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Ensuring Consistent and Supported Standards Across Data and Metadata in a Large Regulatory Filing is Tricky Business

Lisa Brooks, Iris Statistical Computing, Foster City, California, USA
Ann Shiba, Iris Statistical Computing, San Jose, California, USA

ABSTRACT

The Study Data Standardization Plan (SDSP) documented the planned standard versions at the time of the Investigational New Drug (IND) filing. The programs used the latest standard available during development. The define.xml was validated using the versions in the Study Data Standardization Plan. The reviewer guides listed the versions from the programming specification. Now, years later, the eSubmission components are being evaluated for inclusion in a New Drug Application (NDA). The Study Data Standards Catalog no longer supports the implemented standard. There is no electronic tool to check for consistent standards across components or to verify the versions are supported for review. This paper discusses checks, strategies, and procedures to implement after the clinical study report is written but before the submission so that the best electronic data package can be sent to the Food and Drug Administration (FDA) in support of a filing.

INTRODUCTION

Our intended audience are those responsible for submission of clinical study data to the FDA in support of an NDA. These readers would be staff in regulatory, clinical, or biometrics departments at both sponsors and Clinical Research Organizations (CROs). The types of studies we discuss are clinical studies for an NDA that are completed with Clinical Study Reports (CSRs) already finalized and are to be submitted to the Center for Drug Evaluation and Research (CDER). But the information may still be useful for other study types and filings, such as non-clinical, Biologics License Application (BLA), or a data filing to a health authority in another country.

We describe how to best go about ensuring data for studies post-CSR are submitted to FDA with consistent standards implemented across data and metadata. For many NDA data submissions, there are studies with old data in legacy format, collected years ago, and used to program CSR analysis out. Yet sponsors choose the strategy to submit all data, even if not required. FDA's Technical Rejection Criteria for Study Data ("Rejection Criteria")[1] states that the guidance requiring electronic submission of study data[2] for NDAs will begin to be enforced for studies that start after December 17, 2016. Specifically, study data must be submitted in standards specified in the FDA Data Standards Catalog (Catalog)[3] and meet particular rejection criteria or the NDA is subject to refuse to file (RTF). Furthermore, many other specific requirements are set forth in the Study Data Technical Conformance Guide (TCG).[4] There is some respite for industry as the FDA has provided a means to request waivers to submit data in non-supported standards (Waiver)[5] and a means to test your compliance with standards via a sample submission process (Sample).[6] See below for this paper's sections on "REQUEST WAIVERS FROM THE FDA" and "SUBMIT AN ELECTRONIC DATA SAMPLE."

This paper begins by describing how the SDSP can be used in a gap analysis to determine what data you have and in what standard. Once you know what standards you have, we describe how to go about determining if the data is compliant to a given standard and if that standard is supported by FDA. Armed with this information, sponsors can begin developing a data submission strategy and develop the contents of the submission folders. As the development of the submission material progresses, it is important to consider the FDA responses to Waiver requests and Samples submitted. A checklist should be developed that will aid in the evaluation of data packages. Both the checklist and the SDSP should be updated regularly with new information learned.

GAP ANALYSIS UTILIZING THE STUDY DATA STANDARDIZATION PLAN

The goal of a gap analysis is to determine if all studies are accounted for and materials are available to complete an electronic data submission for a drug program. The SDSP is a useful tool during this process.

The TCG calls for an SDSP[7], which is basically a list of all non-clinical and clinical studies intended to support the drug product for its indication. In addition to listing the studies, information regarding study description, start date, and utilized standards is included. There are sections for presenting existing or planned pooled data submissions, non-supported standards (where requested Waivers can be documented), and FDA communication. The document is considered a living document and follows the drug program from IND to NDA. The SDSP should be treated as a controlled document within a sponsor organization and maintained with care while being sent to FDA at important milestones. I would assert that the SDSP is the benchmark reference to all study standards for a drug program.

STANDARDS DOCUMENTED IN THE SDSP

Below is a list of standards that are documented in the SDSP:

Standard Acronym	Standard Name
ADaM	Analysis Data Model
CT	Controlled Terminology (CDISC™* and/or Sponsor Defined)
DEFINE	Study Data Definition File (in XML format)
LOINC	Logical Observation Identifiers Names and Codes
MedDRA	Medical Dictionary for Regulatory Activities
NDF-RT	National Drug File – Reference Terminology
SDTM	Study Data Tabulation Model (includes TDM – Trial Design Model domains)
SEND	Standard for Exchange of Nonclinical Data
SNOMED	Systematized Nomenclature of Medicine
UNII	Unique Ingredient Identifiers
WHO-DD	WHO Drug Dictionary

*CDISC is the Clinical Data Interchange Standards Consortium

WHY A GAP ANALYSIS?

The writing and updating of the SDSP is important to the process of determining gaps in study data and standards. A pre-step in developing a data submission strategy is to determine what studies exist with what data and metadata and in what standard and documenting it in the SDSP. The management of the SDSP becomes more challenging as the number and age of studies increase. The SDSP and the gap analysis are essential in answering the following questions and even more:

- What studies do we have?
- Which studies are pivotal, phase I-III, bridging, QT, included in pooled analysis, or needed for special reports?
- Which studies are important to our filing?
- Which studies will we submit electronic data?
- What are the standards used for each study?
- Are the standards used supported by the FDA?
- What is the status of the studies?
- Can we assess compliance?
- Is there anything to be done about non-compliance?
- When did the study start?
- What has been communicated with FDA concerning the standards?
- Do we have all the source materials for these studies?

A SPECIAL NOTE ABOUT STUDY START DATE

The SDSP template defines a clinical study start date as, "The earliest date of informed consent among any subject that enrolled in the study." If there are screen failures, the date chosen is to be based on the first subject who actually enrolled in the study. This date is important because it determines two things:

1. If your study is subject to the December 17, 2016 requirement date in the Rejection Criteria.
2. Which versions of standards in the Catalog are required and supported. See section, "IS YOUR CDISC DATA COMPLIANT AND SUPPORTED?"

It is sometimes difficult to determine the first date of signed informed consent form (ICF). For example, some phase 1 clinical sites may choose to complete screening using a general and non-study specific ICF form and later have the subject sign a study specific ICF. The date of ICF signature on the case report form (CRF) may be the earlier or the later. Some sleuthing may be required to determine the true date that should be used in the SDSP. A review of the comments entered on the CRF or notes made in the CSR or the trial master file (TMF) may be needed. Take note of the date, the source, and the justification for the study start date once it is determined as this information may be needed as an explanation in the reviewer guides.

SOURCE MATERIALS FOR GAP ANALYSIS AND SDSP

The source material for the SDSP and the data submission package includes protocols, CSRs, ClinicalTrial.gov, Data Management documents such as data review meeting notes, Annotated Case Report Forms (aCRFs), Data Management Plan (DMP) and Coding Guidelines, and Biometrics documents such as specifications, statistical analysis plans (SAPs), reviewer guides, imported data files, and programs. Any document that goes into the TMF including notes to file can be useful in finding information needed for the SDSP and data filing, particularly concerning standards that changed mid-study conduct.

A careful review of programs used to create SDTM, ADaM, and tables, listings, and figures (TLFs) should be conducted to determine if you have all permanent datasets and imported files needed to show traceability of data. These programs should also be reviewed for any hard codes or programmed data corrections. It will take time and effort to determine why hard codes were done and the justification for hard codes need to be explained in the reviewer guides.

All this information should be reviewed during the gap analysis to determine information for the SDSP and the compilation of study materials needed to prepare the study's data and metadata for submission. Many methods can be utilized to perform a gap analysis, but in our experience a list of the study information for the SDSP and check of available source material is best maintained in a spreadsheet. Once the gap analysis is completed this can be transferred over to a document using the SDSP template or the information can be used to update an existing SDSP.

IS YOUR CDISC DATA COMPLIANT AND SUPPORTED?

DETERMINE COMPLIANCE TO STANDARD

Once you have an SDSP it is important to determine if what you discovered about your data is accurate. My suggestion here is to run the data and define.xml through validation software such as Pinnacle 21 Community™ Validator[8] to determine if the data and metadata is compliant with the documented standards. This may be unclear because during the gap analysis you may have read in an SDTM specification that the data was developed using Implementation Guide 3.1.3 but an old version of the SDSP stated 3.1.1. The best path forward is to run validation software using the different standards and select the standard version that provides the validation report with the least warnings and errors. This method is also helpful to determine if MedDRA and CT versions in documentation match up with how the data was actually coded.

DETERMINE IF STANDARD IS SUPPORTED

Once it is very clear which standard versions were used, it is time to determine if those standard versions are currently supported by the FDA Data Standards Catalog. Per the Catalog's Instruction and Column Description tab: "For the purposes of this catalog, "supported" means the receiving FDA Center has established processes and technology to support receiving, processing, reviewing, and archiving files in the specified standard." The description for "Date Support Ends" is: "Sponsors cannot use the standard or terminology after this date. Generally, a waiver process may be available. Sponsors and applicants should consult with their review division. An empty field in this column means that a support end date has not been established." See the screenshot of the Catalog below for where you can find the date a standard's support ends.

Data Exchange Standard	Exchange Format	Standards Development Organization (SDO)	Supported Version	Supported Implementation Guide Version	FDA Center(s)	Date Support Begins (MM/DD/YYYY)	Date Support Ends (MM/DD/YYYY)	Date Requirement Begins (MM/DD/YYYY)	Date Requirement Ends
Study Data Tabulation Model (SDTM)	XPT	Clinical Data Interchange Standards Consortium (CDISC)	1.1	3.1.1	CDER, CBER	Ongoing	01/28/2015		

Therefore, the standards that were documented in the SDSP and confirmed via validation should each be compared against the dates in the Catalog to determine if they will be supported at the time of NDA submission. If the submission date is 6 months to a year off, then it will be necessary to re-evaluate supported standards at each release of the Catalog.

DATA OR METADATA NOT COMPLIANT AND/OR NOT SUPPORTED

If study data as it exists is non-compliant or the standard is not supported, you have some options:

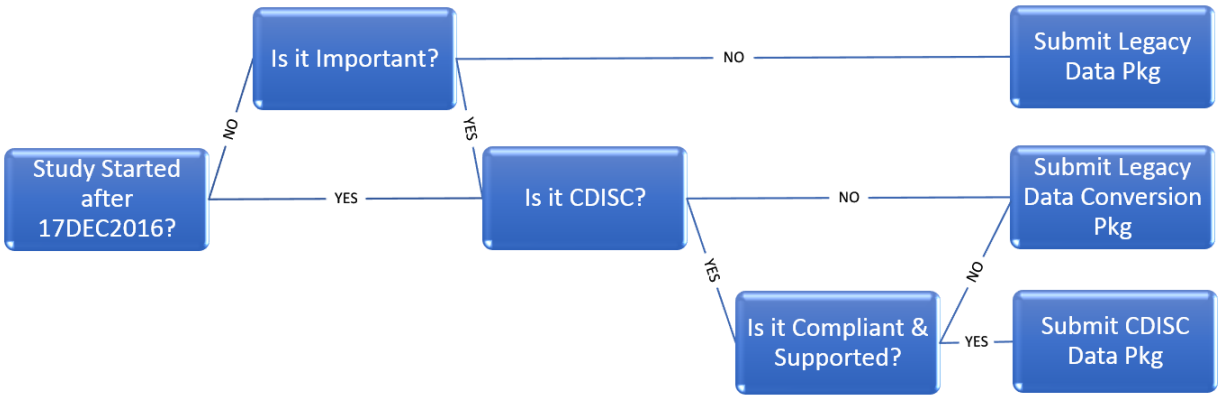
1. If the data and/or metadata is in a supported standard, you can increase compliance by making updates to data attributes and metadata to achieve compliance. This must be done with the goal of maintaining traceability to any up or downstream data or CSR appendix TLFs. I would be very cautious in updating variable values that appear in CSR listings. Any errors or warnings that still exist should be explained in the reviewer guide.
2. If the study started prior to December 17, 2016, you can submit the non-compliant or non-supported data as legacy. See below for this paper's section on "LEGACY DATA PACKAGE."
3. You can submit the non-compliant or non-supported data as legacy and convert the data to a supported and compliant data standard version. See below for this paper's section on "LEGACY DATA CONVERSION PACKAGE."
4. If the data is compliant but not supported, you can submit a waiver request which is discussed later in this paper.
5. If you are still uncertain if your data is compliant then you can submit it as a sample submission which is discussed later in this paper.

DEVELOP A DATA SUBMISSION STRATEGY

Building a data submission strategy for each study can be a daunting task. Especially when there are dozens of studies supporting a filing. The most important question to ask in a submission strategy discussion is, "What should we include in our data submission for each study?" The answers to that question should be documented in an update to the SDSP.

If the study started after December 17, 2016 then it is required that the study is supported by a compliant CDISC data package. However, if the CSR was generated using non-standard or non-compliant data then it is necessary to convert that data to CDISC and submit both the non-standard and the standardized data (in a Legacy Data Conversion Package described below).

If the study started on or before December 17, 2016 then the decision pathway is a little murkier. Below is a diagram that can help in the decision-making process of what sort of data package to submit. Following the diagram is a discussion of each data package and a description of the contents. In the diagram below, important is defined by the sponsor and could include studies that are pivotal, phase I-III, bridging, QT, included in pooled analysis, or needed for special reports



LEGACY DATA PACKAGE

The legacy data package can be submitted for studies in which a sponsor wants to submit electronic data, the study started before December 17, 2016, is not a particularly important study, and is not in CDISC format. A case could be made that important studies should be converted to CDISC for ease in FDA review. Legacy data is meant for data that is ready or can be made ready for electronic submission but does not follow CDISC standards. In the old days we referred to this as "Item 11 Compliant" and the requirements for such data are documented in the 1999 "Guidance for Industry: Providing Regulatory Submissions in Electronic Format — NDAs"[9] under the section "Item 11: Case Report Tabulations (CRTs)." There have been some important changes since then and you can see that

the TCG has superseded some of this information. Most notably, the file blankcrf.pdf is now named acrf.pdf. Although the guidance only refers to the define.pdf, it is acceptable to submit a define.xml in its place, being careful to be clear that CDISC standards were not used. I've done this by changing the header of the define from a named CDISC standard to "Legacy Tabulation Data" or "Legacy Analysis Data" for clarity. Finally, it is important to submit reviewer guides to help the FDA reviewers navigate the data submission with important information. These reviewer guides need to be modified from the existing PhUSE templates[10,11] to provide important information but clearly state that the data is in legacy format and not in CDISC standards. The clinical study data reviewer's guide (cSDRG or csdrg.pdf) accompanies the legacy tabulation data and the analysis data reviewer's guide (ADRG or adrg.pdf) accompanies the legacy analysis data.

Below is a table that describes the electronic common technical document (eCTD) M5 datasets directory structure and its contents for a legacy data package:

Type of Submission Materials	Legacy Data Package
M5 datasets directory structure	- [study] - analysis - legacy - datasets - programs - tabulations - legacy
M5 datasets directory contents	**analysis-legacy-datasets folder:** 1. legacy analysis data 2. define.pdf (or define.xml modified for non-CDISC study) 3. adrg.pdf (modified for non-CDISC study) **analysis-legacy-programs folder:** 1. SAS® programs for legacy analysis derivation 2. SAS programs for analysis tables, listings and figures (TLFs) **tabulations-legacy folder:** 1. legacy tabulation data 2. define.pdf (or define.xml modified for non-CDISC study) 3. acrf.pdf (annotated for legacy tabulation data) 4. csdrg.pdf (modified for non-CDISC study)

LEGACY DATA CONVERSION PACKAGE

The legacy data conversion package is submitted for studies under a few circumstances.

1. A sponsor wants to submit electronic data in CDISC format, the study started on or before December 17, 2016, is an important study, the CDISC data may be needed for a pooled analysis or special report, and/or the data used to generate the CSR appendices was not in CDISC format.
2. The study started after December 17, 2016, CDISC study standards are required, and the data used to generate the CSR appendices was not in CDISC compliant format. In this case both SDTM and ADaM compliant data are required for submission.
3. The FDA may request that data be submitted in CDISC format even if it is not required.

The legacy data is submitted in order to support the CSR appendices and would follow the Item 11 requirements described in the above section of this paper. The CDISC data is submitted in order to aid FDA review and perhaps to be used in pooled analysis or a special report. Traceability between the legacy data, CDISC data, and the CSR appendices is established via the creation of the Legacy Data Conversion Plan and Report[4,10] Appendix to the cSDRG and/or ADRG.

Below is a table that describes the electronic common technical document (eCTD) M5 datasets directory structure and its contents for a legacy data conversion package:

Type of Submission Materials	Legacy Data Conversion Package
M5 datasets directory structure	- [study] - analysis - adam - datasets - programs - legacy - datasets - programs - tabulations - sdtm - legacy
M5 datasets directory contents	**analysis-adam-datasets folder:** 1. ADaM data 2. define.xml 3. adrg.pdf (with Legacy Data Conversion Plan and Report Appendix, if needed) **analysis-adam-programs folder:** 1. SAS programs for ADAM derivation **analysis-legacy-datasets folder:** 1. legacy analysis data 2. define.pdf (or define.xml modified for non-CDISC study) **analysis-legacy-programs folder:** 1. SAS programs for legacy analysis derivation 2. SAS programs for analysis TLFs **tabulations-sdtm folder:** 1. SDTM and TDM 2. define.xml 3. acrf.pdf (annotated for SDTM data) 4. csdrg.pdf (with Legacy Data Conversion Plan and Report Appendix, if needed) **tabulations-legacy folder:** 1. legacy tabulation data 2. define.pdf (or define.xml modified for non-CDISC study) 3. acrf.pdf (annotated for legacy tabulation data)

CDISC DATA PACKAGE

The CDISC data package is submitted for studies that had CSR appendix TLFs generated from ADaM data which was generated from SDTM data. If the study started after December 17, 2016, data in CDISC format is required for an NDA submission.

Type of Submission Materials	CDISC Package
M5 datasets directory structure	- [study] - analysis - adam - datasets - programs - tabulations - sdtm

Type of Submission Materials	CDISC Package
M5 datasets directory contents	**analysis-adam-datasets folder:** 1. ADaM data 2. define.xml 3. adrg.pdf **analysis-adam-programs folder:** 1. SAS programs for ADAM derivation 2. SAS programs for analysis TLFs **tabulations-sdtm folder:** 1. SDTM and TDM 2. define.xml 3. acrf.pdf (annotated for SDTM data) 4. csdrg.pdf

REQUEST WAIVERS FROM THE FDA

If the sponsor wants to submit data in a standard version that is no longer supported by FDA, it is important submit a waiver request.[5] The process is well described and straight forward. The FDA eData team typically responds within 30 days of the request and it is my experience that waivers are granted easily for old studies. In our request for waivers in the past, we have tried to send the requests in bulk, in one request. However, in most cases, we have had to follow up at a later time with additional requests because we had identified an additional study with unsupported standards. Also, the Catalog is updated several times a year and a previously supported standard may become unsupported in the timeframe of your NDA submission. For electronic data Samples, the submission is limited to one study and one sample submission of each standard. The metadata should be sent along with the Sample, that is, define.xml, acrf.pdf, csdrg.pdf, and adrg.pdf.

SUBMIT AN ELECTRONIC DATA SAMPLE

An electronic data Sample will prove to be invaluable as you discover how best to go about making sure your data is ready for submission. The process is a bit more involved than a Waiver, but the instructions on the website are quite clear.[6] An application number must be requested prior to submitting the Sample. We only discuss submitting a data Sample in this paper, but the website also covers how to submit a test of the eCTD XML backbone. The FDA ESUB-Testing team typically responds within 30 days, but recently there has been responses as late as 60 days. We have found that the information provided in issues reported by FDA have been clear and easily understood by staff in Biometrics familiar with these types of findings. However, the regulatory and clinical group who are not as familiar with these error reports may be taken aback from the volume of findings. It is best to have these reports parsed by the subject matter experts in Biometrics groups with explanations and action plans for better understanding. For example, if a study did not collect values for criteria for serious adverse event this may cause thousands of errors. However, there is a very simple and relevant explanation and is not a cause for alarm.

Technical issues identified by FDA in the findings report should be addressed prior to submitting the NDA. Updated or corrected Samples should not be re-submitted for review. Note, the review of a sample submission does not involve any sort of scientific review and does not go to the drug review team at FDA. In the next section I will talk about developing a submission package checklist with items that should be reviewed that won't be identified via electronic validation. You will find that issues identified by FDA ESUB-Testing team in a Sample will be very helpful in perfecting this checklist.

DEVELOP A SUBMISSION PACKAGE CHECKLIST

There are many requirements identified in the TCG, CDISC implementation guides, define specification, and the use of the PhUSE reviewer guide templates that cannot be electronically checked. But they do need to be verified prior to submission and it involves a manual review process. A checklist is important to make sure all aspects of the data packages have been reviewed. Below is a list of items that should be considered for manual review. We make no warranties about this checklist and the sponsor should be careful in the development of their own checklist based on what they have learned from studying current FDA guidelines, sample submissions and study specific data strategies. The list below includes types of checks that would typically be included in a submission folder for a CDISC study. Similar checklists should be created for legacy tabulation and analysis data.

Data Pkg Component	Types of Checks to Include (example)
ADaM data	• Meets Technical Rejection Criteria (contains an ADSL) • Pinnacle 21 was run with correct options • Dataset size (datasets are less than 5 gigabyte or split) • Filenames meet regulatory publishing requirements
adrg.pdf	• Complete and well written (all sections match the PhUSE template) • Reviewed by study statistician • Consistent with external documents (matches with the protocol and SAP) • Standards referenced are consistent with SDSP, cSDRG, data and define files • Irregularities are documented with explanation • Pinnacle 21 Validator issues are documented and explained • Legacy Data Conversion Plan & Report Appendix is included as needed
ADaM define.xml	• Meets Technical Rejection Criteria (define.xml is in a supported version) • Standards are supported (ADaM version documented is supported) • Global variables match the study protocol • Bookmark section includes functional external and internal links • Datasets section is accurate (Purpose column has the value of "Analysis") • Derivation and Comments are well formed (derivations must include a comment) • Parameter Value Level Metadata includes all possible values • Computational algorithms use English language and not SAS lingo • External dictionaries are consistent with SDSP, ADRG, SDRG, data and SDTM define.xml • Pinnacle 21 issues are addressed or explained well in adrg.pdf
SAS programs for ADAM and analysis TLFs	• Filenames meet regulatory publishing requirements • Filename meets requirement in TCG • All SAS programs are present • Programs are appropriate without excessive comments or heavy use of macros
SDTM and TDM Data	• Meets Technical Rejection Criteria (contains ts.xpt) • Pinnacle 21 was run with correct options • Dataset size (datasets are less than 5 gigabyte or split) • Filenames meet regulatory publishing requirements • TDM matches protocol and dm.xpt • ti.xpt includes all versions of inclusion/exclusion criteria from the protocol • Treatment emergent flag is included in SUPPAE
acrf.pdf	• All fields are fully annotated • All annotated variables are documented in define.xml • Duplicate pages are marked "For annotations see CRF page X" • Consistent SUPPQUAL annotations are used ("SUPPXX.QVAL where QNAM=XXX") • Meets TCG requirement (filename is acrf.pdf) • Meets metadata submission guidelines[12] (bookmarked by timepoints and topics) • Formatted for FDA ease (Page X of Y footnote matches the PDF page number)
csdrg.pdf	• Complete and well written (all sections match the PhUSE template) • Reviewed by study programmer or statistician • Consistent with external documents (matches with the protocol) • Standards referenced are consistent with SDSP, ADRG, data and defines • Irregularities are documented with explanation • Pinnacle 21 Validator issues are documented and explained • Inclusion/Exclusion Appendix includes original and amended criteria • Legacy Data Conversion Plan & Report Appendix is included as needed

Data Pkg Component	Types of Checks to Include (example)
SDTM define.xml	• Meets Technical Rejection Criteria (define.xml is in a supported version) • Standards are supported (SDTM version is supported) • Global variables match the study protocol • Bookmark section includes functional internal and external links • Datasets section is complete (datasets are in logical or alphabetical order) • Derivation and Comments are well formed (computational algorithm present) • Value Level Metadata are complete • External dictionaries are consistent with SDSP, ADRG, SDRG, and define files • Pinnacle 21 issues are documented and explained • Origin type has correct values

CONCLUSION

It might be tricky, and it may take a lot of work, but it is possible to prepare NDA electronic data submission packages with consistent and supported standards. This paper has provided some checks and processes to use to ensure consistency among specific submission components. It is good practice to compare all documents and submission files for data standard consistency. If inconsistencies are found, sponsors must decide which document or file to update keeping in mind that the SDSP is a living document and can be amended up to the submission of the NDA. It is important to prepare these packages for submission while continuing to update the SDSP, sending additional waivers, and maintaining the checklist based on lessons learned. The potential ramifications from standards being inconsistently documented or applied can be quite serious and involve information requests, delays, and in the worst case, a refuse to file.

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RECOMMENDED READING

cSDRG Project Teams, PhUSE Optimizing the Use of Data Standards Working Group. “Best Practices for Documenting Dataset Metadata: Define-Xml Versus Reviewer’s Guide” PhUSE website, November 2018
https://www.phuse.eu/cs-deliverables-under-review
https://www.phuse.eu/white-papers (you can find it here when finalized)

CONTACT INFORMATION

Your comments and questions are valued and encouraged. Contact the author at:

Lisa Brooks
Iris Statistical Computing
Foster City, CA 94404
Email: lisa@irisstatcomp.com
Web: http://www.irisstatcomp.com