Nonclinical Study Data Specifications and CRO-Sponsor Workflows for FDA SEND Compliance

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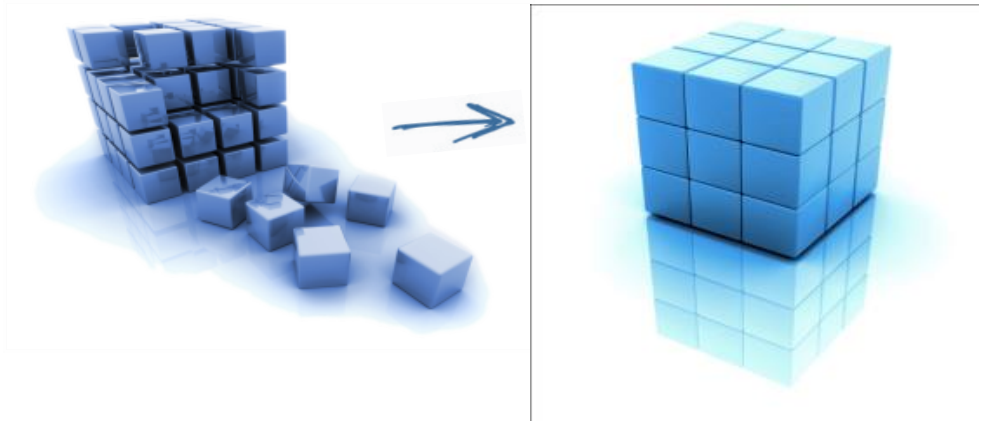
Michael Dorato, Smithers Avanza



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Agenda

Topic	Presenter
Submission and Review Workflows at the FDA	Kristi Johnson
Current State of SEND in the Industry	Kristi Johnson
Challenges in Preparing SEND Datasets and CRO-Sponsor Workflows to Improve Data Quality	Kristi Johnson
Perspectives from a CRO	Michael Dorato
Summary, Q&A	All

Data flow at the FDA from submission to review

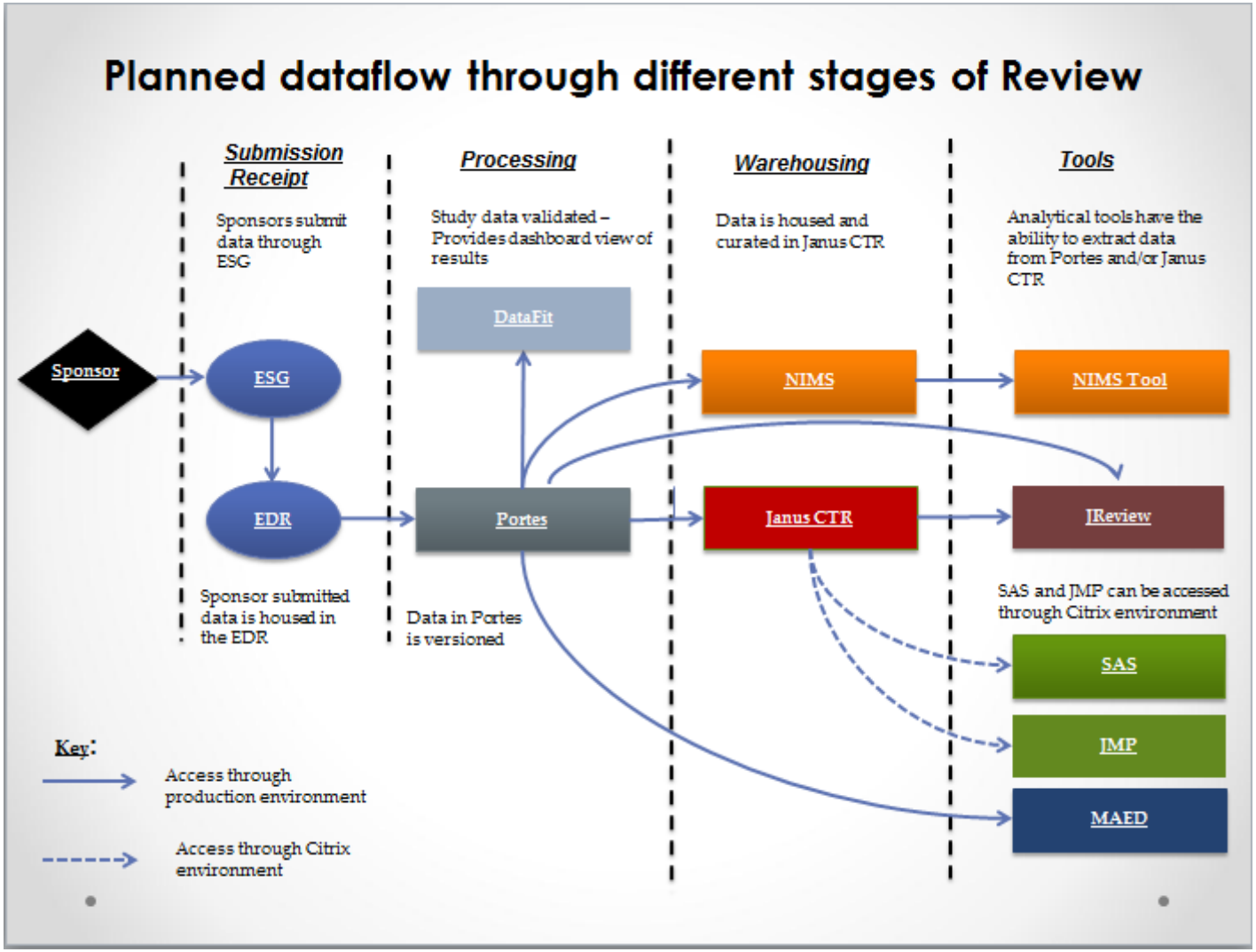


Diagram courtesy of Booz Allen Hamilton on behalf of FDA CDER

SEND Study Data Review Workflows at FDA CDER

- ✓ SEND datasets packaged in the M4 folder of eCTD submissions are received
- ✓ The Portes software versions the available studies in the submissions
- ✓ NIMS picks up new studies from Portes through automated workflows
- ✓ All SEND files are validated against CDISC and FDA validation rules
  - Dashboard populated
  - Validation reports, Define.xml and SDRG files are made available
  - Studies with “no validation errors” are loaded and ready for pharm/tox review
  - Studies with “validation errors” are not loaded; returned to submitter
- ✓ Reviewers access study data through tools like the ToxVision SEND data browser
  - Review tabulated or graphical views of findings and signals
  - Create clubbed groups or generate “sponsor groups” with exclusions
  - Check against Study Report to verify signals of interest

Potential Data Problems & Consequences to Sponsors

- ✓ Validation checks only assess the data format against rules
  - Failure means the data will not be loaded for review
  - Success can still mean issues at other stages
- ✓ Define.xml and study data files do not match (missing, or unexpected domains)
- ✓ If reviewers discover variance in summary data between re-constituted SEND trial sets to sponsor defined groups in the study report – ***Raises questions about the submission!***
- ✓ If reviewers see a signal in Lab-test data or incidence counts not visible in the study report individual subject results – ***Raises questions about the submission!***
  - Why are the individual data not the same in SEND and Study Report?
- ✓ If there are insufficient domains or data for the purposes of review and if the data is available in the study report – ***Raises possible request for additional data to be submitted***

Current Industry Situation regarding SEND

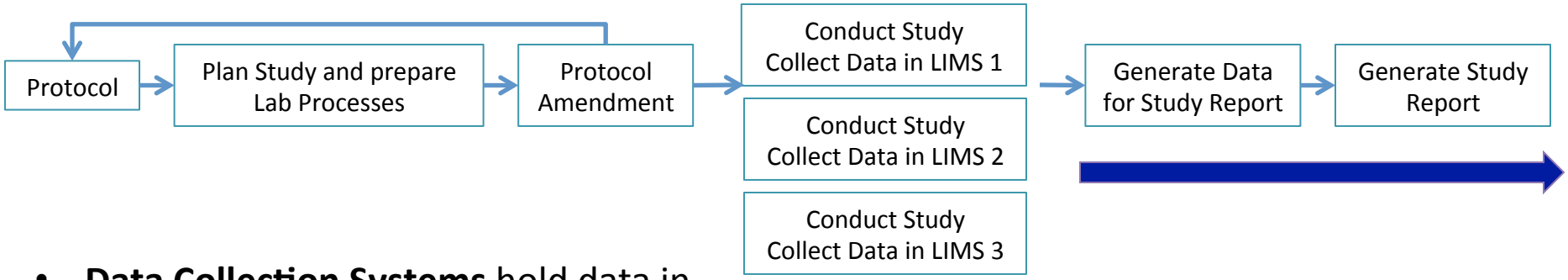
1. Increasing evidence that validating a SEND dataset for conformance to the standard is necessary *but simply not sufficient* to be SEND ready
   - SEND datasets that do not match tabulated data in the reports OR that are missing chunks of data will appear ***untrustworthy*** to FDA reviewers
2. The FDA's test submission process only provides a validator report which indicates if there are errors:
   - This is an *extremely low bar* to judge CRO and sponsor readiness
   - Only a real submission to the FDA will trigger regulatory review of the SEND data and the accompanying study report
   - **Sponsors, do you want to wait until you have a real submission to verify your providers?** ***Delays due to rejected data or questions about data integrity?***

Sponsor and CRO Challenges with SEND Preparation

A complete SEND submission should include *standardized SEND datasets* plus the *define file* and a *Study Data Reviewer's Guide*

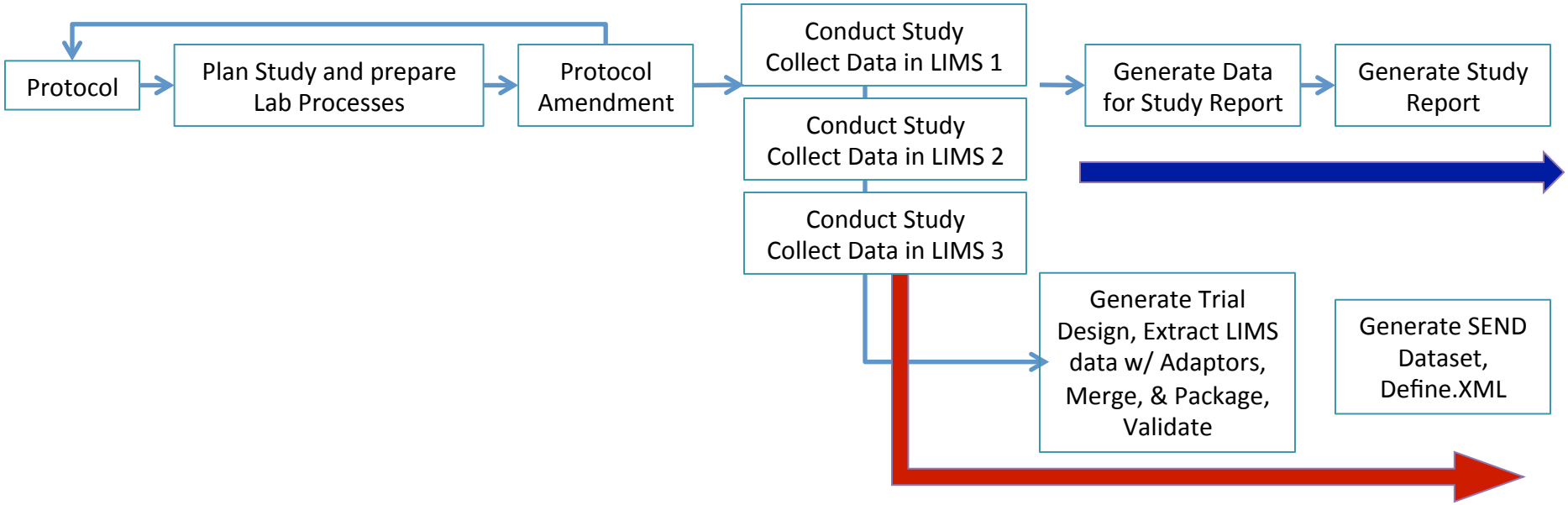
- ✓ Studies include data from various data providers/systems - must **harmonize and assemble** these different data streams into a single package
- ✓ Providing SEND datasets **technically conformant** with the CDISC standard, controlled terminologies and FDA specific validation rules
- ✓ Ensuring that the SEND data for every study is ***fit for FDA review***:
  - **Consistent** with the study report
  - **Complete** with respect to all of the reportable data

Current Study Reporting Processes



- **Data Collection Systems** hold data in proprietary data models not easily accessed other than through system reports
- Keeping up with the collection system versions, data model changes and terminology changes is complex
- LIMS data are held in a GLP store
- LIMS data is transformed into preferred terms and study designs for Study Data publication by the Principal Investigator – *see the process flow*

Pitfalls of separate SEND & study reporting processes



- SEND datasets are generated by a parallel process possibly by different people using Trial Designs needed for SEND. The data is reported using "preferred" terminology of the toxicologists. *These do not match the study report's dose groupings - see* →
- Study Reports are signed by the Study Director. The SEND Dataset must also be signed by the Sponsor or preparer.
- Because the two are constructed using disparate processes, they need NOT be consistent - to prove that they have the ***right quality, consistency and completeness*** is difficult, expensive, and time consuming

Examples of Data Conformance, Consistency and Completeness Issues in SEND Datasets & Submissions

Failure to comply with the SEND Standard

	STUDYID	DOMAIN	USUBJID	MASEQ	MATESTCD	MATEST	MAORRES	MASTRESC	MASPEC	MAANTREG	MALAT	MADTC	MADY
1	ABC123	MA	1	1	GROSPATH	Gross Pathological Examination	Enlargement	Enlargement	LYMPH NODE	BILATERAL		9/21/2015	48
2	ABC123	MA	2	1	GROSPATH	Gross Pathological Examination	Discoloration, Pale	Pale	SPLEEN			9/21/2015	48
3	ABC123	MA	3	1	GROSPATH	Gross Pathological Examination	Discoloration, Pale	Pale	LIVER			9/21/2015	48
4	ABC123	MA	4	1	GROSPATH	Gross Pathological Examination	Normal	NORMAL	ALL TISSUES			9/21/2015	48
5	ABC123	MA	5	1	GROSPATH	Gross Pathological Examination	Normal	NORMAL	ALL TISSUES			9/21/2015	48
6	ABC123	MA				Pathological Examination	Normal	NORMAL	ALL TISSUES			9/21/2015	48
7	ABC123	MA				Pathological Examination	Normal	NORMAL	ALL TISSUES			9/21/2015	48
8	ABC123	MA				Pathological Examination	Normal	NORMAL	ALL TISSUES			9/21/2015	48
9	ABC123	MA				Pathological Examination	Normal	NORMAL	ALL TISSUES			9/21/2015	48
10	ABC123	MA				Pathological Examination	Normal	NORMAL	ALL TISSUES			9/21/2015	48
11	ABC123	MA	11	1	GROSPATH	Gross Pathological Examination	Not Collected	Not Collected	SKIN			9/21/2015	48
12	ABC123	MA	11	2	GROSPATH	Gross Pathological Examination	Discoloration, Pale	Pale	LIVER			9/21/2015	48
13	ABC123	MA	11	3	GROSPATH	Gross Pathological Examination	Enlargement	Enlargement	LIVER			9/21/2015	48
14	ABC123	MA				gical Examination	Normal	NORMAL	ALL TISSUES			9/21/2015	48
15	ABC123	MA				gical Examination	Normal	NORMAL	ALL TISSUES			9/21/2015	48
16	ABC123	MA				gical Examination	Normal	NORMAL	ALL TISSUES			9/21/2015	48
17	ABC123	MA				gical Examination	Discoloration, Pale	Pale	KIDNEY	BILATERAL		9/21/2015	48
18	ABC123	MA				gical Examination	Normal	NORMAL	ALL TISSUES			9/21/2015	48
19	ABC123	MA				gical Examination	Normal	NORMAL	ALL TISSUES			9/21/2015	48
20	ABC123	MA				gical Examination	Normal		ALL TISSUES			9/21/2015	48
21	ABC123	MA	19	1	GROSPATH	Gross Pathological Examination	Nodule		SKIN			9/21/2015	48
22	ABC123	MA	20	1	GROSPATH	Gross Pathological Examination	Nodule		SKIN			9/21/2015	48
23	ABC123	MA	21	1	GROSPATH	Gross Pathological Examination	Normal		ALL TISSUES			9/21/2015	48
24	ABC123	MA	21	2	GROSPATH	Gross Pathological Examination	Normal		ALL TISSUES			9/21/2015	48
25	ABC123	MA	21	3	GROSPATH	Gross Pathological Examination	Normal	NORMAL	ALL TISSUES			9/21/2015	48
26	ABC123	MA	21	4	GROSPATH	Gross Pathological Examination	Normal	NORMAL	ALL TISSUES			9/21/2015	48
27	ABC123	MA	22	1	GROSPATH	Gross Pathological Examination	Normal	NORMAL	ALL TISSUES			9/21/2015	48
28	ABC123	MA	23	1	GROSPATH	Gross Pathological Examination	Enlargement	Enlargement	Lymph Nodes	BILATERAL		9/21/2015	48
29	ABC123	MA	24	1	GROSPATH	Gross Pathological Examination	Normal	NORMAL	ALL TISSUES			9/21/2015	48
30	ABC123	MA	25	1	GROSPATH	Gross Pathological Examination	Normal	NORMAL	ALL TISSUES			9/21/2015	48
31	ABC123	MA	26	1	GROSPATH			NORMAL	ALL TISSUES			9/21/2015	48
32	ABC123	MA	27	1	GROSPATH			NORMAL	ALL TISSUES			9/21/2015	48
33	ABC123	MA	28	1	GROSPATH			NORMAL	ALL TISSUES			9/21/2015	48
34	ABC123	MA	29	1	GROSPATH			NORMAL	ALL TISSUES			9/21/2015	48
35	ABC123	MA	30	1	GROSPATH			Nodule	SKIN			9/21/2015	48
36	ABC123	MA	31	1	GROSPATH	Gross Pathological Examination	Nodule	Nodule	SKIN			9/21/2015	48
37	ABC123	MA	32	1	GROSPATH	Gross Pathological Examination	Enlargement	Enlargement	KIDNEY	BILATERAL		9/21/2015	48
38	ABC123	MA	33	1	GROSPATH	Gross Pathological Examination	Discoloration, Pale	Pale	KIDNEY	BILATERAL		9/21/2015	48
39	ABC123	MA	34	1	GROSPATH	Gross Pathological Examination	Normal	NORMAL	ALL TISSUES			9/21/2015	48
40	ABC123	MA	35	1	GROSPATH	Gross Pathological Examination	Normal	NORMAL	ALL TISSUES			9/21/2015	48

Modifier has been incorrectly populated as the base finding

Specimen that was not collected has not had status populated as "NOT DONE"

Specimen modifier has been incorrectly classified

Variable populated with term not present on appropriate CT list

Consequences of Data Quality Issues

- ✓ Data consistency issues between the SEND data and study report may cause reviewers to question the ***trustworthiness*** of the data
- ✓ The SEND dataset lacks data present in the study report. This can cause reviewers to question why those data were excluded, and ***delay the review process***
- ✓ Specimen information missing for Clinical Chemistry measurements and Gross Pathology. Datasets are ***difficult to review and interpret*** causing further delays
- ✓ Inability to load dataset due to syntax errors within Define.XML – ***affects validation and automated loading***

How to address data quality, consistency and completeness issues in SEND datasets

CRO-Sponsor workflows to improve data quality

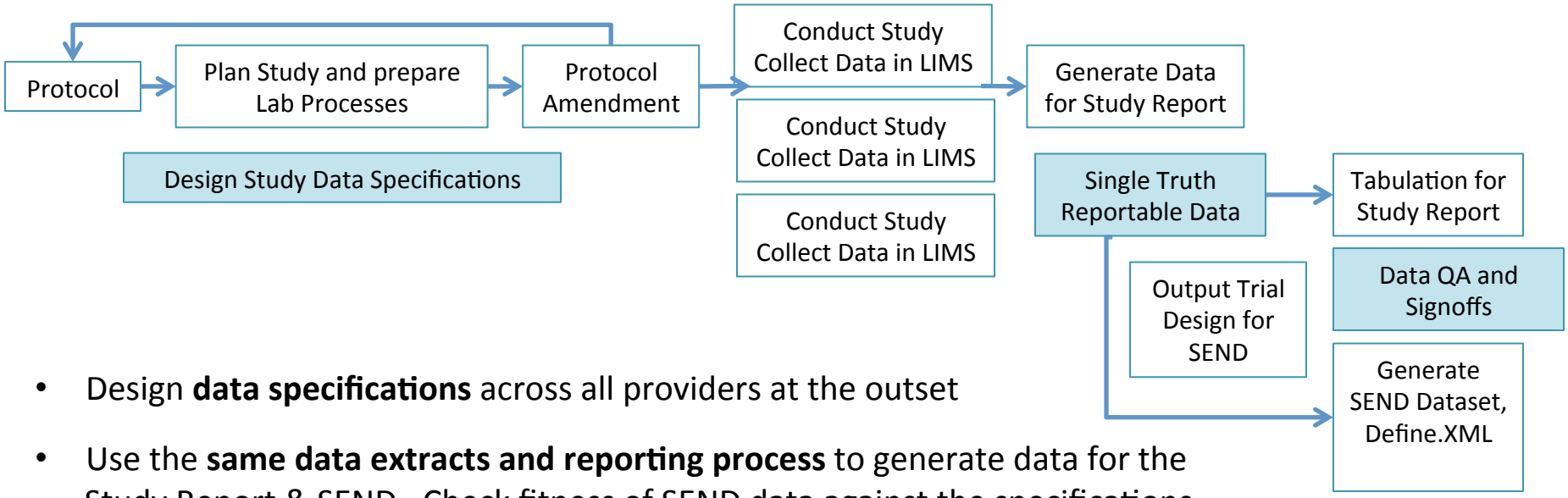
1. **Study Data Specifications:** Plan for SEND and specify expectations with each provider against which progress and performance can be measured and controlled

2. **Single Truth Data Resource**: Use the same data resource in a "single truth" repository for both study reporting and automation of SEND transformation workflows

3. **QA/QC tools and governance processes**: for a high quality product with reduced costs

Specify, Generate and Review Reportable Data

Data for study reporting and SEND in a common repository



- Design **data specifications** across all providers at the outset
- Use the **same data extracts and reporting process** to generate data for the Study Report & SEND. Check fitness of SEND data against the specifications
- Maintain **"single-truth"** of collected data in an accessible data store for consistency between study reports and SEND Datasets
- Represent **reportable data** in a repository:
  - ✓ Data for tabulation or analysis for Study Reports in dose groups
  - ✓ Data for columnar representation in SEND Trial Design and Trial Sets using CDISC terminology
  - ✓ Final SEND datasets for delivery to sponsors, or by sponsors for submission to the FDA
- Apply **data QA tools/processes** for final release of submission ready SEND packages

Planning for SEND at Study Start

- ***Optimize*** protocol template to capture SEND required variables
  - Example: Include “Sponsor Identifier” and “Study Monitor” as fields to be populated in the study protocols
- ***Harmonize*** terms from Controlled Terminology (CT) lists in study protocol template and LIMS systems
  - Example: Report study type using the same terms from the CDISC CT List
- ***Uniformity*** in data collection. Ensure all data are collected in the same format.
  - Makes automation of SEND datasets across different data types possible
- ***Specify*** your SEND dataset during study planning. Ensures consistency in naming conventions across disparate data sources.

Using the Study Protocol to Specify SEND Domains

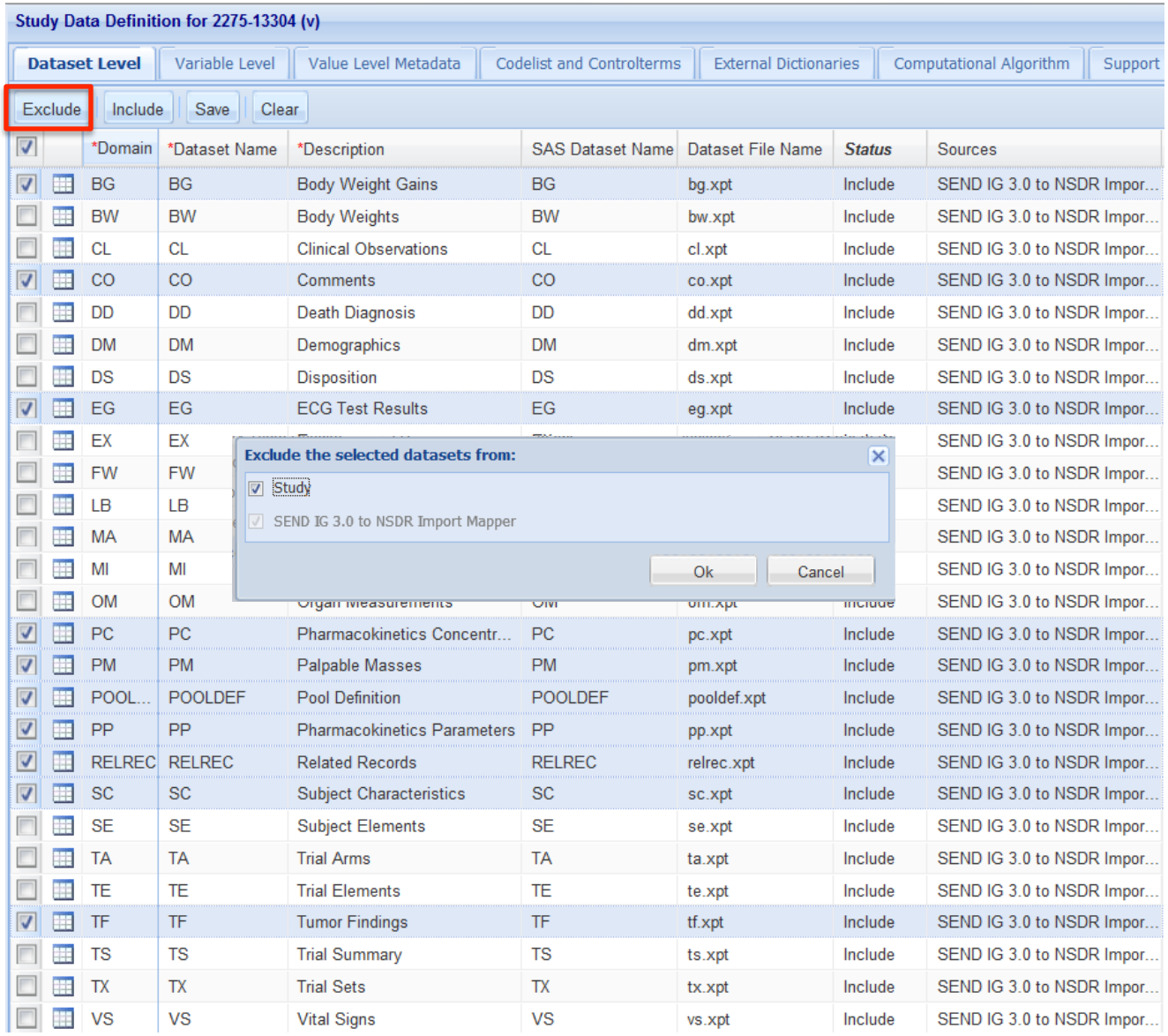
15.3 Observations of Animals Starting on Study Day 1

Animals will be observed and data will be recorded as indicated in the following table.

Table 6: Observations of Animals Starting on Day 1

Procedure	Corresponding SEND Domain
Cageside Observations (mortality, moribundity, and general health)	Clinical Observations
Physical Examinations (skin and fur characteristics, eye and mucous membranes, respiratory, circulatory, autonomic and central nervous systems, somatomotor and behavior patterns, and injection sites)	Clinical Observations
Dermal Observations (Draize Scoring)	Clinical Observations
Body Weights	Body Weights
Food Consumption - Quantitative	Food Consumption
Ophthalmologic Examinations	Clinical Observations
Body Temperature	Vital Signs

Specify SEND Domains - example



Using Study Design to build the SEND Trial Design

15.1 Group Designation and Dosage Levels

Animals will be assigned to groups as noted in the table below.

Table 5: Group Designation and Dosage Levels

Group	Treatment	Test Article Dosage (mg/kg)	Number of Animals			
			Main Phase		2-Week Recovery Phase	
			Males	Females	Males	Females
1	Control Article	0	5	5	5	5
2	Test Article	5	5	5	5	5
3	Test Article	10	5	5	5	5
4	Test Article	50	5	5	5	5

Trial Sets	
1NR	Vehicle Control once daily, Nonrecovery
2NR	5 mg/kg once daily, Nonrecovery
3NR	10 mg/kg once daily, Nonrecovery
4NR	50 mg/kg once daily, Nonrecovery
1R	Vehicle Control once daily, Recovery
2R	5 mg/kg once daily, Recovery
3R	10 mg/kg once daily, Recovery
4R	50 mg/kg once daily, Recovery

Treatment Elements	
TRT01	Vehicle Control
TRT02	5 mg/kg Drug, once daily
TRT03	10 mg/kg Drug, once daily
TRT04	50 mg/kg Drug, once daily
RECO	Recovery

Trial Arms	Order of Elements
1	TRT01
2	TRT02
3	TRT03
4	TRT04
1R	TRT01, RECO
2R	TRT02, RECO
3R	TRT03, RECO
4R	TRT04, RECO

Specifying Trial Design Domains

	Codelist Name					Short Codelist Name			
	*Name	*Short Name	C...	SAS ...	D...	Name	Short...	Co...	S...
	Element Co...	ETCD			text				
	Element	**ELEMENT**			**t...**				
	Laboratory...	LBSPEC			text				
	Clinical Pat...	LBTEST			text				

*Submission Value	Preferred Term	Submission...	Preferred S...	Rank	Ord...	Code	Ext...
Vehicle Control							
5 mg/kg Drug, once daily							
10 mg/kg Drug, once daily							
50 mg/kg Drug, once daily							
Recovery							

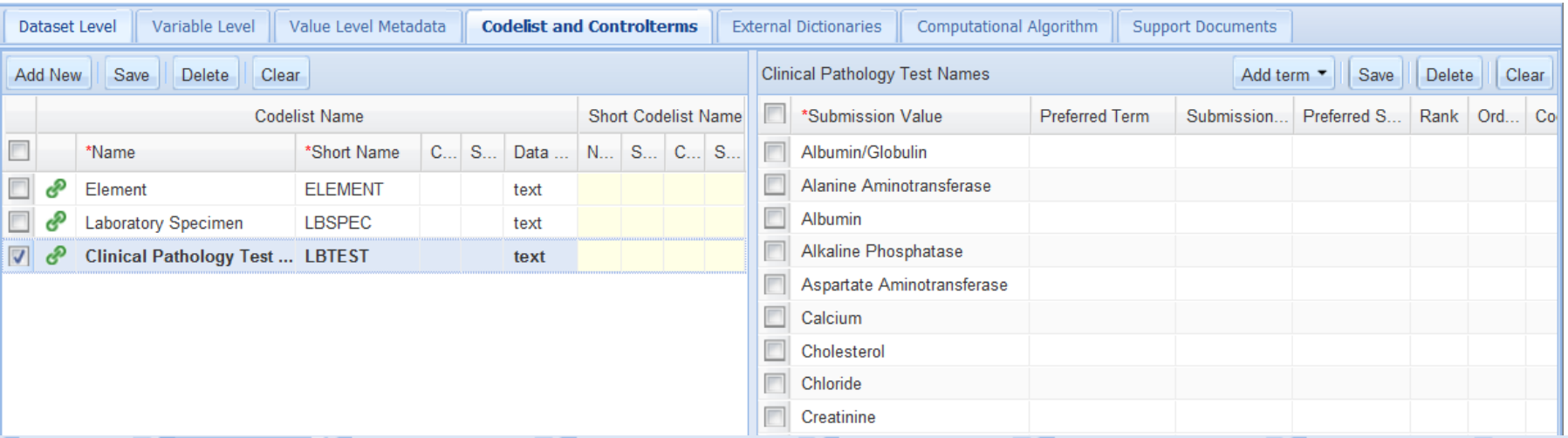
Study Data Definition for 2275-13304 (v)

Dataset Level | **Variable Level** | Value Level Metadata | Codelist and Controlterms | External Dictionaries | Computational Algorithm | Support Documents

Exclude | Include | Save | Clear

*Domain	*Variable Name	Description	Value Coded By	Codelist or External Codelist or Format	Role	SAS Field Name
TE	STUDYID	Study Identifier			Identifier	STUDYID
TE	DOMAIN	Domain Abbreviation			Identifier	DOMAIN
TE	ETCD	Element Code			Topic	ETCD
TE	ELEMENT	Description of Element	Codelist	Element	Synonym Qualifier	ELEMENT
TE	TESTRL	Rule for Start of Element			Rule	TESTRL
TE	TEENRL	Rule for End of Element			Rule	TEENRL
TE	TEDUR	Planned Duration of Element			Timing	TEDUR

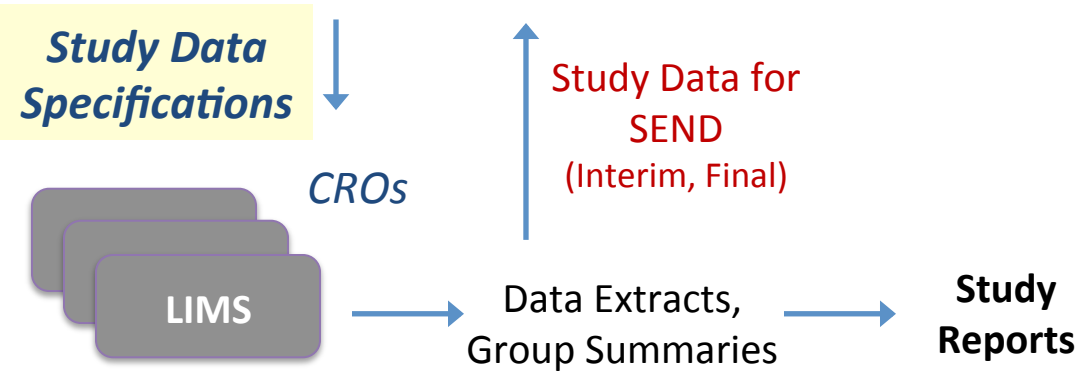
Specifying Controlled and Preferred terms for SEND



*Domain	*Variable Name	Description	Value Coded By	Codelist or External Codelist or Format	Role	SAS Field Name
LB	STUDYID	Study Identifier			Identifier	STUDYID
LB	DOMAIN	Domain Abbreviation			Identifier	DOMAIN
LB	USUBJID	Unique Subject Identifier			Identifier	USUBJID
LB	POOLID	Pool Identifier			Identifier	POOLID
LB	LBSEQ	Sequence Number			Identifier	LBSEQ
LB	LBGRPID	Group Identifier			Identifier	LBGRPID
LB	LBREFID	Specimen Identifier			Identifier	LBREFID
LB	LBSPID	Sponsor-Defined Identifier			Identifier	LBSPID
LB	LBTESTCD	Lab Test or Examination Sh...			Topic	LBTESTCD
LB	LBTEST	Lab Test or Examination Na...	Codelist	Clinical Pathology Test Names	Synonym Qualifier	LBTEST

A global SEND process for CROs and Sponsors

Specify	Validate	Merge	Package	Review
• Collaborate with sponsor & other data providers to define study data Specifications • Define data expected from each provider	• Fitness checks against specification • Performed for each provider	• Collate data from each provider • Create single SEND dataset • Attach supporting documents	• Check SEND data against validation rules • Generate submission ready SEND datasets	• Assess quality using tools to re-create sponsor defined groups for risk-based comparison to reports



Getting SEND done right

- "***Fit for review***" SEND datasets for FDA submissions must be complete, consistent and technically compliant

- Don't run two separate processes for SEND and study reports to avoid *data quality, increase downstream costs and delay FDA reviews* once submitted

- High quality SEND datasets with reduced costs can result from:
  - ✓ Establishing data specifications and ensuring that the right data are collected ("***Plan the Work***")
  - ✓ Using a single truth data resource for study reporting and automation of SEND data assembly ("***Work the Plan***")
  - ✓ Applying tools to easily compare reports and SEND datasets ("**Review the Work Product**")

Perspectives on SEND from a CRO

Michael A. Dorato, PhD, DABT, Fellow ATS
Executive Vice President
Smithers Avanza Toxicology Services

Starting your SEND Journey?

- Assign a point person with appropriate responsibility, accountability and operational knowledge
- Evaluate QA/QC processes
  - **QAU must be engaged with your operational processes**
    - Data correction procedures must address source data, not just report output
- Determine SEND Strategy
  - SEND internal ownership
    - Timing?
  - **SEND As A Service**
    - Selection of a qualified partner

Plan for SEND at Study Start

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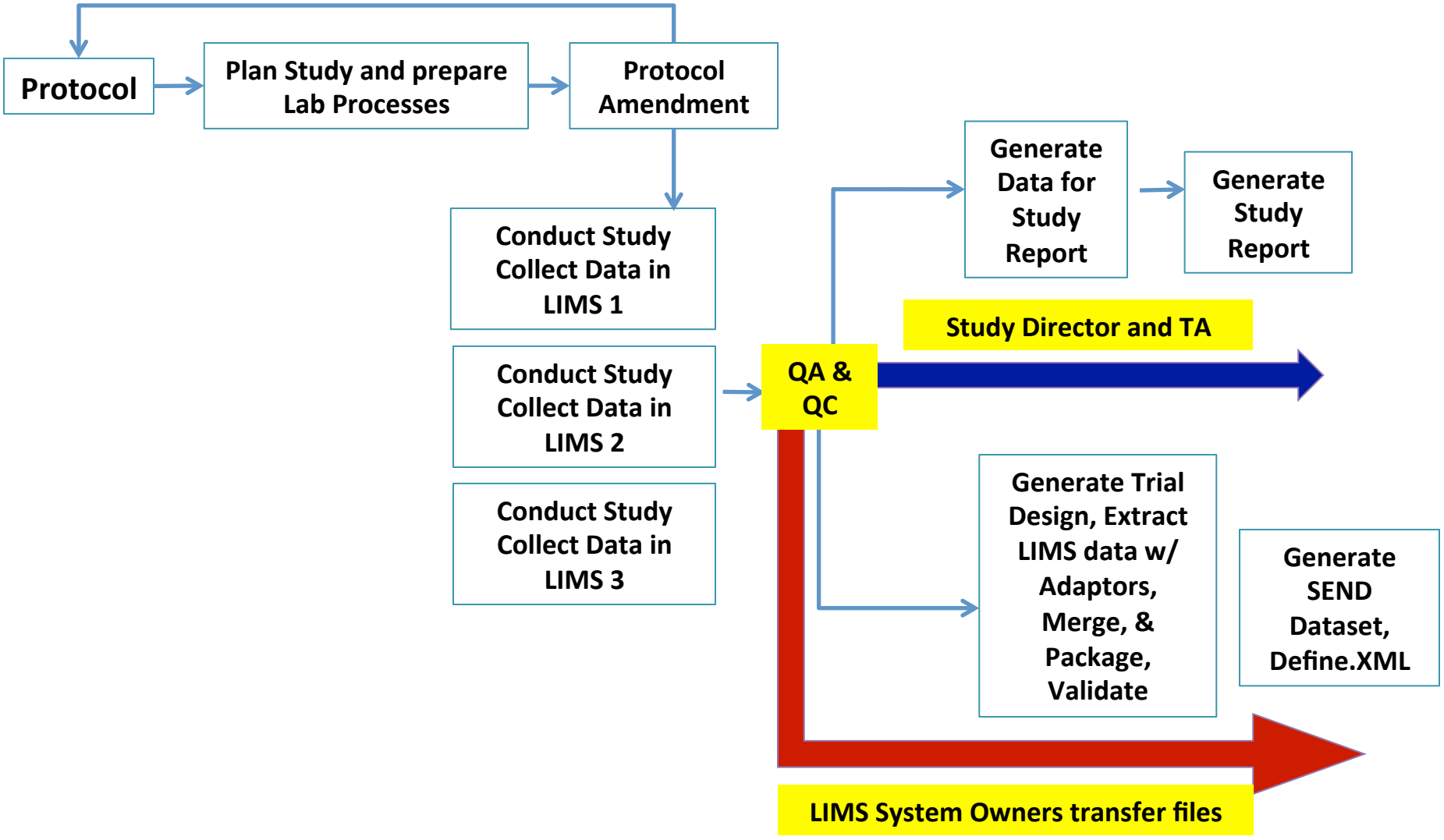
Body Weights	Body Weights
Food Consumption - Quantitative	Food Consumption
Ophthalmologic Examinations	Clinical Observations
Body Temperature	Vital Signs

Use the Study Protocol to Specify SEND Domains

Maximize the Use of your LIMS Systems

- Current laboratory processes were not designed with SEND in mind: "***Optimization, Uniformity, Harmonization***"
  - Information necessary for preparation of SEND data sets is not necessary to set up studies in your system (*Optimize*)
    - Example: Include "Sponsor Identifier" and "Study Monitor" as fields to be populated in the LIMS system
- Maximize use of electronic data collection (*Uniformity*)
- Utilize Controlled Terminology (CT) lists in protocol template and LIMS (*Harmonize*)
  - Establish hierarchy for proper SEND mapping

QA/QC Process



Conclusion: Advice

SEND Impacts Everything!

Plan Now!