Providing Regulatory Submissions in Electronic Format – Standardized Study Data*

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)

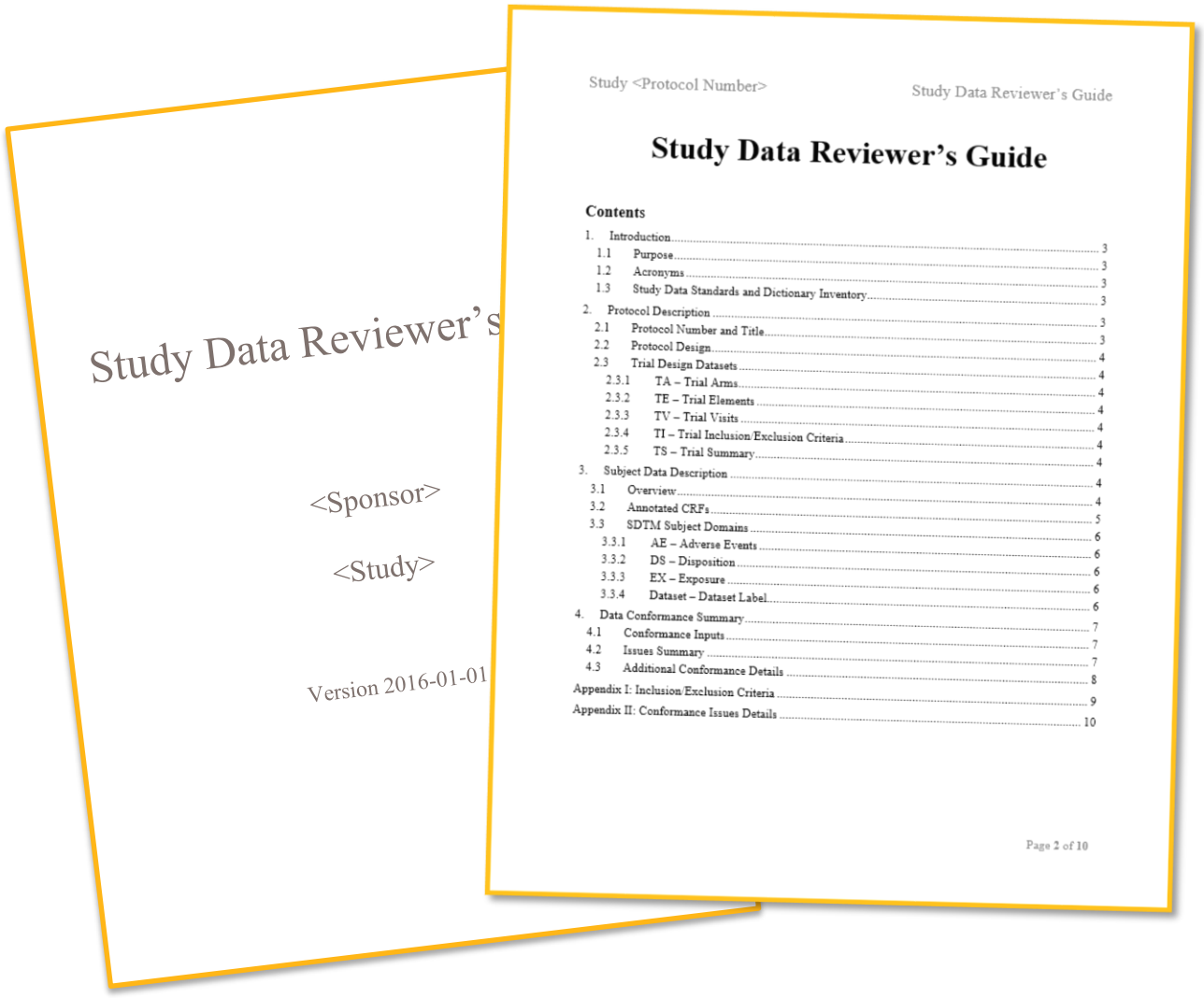
October 2015

Start with the End in Mind: Example Data Integration Plan (DIP)



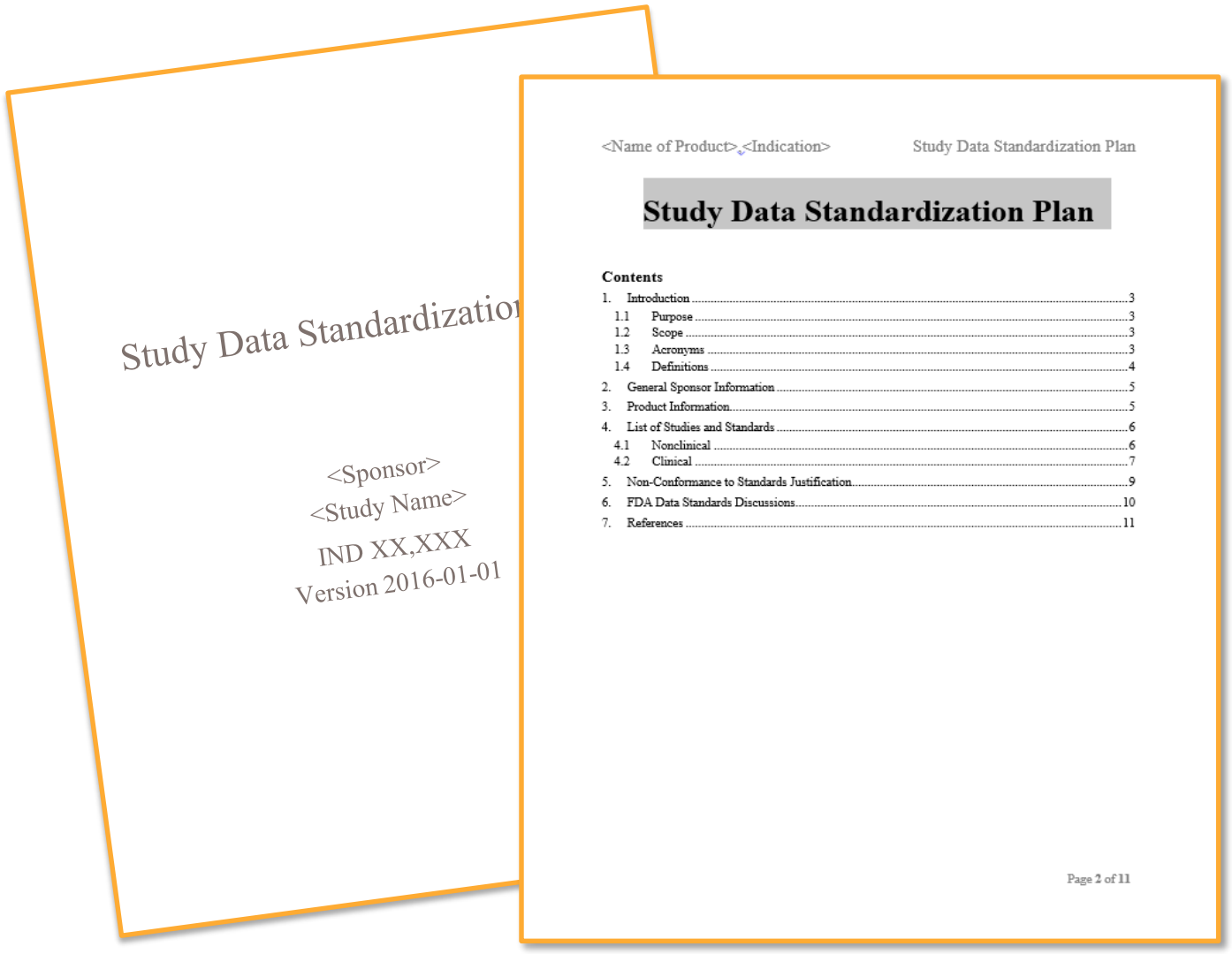
- Summary document that highlights how individual studies will be harmonized
- Provides additional information beyond what is available in the integration specifications
- Highlights key activities performed in the integration

Know the Preferences: One example – Study Data Reviewer's Guide



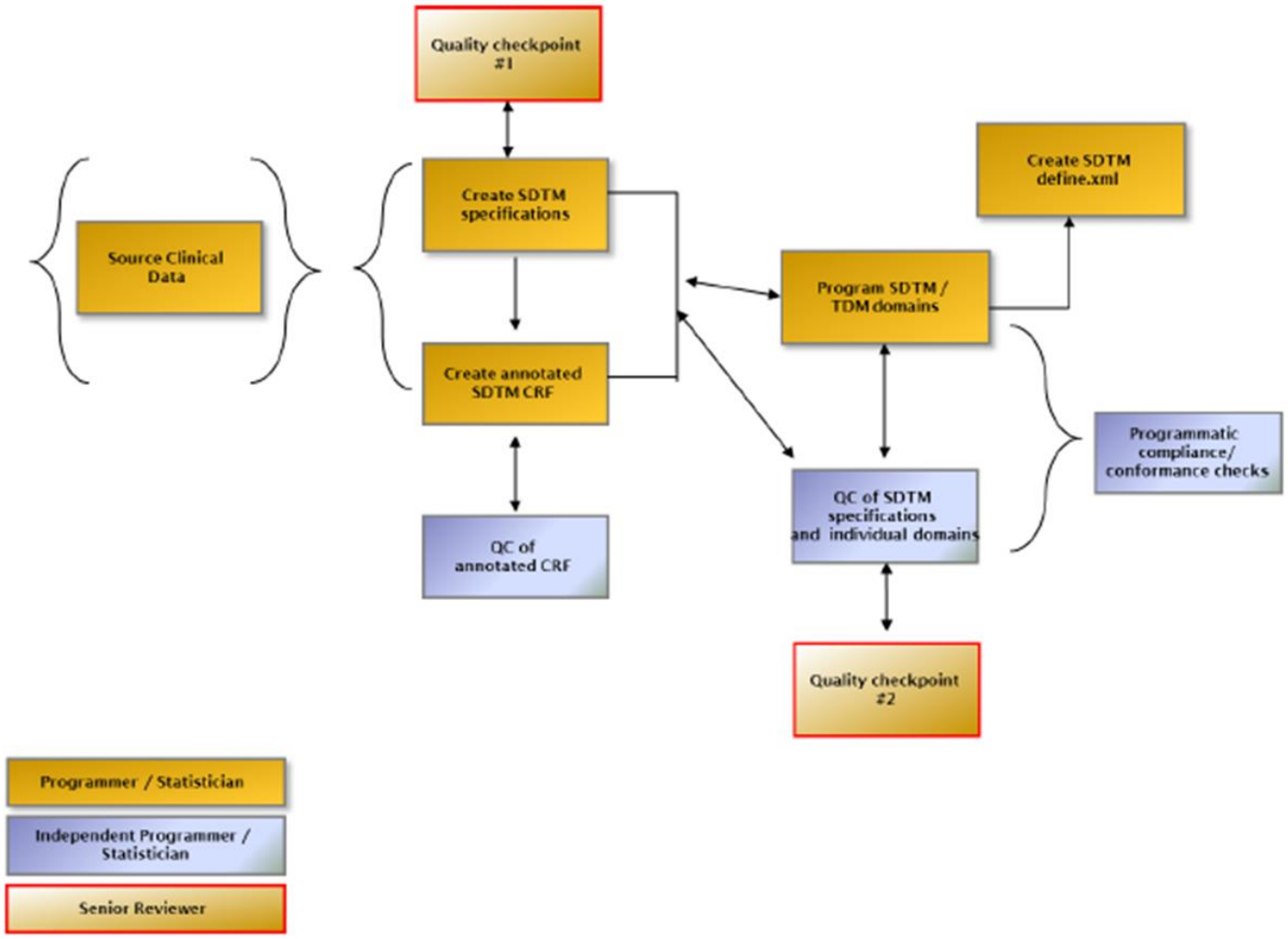
- Use the PhUSE standard templates and completion guidelines
- Create a company SDRG interpretation guide
- Checklists for Completion and Review
- Standard responses for conformance issues
- Find ways to automate the creation of sections from other reports or metadata

Have a Plan: Study Data Standardization Plan (SDSP)



- Plan for describing the data standardization approach for all studies and integrations
- The plan will be used in communication with FDA to assist in identifying potential data standardization issues as the preparations are made for the submission
- The plan can be used to communicate with FDA at a moment's notice the historical, current, and planned information about the development of the compound and indication
- Creates a High Quality data centric focus across the organization

Develop consistent and thorough processes: Quality SDTM domain & define.xml process



- Assuming your organization has a sound validation methodology and programming processes
- Start with Checklists to fill in Quality gaps
- Evaluate if that training program and checklist is really a needed Work Instruction (WI)
- Periodically review templates tied to SOPs/WIs to ensure they are up-to-date with the evolving standards
- Communicate often, Train, and Document

Build Systems – Do It Yourself or Buy It Off the Shelf?

- Do It Yourself
  - Flexible
  - Can be tailored on a case by case basis
  - Potentially easier to insert into established process flows
  - Requires expertise
  - Requires development
  - Requires maintenance
  - Potential bottleneck for support – what happens if key support personnel are sick, on vacation, or have competing priorities?
- Off the Shelf
  - Quick
  - Consistent look and feel
  - Maintenance and support are shifted to the provider
  - May be difficult to integrate with current processes
  - Can be difficult to customize
  - May not do everything

Summary

- Remember the goal is to get drugs, biologics and devices to market quicker with ultimate patient safety in mind
- As a bare minimum, your organization must have a sound validation methodology and solid programming processes
- High quality clinical data submission deliverables assist FDA reviewers in support of actual review activities
- They reduce the need for post-submission Requests for Information/Data resubmission
- A manual process might work best for one company with checklists where automated systems/tools work best for another
- There are no short cuts with **quality**

Questions?

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