Paper XXnn

An Overview of the OCS Core DataFitness Service

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ABSTRACT

The evaluation of submission data quality is an important step for the review process of new drug applications. Due to previous successes with providing data quality information to clinical safety reviewers through JumpStart, the Office of Computational Science (OCS) has been exploring new ways to convey data quality information for CDER applications to more reviewers in a shorter timeframe. The development of the Core DataFitness Service (CoreDF Service) seeks to solve this issue by providing automatically generated data quality reports to more review teams within CDER. CoreDF Reports can be used alone or in combination with additional deskside support. In summary, CoreDF Reports combined with deskside support provide clinical reviewers an assessment on the quality of the submission data and provide them a deeper understanding of relevant data quality issues.

INTRODUCTION AND PURPOSE

The purpose of this paper is to outline the development and implementation of the OCS Core DataFitness Service (CoreDF Service) at the FDA. The OCS offers the CoreDF Service to help reviewers assess the quality of clinical study data, including identifying data conformance issues to data standards, early in the review cycle. The CoreDF Service includes a set of data quality reports and a deskside support session to help reviewers navigate the reports.

Clinical review teams benefit from the CoreDF Service as it helps them identify potential data quality issues in an application that could impact filing and review times. Additionally, it improves the reviewer understanding of submission study data, the types of analyses that can be performed using the data and identifies potential information requests for the sponsor.

COMPONENTS OF THE COREDF SERVICE

The CoreDF Service is automatically provided for all new drug applications and consists of two primary components: the generation of validation reports and a deskside support session conducted to help Clinical Reviewers understand the

contents of these reports. For a supplemental drug application, where this service is not automatic, the Clinical Reviewer can also request the CoreDF Service through the OCS Service Deck. The service is provided to the Clinical Reviewers within 3-5 business days of the FDA's receipt of clinical data.

To construct the reports, business rules are run that check New Drug Application (NDA) data for compliance against the Study Data Tabulation Model Standard. Each report is produced in Excel and organized with an Overview and subsequent detailed findings sections.

The Overview section contains a summary that details metadata about the study (e.g. MedDRA version, SDTM IG version), a listing containing reports that expedite common Clinical Reviewer tasks and a findings listing containing all business rules violated. All items in the Overview section are linked to their respective detailed findings elsewhere in the report.

Example Summary section on the Overview of a CoreDF Report (Figure 1):

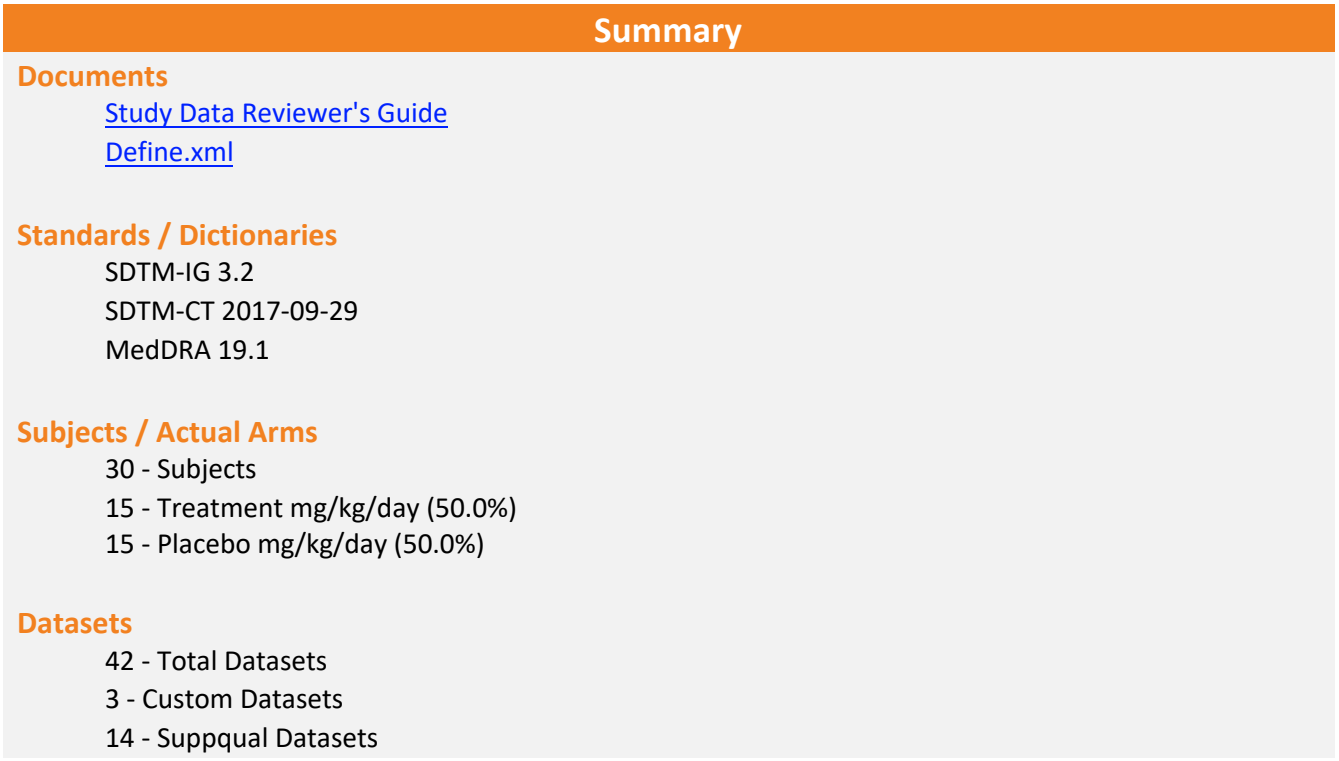

Figure 1 Summary section on the Overview tab

In this example, links to the SDRG and define.xml files are provided, standards and dictionaries used are listed, a breakdown of subjects is provided, and information about datasets is listed.

Example Reports section on the Overview of a CoreDF Report (Figure 2):

Reports
Deaths
Death Summary
Death Details
Death Reconciliation
Adverse Events
Adverse Events Coding Quality
Disposition
Disposition Coding Quality
Supplemental Info
Supplemental Contents

Figure 2 Reports on the Overview section

As shown in this example, reports are provided to expedite common Clinical Reviewer tasks. These include adverse event and disposition coding quality reports, reports related to subject deaths, and a report listing supplemental domains and variables included with a submission. These reports enable Clinical Reviewers to complete common review tasks more quickly and without having to organize, sort or join data on their own. These reports also highlight potential records of interest that would otherwise be very time-consuming to identify.

Example Findings section on an Overview tab of a CoreDF Report (Figure 3):

Findings
Demographics
5 (16.7%) of randomized subjects were not treated
15 (3.8%) of randomized subjects are missing Subject Reference End Date/Time (RFENDTC)
1 (< 0.1%) of subjects are missing Date/Time of Informed Consent (RFICDTC)
Disposition
84 (0.9%) of disposition statuses or protocol milestones are potential duplicates
Exposure
141 (2.0%) of treatments occurred after Date/Time of Last Study Treatment (RFXENDTC)
Comments provided in SUPPQUAL instead of Comments (CO) domain
Adverse Events
6 (< 0.1%) of adverse events have neither severity or toxicity grade populated
723 (12.0%) of events are missing end time-point
Laboratory
1 (< 0.1%) of baseline observations are missing Standard Results (LBSTRESC)
6 (< 0.1%) of laboratory test results are potential duplicates
Vital Signs
No significant findings
Other
22 (100.0%) of derived variables in Define.xml are missing computational algorithms

EPOCH variable was not provided

Figure 3 Findings section on the Overview tab

As shown in the above example, findings are organized by domain – Demographics, Disposition, Exposure, Adverse Events, Laboratory, Vital Signs and Other. Findings that pertain to multiple domains or to a domain other than one of the domains explicitly listed (e.g. Demographics, Exposure, etc.) are included in Other. Each finding listed in the 'Findings' section is hyperlinked to a detailed report of that finding, containing information about the finding, it's potential impact, and up to 10,000 records of relevant data, as shown in Figure 4 and Figure 5.

No Exposure record found for subject

Finding

5 (16.7%) of randomized subjects were not treated

Impact

Missing useful information to speed up your own exploration and analysis.

USUBJID	ARM	ACTARM
000-000-001	COHORT 4: OBSERVATION COHORT	COHORT 4: OBSERVATION COHORT
000-000-005	COHORT 4: OBSERVATION COHORT	COHORT 4: OBSERVATION COHORT
000-000-007	COHORT 4: OBSERVATION COHORT	COHORT 4: OBSERVATION COHORT
000-000-011	COHORT 4: OBSERVATION COHORT	COHORT 4: OBSERVATION COHORT
000-000-015	COHORT 4: OBSERVATION COHORT	COHORT 4: OBSERVATION COHORT

Figure 4 Example report for finding '5 (16.7%) of randomized subjects were not treated'

Neither AESEV or AETOXGR is populated

Finding

6 (< 0.1%) of adverse events have neither severity or toxicity grade populated

Impact

Missing values lack analytical value.

USUBJID	AESEQ	AETERM	AEDECOD	AETOXGR	AESTDTC
000-000-009	2	axillary vein thrombosis	Axillary vein thrombosis		2015-04-10
000-000-009	3	herpes labialis	Oral herpes		2015-04-04
000-000-027	3	Cystitis	Cystitis		2015-06-22
000-000-027	4	Cystitis	Cystitis		2015-07-06
000-000-030	5	Herpes of nose-upper mouth	Herpes virus infection		2015-03-23
000-000-030	7	Pain to the joints of the hands	Arthralgia		2015-10-14

Figure 5 Example report for finding '6 (< 0.1%) of adverse events have neither severity or toxicity grade populated'

CoreDF Analysts meet with Clinical Reviewers to guide them through all aspects of the CoreDF Reports. This includes explanations of all Summary, Report and Findings sections. Analysts also guide Clinical Reviewers through each finding in detail, explaining the meaning or potential impact of the finding and even demonstrating

identified issues within the Study Data Tabulation Model (SDTM) data if necessary. Analysts are also able to address Clinical Reviewer's questions in the session, most of which relate to data standards, potential impact of findings and general contents of the data package. These meetings and the opportunities to guide reviewers through their CoreDF Reports therein constitute the service component of the CoreDF Service.

RELATIONSHIP TO THE OTHER OCS SERVICES AND OFFICES

CoreDF is an important component in the OCS service portfolio which includes JumpStart, KickStart, the OCS Service Desk and others. Currently, CoreDF serves as the primary effort to provide automated data quality reporting to FDA Clinical Reviewers for all new applications. It is also a complementary service to the JumpStart and KickStart services, both of which provide high-touch, in-depth support on data quality and safety analyses tailored to specific applications for a limited number of applications.

LOOKING AHEAD

In the near future, OCS seeks to partner with more Offices within CDER who are interested in automated data validation in order to reduce the time it takes to understand the submission data package. These partnerships will take the existing CoreDF Service and expand it to meet the more specific needs of individuals Offices.

Additionally, OCS is currently working to include traceability reporting as part of the CoreDF Service. This reporting would help reviewers trace Analysis Data Model (ADaM) data elements back to their SDTM origins. Finally, OCS will expand the CoreDF service to support nonclinical reviewers by providing a set of reports identifying data conformance issues to Standard for Exchange of Nonclinical Data (SEND) in nonclinical studies early in the review cycle.

CONCLUSION

The FDA Office of Computational Science continually explores new ways to provide data quality information for CDER applications early in the review cycle to more reviewers. The development of Core Data Fitness (CoreDF) service provides automatically generated data fitness reports to a bigger number of review teams within CDER, allowing Clinical Reviewers evaluate the quality of the submission data and improve the efficiency of the review. OCS will continue to develop and expand CoreDF services through partnerships and the evaluation of non-clinical SEND data.

CONTACT INFORMATION

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