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Stay Ahead of the Curve: How to implement New FDA Recommendation Study Data Standardization Plan (SDSP) in your organization?

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ABSTRACT

The Study Data Standardization Plan (SDSP) is a living document and assists the Food and Drug Administration (FDA) in identifying potential data standardization issues early in the development program. As the FDA has begun to request sponsors to provide a SDSP, it may not be that long until this new FDA recommendation becomes a new FDA requirement. Initial recommendations have been provided through a PhUse sponsored limited duration team. We have taken these recommendations and expanded the tools and process necessary to help the sponsor implement the SDSP within their organization.

INTRODUCTION

Gaining agreement with the FDA on data and data standards for submissions may cause delays in submissions or drug approvals. The SDSP is a living document that provides an avenue to gain FDA agreement on data standards early in a program and concurrence as the program progresses. This early alignment is beneficial both internally and with the FDA reviewer. This communication tool serves to ensure that the FDA reviewers understand and accept the data standards the sponsor is using for each study and for pooled analysis.

This paper will define the tools necessary to implement the use of SDSP in your organization including identification of sponsors and key stakeholders, process and RACI development, early adopter selection and implementation, timelines, and management of long-term implementation. These tools can be applied to implementation of the SDSP in small, mid-size and large pharmaceutical companies.

Do you remember the time you first implemented any process related to SDTM or ADaM? Do you remember the time you introduced any change in your current process within your statistical programming group? As with previous implementation strategies there needs to be a clear point of ownership and accountability. In this case, accountability and responsibility for SDSP implementation is not limited to the statistical programming group but requires cross functional collaboration between various functional groups within the organization. Therefore, careful coordination is required to identify and develop an appropriate process and communication pathways between these groups to assure the requirements of the document have been met and communicated at the appropriate stage gates with the FDA. To add to the complexity, the SDSP document is maintained throughout lifecycle of the Investigational New Drug (IND) requiring the need for additional steps to be identified to assure accountability and completion is clearly understood at each stage of the development process.

SDSP BACKGROUND

The SDSP document is referenced in the FDA Guidance Providing Regulatory Submissions in Electronic Format – Standardized Study Data, December 2014. Section 2 of the Study Data Technical Conformance Guide (TCG) recommends that sponsors plan for the submission of standardized data using a SDSP. Based on the recommendations by the FDA to provide this document, a PhUse Limited Duration Team was established in July 2014 to develop tools and guidelines for the industry for completion and submission of the document. With the SDSP template and guidance available from Phuse, FDA is welcoming earlier interaction with sponsors regarding use of data standards in this preferred format. Resources including sample SDSP template, completion guidelines, examples and suggestions on sponsor implementation are available as indicated in Figure 1 at the website: https://www.phuse.eu/css-deliverables.Sponsors should familiarize with these tools and utilize as a first step towards implementation of the SDSP in their organization.

Figure 1. PhUse SDSP Resource

Overall the SDSP template contains the following key components:

- Cover page and revision history
- Sponsor and product information
    - Contact name and email
    - Product name, IND number, indication & population
- List of studies and standards used
    - Nonclinical
    - Clinical
    - Pooled
- Justification of studies not conforming to current acceptable standards
- Record of sponsor/FDA standards discussions/decisions
- CBER submissions require an extra appendix containing five sections: Introduction, SDTM datasets, Supplemental qualifiers, ADaM datasets, and Integrated Summary of Safety (ISS) and Integrated Summary of Efficacy (ISE). The SDSP CBER Appendix is specifically for studies and pools that are planned to be submitted to CBER.

It is recommended to keep the format of the template consistent with the PhUse recommended format, however sponsor specific direction can be added to each section to aide teams in completion of the document.

SPONSOR BENEFITS TO IMPLEMENT SDSP

As previously noted, SDSP is currently a recommendation from the FDA, not a requirement. However, we have seen the FDA proactively requesting sponsors to submit a SDSP. Implementing the SDSP in your organization has many benefits to both the FDA and your organization.

As early as the Pre-IND meeting and continuing through various stage gates described in more detail below, the sponsor can proactively communicate data standards for each study and pooling data standards at an earlier stage in development. The document also provides an opportunity for the sponsor to communicate noncompliance with the standards. Further this document provides a means of tracking discussions and agreements with the FDA. This document will also serve to drive decisions about legacy data conversion and up-versioning of data standards to allow for pooling of data across studies at a much earlier time than pre-NDA meetings.

Within your organization, the SDSP brings internal focus and agreement to the standards throughout the project lifecycle versus an ad hoc process driven by individual studies. In addition, the availability of the

SDSP provides an important reference for all functional groups. SDSP is also a valuable tool to highlight gaps in planning.

DEVELOPMENT OF SDSP PROJECT CHARTER

SDSP implementation in your organization should be carefully crafted. The first step is to Identify project sponsors. The head of statistical programming should be one of the sponsors due to subject matter content. Depending on your organization size and culture, you may also consider the head of project management and head of regulatory affairs. Having these three heads as your project sponsor, will provide strategic backbone to your implementation and increase the likelihood of project success.

In addition to identifying project sponsors, development of a project charter will help to provide the framework necessary to help manage SDSP implementation. A solid business case and justification should be clearly outlined to support the project framework. The project charter should be created with support and in alignment with the project sponsors.

Key components of a project charter, at a minimum, include the following:

- Define the Problem statement,
- Identify in scope and out of scope items as agreed upon with project sponsors and among project team.
- Identify Risks and Mitigation strategies
- Identify document related dependencies, such as the clinical development plan or Integrated Safety Summary (ISS).
- List project sponsors and project team members.
- Document the implementation plan outlining short term and long-term project deliverables with delivery dates.

CREATION OF SDSP PROJECT TEAM AND STAKEHOLDER ANALYSIS

Identification of key stakeholders is critical to the success of the project. Figure 2 provides an example of a stakeholder register based on our experience. Suggested roles will be discussed in further detail in the next section. Roles may vary in your organization. Completion of a Stakeholder Register can help to clearly define the key roles required for SDSP completion and can be used to build your initial project implementation team.

Project Sponsor	Project Team	Other Stakeholders
• Head of statistical programming group • Head of clinical project management • Head of regulatory affairs	A representative from • Statistical programming • Biostatistics • Data management • Clinical project management • Non-clinical • Regulatory affairs • Drug safety • Clinical development • Submission management	• FDA • CBER • CDER • Phuse • Members of individual study team • CRO

Figure 2. Stakeholder Register

We highly recommend active stakeholder management since SDSP implementation will include multiple roles within the Clinical Development group of your organization. As part of stakeholder analysis, the current engagement level of all stakeholders needs to be compared to the planned engagement levels required for successful project completion. A stakeholder engagement matrix as shown in Figure 3, can be used to document current (C) and desired (D) engagement level of stakeholders. Stakeholder engagement can be classified as following:

- Unaware: Unaware of SDSP project or its impact to the organization.
- Resistant: Resistant to the SDSP implementation in the organization.
- Neutral: Aware of the SDSP implementation, yet neither supportive nor resistant.
- Supportive: Aware of SDSP implementation project and its potential impact and supportive to the change
- Leading: Actively engaged in ensuring the SDSP implementation is a success

Through this analytical process, actions and communication plan can be developed to close gap between current and desired level of engagement.

Stakeholder	Unaware	Resistant	Neutral	Supportive	Leading
Statistical Programming				D	C
Regulatory Affairs			C	D	
Project Management				C D	
Non-Clinical		C		D	
Clinical Development	C			D	

Figure 3. Stakeholder Engagement Assessment Matrix

DEVELOPMENT OF RACI

A RACI matrix is the simplest, most effective means for defining and documenting project roles and responsibilities. Knowing exactly who is responsible, who is accountable, who needs to be consulted, and who must be kept informed at every step will significantly improve your chances of project success.

Figure 4 provides an example of RACI created to support SDSP implementation. Please note that RACI may vary for your organization based on roles and job descriptions.

It is critical to understand the components of the SDSP document and identify the key members who are necessary to deliver a complete and quality document. This should be evaluated on a case by case basis to accommodate an organizations specific structure. Below are suggested ownership, roles and responsibilities for consideration in your organization.

STATISTICAL PROGRAMMING

Since the SDSP is largely a Statistical Programming group deliverable, this functional line is responsible for completion of the majority of the sections within the document and is accountable for the document deliverable including coordination and oversight of functional line input, team review, and document approval. However, in a large organization, the Statistical Programming group is not typically involved before IND approval. In this case, you can introduce split-accountability where the Non-clinical functional organization is accountable for those activities before IND approval.

If there is a position of a programming compound lead within the organization, this role should oversee SDSP related document completion tasks while delegating overall document approval to the Head of the Statistical Programming group. Various study lead programmers may assist the compound lead with specific information to fill in the SDSP. If there is a separate Data Standards group, the compound lead should consult with this line for additional input to the document.

REGULATORY AFFAIRS

The Regulatory lead is responsible to fill in sponsor (Section 2) and product information (Section 3) of the template and will be accountable to lead discussions before and after FDA meetings and interactions. In addition, they will help craft language for any agreement on standards (Section 6) the company reaches with FDA.

BIOSTATISTICS

The Biostatistician in concurrence with the Clinical Development Lead will be accountable for consistency review of data presentation and strategy contained in other key documents such as Clinical Development Plan.

DATA MANAGEMENT

Data Management will be a contributor to the document and involved in overall team review. As this group is part of Biometrics, they will be informed for completion of most tasks and will provide valuable feedback on team review.

PROJECT MANAGEMENT

A project manager will be informed on the status for most activities to confirm completion of milestones within agreed upon timelines and may help to coordinate completion of various tasks by providing direction to help gain alignment with multiple functional groups.

NON-CLINICAL

This non-clinical functional line will be responsible for filling in Section 4.1. containing non-clinical information. Also, in a larger organization where the Statistical Programming line is not involved early in development, the sponsor should consider assignment of overall accountability for documentation completion to this functional line for programs through IND approval. After IND approval, accountability should be transitioned to the Statistical Programming functional line.

DRUG SAFETY

The Drug Safety organization can help to provide feedback on data standards for planned studies as it relates to medication and adverse events dictionary usage. In addition, they should be a reviewer of the overall document prior to final approval.

CLINICAL DEVELOPMENT

The clinical lead will be responsible for consistency review against other key clinical documents that require alignment with the SDSP. They will also be responsible for team review of overall completion and will be informed on SDSP progression.

SUBMISSION MANAGEMENT

Upon approval the Submission Management group will create hyperlinks between sections (section 4 and section 5; section 5 and section 6). They will also convert the document to PDF and help set PDF properties per the PhUse guidelines and submit the document to the agency and archiving of documentation.

Task \ Role	Statistical Programming	Regulatory Affairs	Biostatistics	Data Management	Project Management	Non-clinical	Drug Safety	Clinical Development	Submission Management
Section 1: SDSP Initiation and Update									
SDSP Initiation and Inform Study Team	A	R	I	I	I	I	I	I	I
Author Title Page, Section 2 General Sponsor Information and Section 3 Product Information	A	R			I				
Ensure SDSP discussed at IND Kick-off meeting	A	R	I	I	I	I	I	I	I
Author and Updates to Section 4.1 List of studies and standards: Non-clinical	A				I	R			
Author and Updates to Section 4.2 List of studies and standards: Clinical	A, R		C		I		C	C	
Author and Updates to Section 4.3 List of studies and standards: Pooled studies	A, R		C		I		C	C	
Author and Updates to Section 5 Non-conformance to supported standards justification	A, R	C	C		I	R	I	C	
Author and Updates to Section 6 FDA Data standards discussions	A, R	R	C		I	C	I	C	
CBER Appendix (must be in place prior to EOP II meeting)	A, R		C		I			C	
Section 2: Document Review, QC, Approval and Submission									
Team Review	A, R	R	R	R	R	R	R	R	R
Perfrom Consistency Review Against Clinical Development Plan if applicable	I		A, R		I			R	
Perform Consistency Review against Module 5 Reviewer's guides for NDA/BLA submissions if applicable	A, R				I				
Confirm all comments have been incorporated from Team Review and QC	A, R				I				
QC of document	A, R				I	R			
Approval of SDSP	A, R								
Inform Team about approved SDSP	A, R	I	I	I	I	I	I	I	I
Document Preparation and FDA Submission	A	I	I	I	I	I	I	I	R
Section 3: FDA Meeting: Pre IND meeting, EOP II meeting, Type C meeting, Pre-NDA/BLA meeting, Pre-sNDA/sBLA meeting									
Lead Pre-meeting or pre-submission team discussion on initial SDSP (or updates, as needed).	C	A, R	C	C	C	C	C	C	
Lead Post Meeting disussion on Regulatory feedback	C	A, R	C	C	C	C	C	C	
Lead Meeting discussion on any other FDA notification	C	A, R	C	C	C	C	C	C	

Legend:
R: Responsible for completing activity or plays major role
A: Accountable for activity completion; provides leadership
C: Denotes significant support or input; not optional
I: Informed of progress

Figure 4. SDSP RACI

OVERALL SDSP PROCESS FLOW AND SUBMISSION STAGE GATES

PROCESS FLOW

The SDSP document is intended to be started at the pre-IND stage. All the studies (non-clinical and clinical) known at this point (completed, ongoing, and planned) should be included in the SDSP. The SDSP should continue to be updated with new information for new planned, ongoing and completed studies prior to meetings or communications with FDA where the SDSP will be discussed. One SDSP document should be created and maintained per IND. A separate SDSP should be created for each supplemental submission (sNDA or sBLA). A clear change history of the SDSP should be kept for transparency and ease of review. The SDSP should be updated to include any agreements reached with the FDA throughout the life cycle of the program. A high-Level process flow for completion and updates is provided in Figure 5 below.

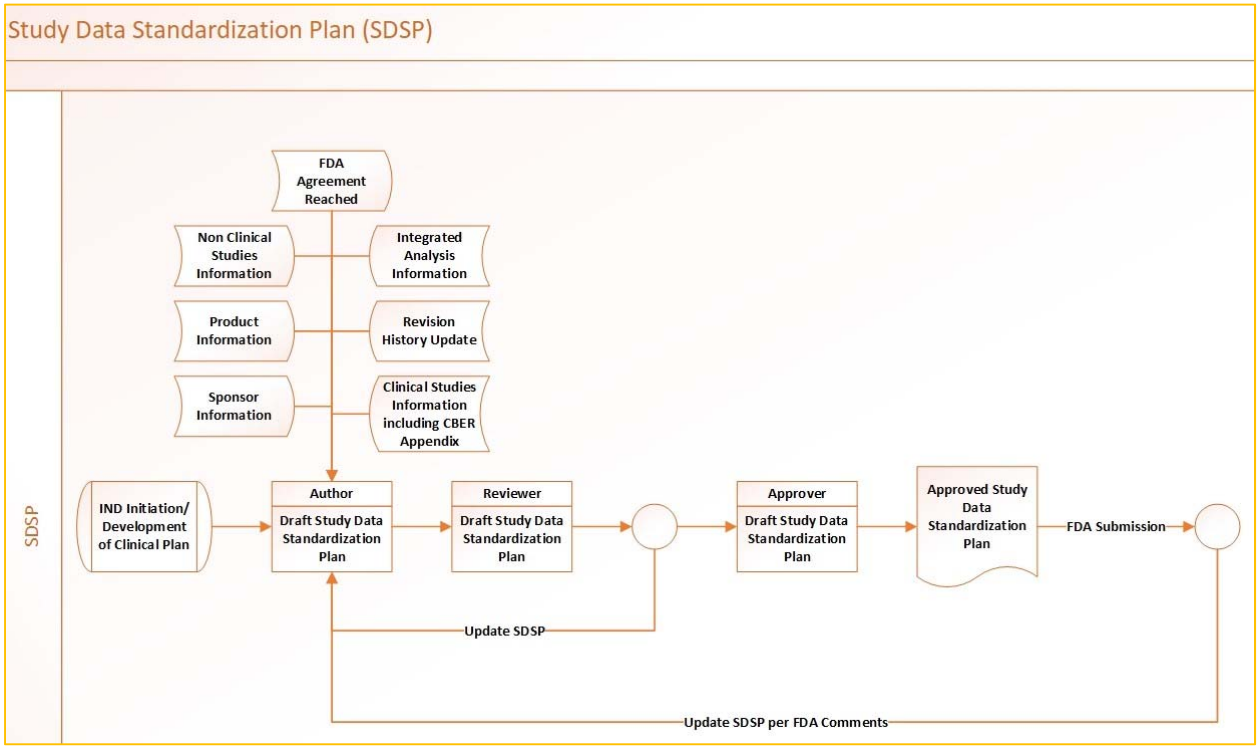

Figure 5. Overall SDSP Process

SUBMISSION STAGE GATES

Various stage gates where the SDSP could be shared with the FDA for the initial IND and for supplemental submission are shown in Figure 6. For initial IND, it is expected to update and share the SDSP at pre-IND, end of phase II, type C and pre-NDA/pre-BLA meeting as well as included in IND and NDA/BLA submission. For supplemental submission, the expectation is to update and share the SDSP at pre-sNDA/pre-sBLA meeting and included in sNDA/sBLA submission.

Please refer to the PhUse guidelines to find the FDA expectations from the sponsor at each stage gate.

CBER APPENDIX

When SDSP is submitted to CBER, please also include CBER appendix. Please note that CBER appendix should be shared with CBER no later than EOP II meeting.

- CDER: Submit SDSP at stage gates, not CBER Appendix

- CBER: Submit SDSP and CBER Appendix at stage gates

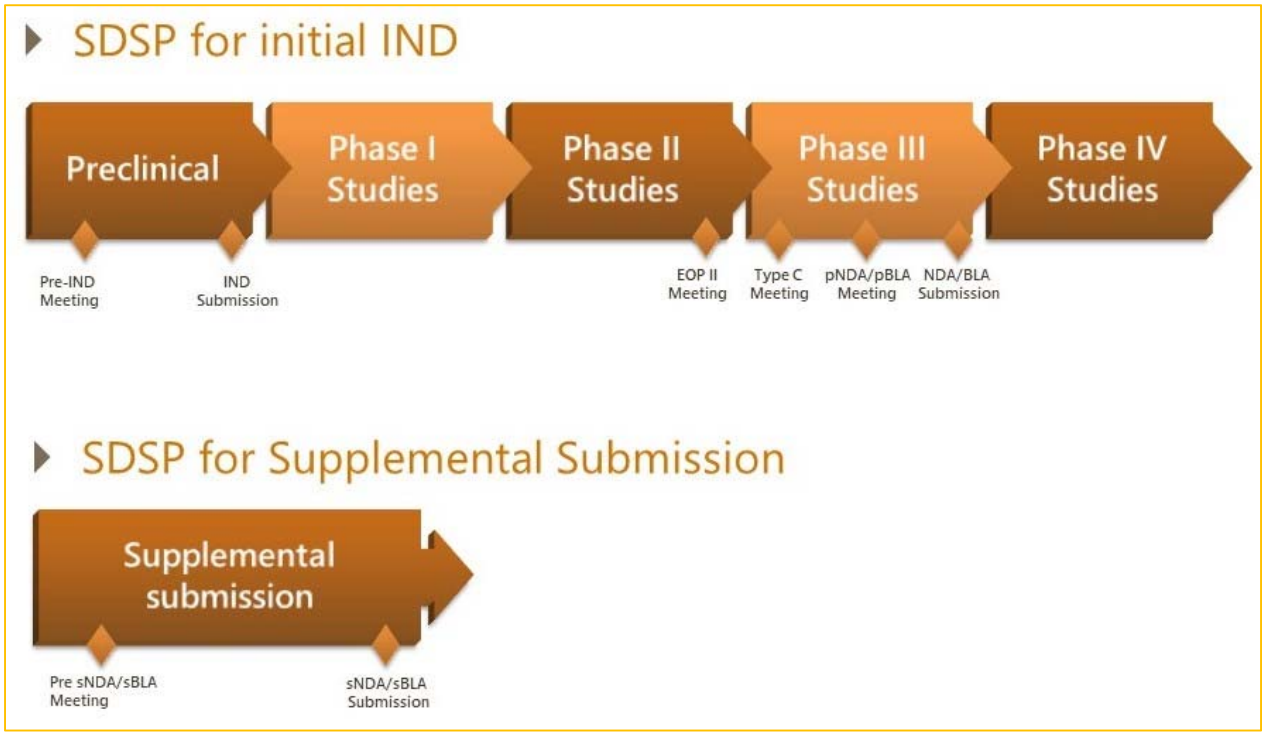

Figure 6. SDSP Stage Gates

PILOT PROJECT SELECTION

Obtaining preliminary information from pilot projects will help to gain valuable feedback on your proposed. process framework. In addition, achieving success of an initial SDSP submission and demonstrating the value of FDA feedback will help to validate the importance and positive impact of early FDA interactions in this space. It is recommended to select a project from each of the three regulatory milestones listed below:

1. Projects ready for Pre-IND meeting or IND submission
2. Projects ready for EOP II meeting or Type C meeting
3. Projects ready for pre sNDA or sBLA meeting

Selection of a pilot project from each of the three milestones will help to gain valuable feedback on current gaps in your proposed process, frequently asked question or concerns, and robustness of the RACI so that revisions can be made to internal processes prior to enterprise level implementation.

A proposed list of early adopters should be provided to the project sponsor and functional line management for approval prior to approaching individual teams.

LONG TERM IMPLEMENTATION

Once an overall process is defined with in your organization; communication, consistency, and reproducibility are key to assuring success for an enterprise level implementation. Focus on the three key areas below will help to support a successful long-term implementation plan.

FORMALIZED PROCEDURES AND TEMPLATES

Inclusion of the template and overall process as part of a Standardized Operating Procedure (SOP) will help to enforce the consistent completion of the SDSP and provide the necessary framework for teams to understand company expectations and FDA recommendations for completion and provision of a high-quality document. This will also serve to provide clear documentation history of revisions to templates and/or roles and responsibilities as updates are needed.

DEVELOPMENT OF TRAINING AND AVAILABILITY OF PROCESS TOOLS

All functional lines assigned in the RACI should undergo training to understand the template, process, RACI and overall timelines for deliverables so there is a clear understanding of expectations. Outside of a formal SOP, it may also be useful to set up a site to include frequently asked questions, sample documentation, a link to the PhUse website and any additional information that teams may find valuable outside of the requirements outlined within the defined SOP.

Training should be completed prior to SOP implementation or in the case of early adopter teams, training should be provided to each team prior to completion of the template for their project.

CENTRAL STORAGE OF DOCUMENTATION

A consistent, clearly defined location should be delegated for storage of the SDSP for each project. As the SDSP may get updated and submitted several times through the course of an IND program, the team must know where to find the most recent version to understand previous Regulatory agreements, revise as needed, and store subsequent approved versions for future interactions. This location should be consistent across all programs.

A process for tracking feedback, sharing responses, and identifying trends across programs should also be defined. This will help provide value added information to other teams and help to support proactive planning for other programs.

CONCLUSION

Constructing an effective process and plan within your organization for the submission of the SDSP to the FDA will have a positive impact on providing the framework necessary to receive early and continuous feedback from the Agency on data standards. Making a key investment upfront to assign clear ownership and designate a formal approach to document completion and submission, such as outlined in this paper, will assure a consistent and reliable methodology at an enterprise level. Using these tools and practices can provide the teams valuable insight throughout the lifecycle of the program and prevent last minute rework and submission delays. Early and continuous communication with the Agency is crucial for increasing the likelihood of success of downstream deliverables and it takes a team working together to achieve this goal.

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