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Standards Governance – a First Insight

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ABSTRACT

Implementing a new data standard does not immediately make life easier or lead to success. It is only a start, especially if there is more than one standard in place, e.g. CDISC (Clinical Data Interchange Standards Consortium) SDTM (Study Data Tabulation Model), CDISC ADaM (Analysis Data Model), NCI (National Cancer Institute) Controlled Terminology. The consequence is the requirement for a sophisticated concept of how to maintain the standard(s), especially with regard to ongoing updates due to internally and/or externally driven change requests and the requirement for a system to deal effectively with the requirements of the projects/trials.
This presentation shows the approach to standards governance in the area of Data Management and Biostatistics within Merck Serono from the view of standards governance for SDTM.

INTRODUCTION

Standards governance has become an important topic since CDISC standards became mandatory for electronic submission to the FDA. At Merck Serono, trial conduct and the creation of CDISC SDTM are outsourced for nearly all trials, whereas the development and governance of the Merck Serono data standards is kept in-house. Based on a new working instruction for standard governance at Merck Serono the experiences with this new standard governance process are described in this presentation.

MERCK SERONO STANDARDS

The following standards are elements of the Merck Serono standard governance process: General Data Standards Collection Modules (electronic CRF, paper CRF modules), Therapeutic Area Data Standards Collection Modules (electronic CRF, paper CRF modules), SDTM standards (annotated CRF modules, SDTM data model), ADaM standards (ADaM data model, Biostatistics output standards), Controlled Terminology (CT) and Value Level Metadata (VLM). Standardization is expected to reduce timelines, resources and programming effort, and to improve processes and the communication within the company and with our external partners.

MERCK SERONO SDTM STANDARDS

Current CDISC SDTM standards build a solid ground for generating SDTM data. Nevertheless the SDTM IG (Implementation Guide) includes a lot of implementation options, which leave room for interpretation. Additionally there are therapeutic area standards published by CDISC, but there are a lot of therapeutic areas still missing. Also the Controlled Terminology does not fit completely our needs. These are the reasons why we need company-specific SDTM standards. The company-specific standards, together with accompanying guidelines, allow a harmonized approach across the Merck Serono projects.

The Merck Serono SDTM data model consists of three different model definitions.
The SDTM DOMAIN model contains:

- Overview sheet with all SDTM domains used at Merck Serono, including all general SDTM domains defined by CDISC and the sponsor-defined domains
- Definition/Listing of all variables (metadata) for each single domain

The SDTM Controlled Terminology (CT) model contains:

- Definition/Listing of the CT specified for the Merck Serono SDTM model. Based on NCI (National Cancer Institute) published SDTM terminology including the Merck Serono sponsor specific extensions and the appropriate metadata required for maintenance and populating the define.xml

The SDTM Value Level Metadata (VLM) model contains:

- Definition/Listing of the VLM (e.g. --TESTCDs) specified for the Merck Serono SDTM model. Based on assumptions to collect appropriate metadata required for maintenance and populating the define.xml (e.g. enable nesting of VLM in define.xml)

The Merck Serono SDTM standards consist of several documents which are updated on a regular basis. The frequency of updates depends on the number and importance of new releases by CDISC and the NCI.

PEOPLE/ROLES/RESPONSIBILITIES

GOVERNANCE TEAMS

There are four different governance teams:

- General Data Standards Team, responsible for general electronic CRF and paper CRF modules
- Therapeutic Area Data Standards Team, responsible for electronic CRF and paper CRF modules created for one therapeutic area
- SDTM Team, responsible for annotated CRFs, SDTM data model, CT and VLM
- ADaM Team, responsible for ADaM data model, CT and VLM

The governance teams are responsible for development of new standards, maintenance, management and documentation of the standards, and training on the standards. Additionally they are providing expert guidance on the application of the standards.

SDTM ROLES AND RESPONSIBILITIES

To perform the SDTM governance we defined four different roles.

- SDTM Expert
  - 1st level support for SDTM related topics within Data Management (at Merck Serono called Global Clinical Data Sciences)
  - No independent decision making
- SDTM Independent Expert
  - (1st and) 2nd level support for Data Management and SDTM expertise
  - Mentorship for SDTM Experts
  - Support for Librarians
- SDTM Librarian
  - Decision maker for Exemption Forms
  - Creation, maintenance and documentation of the SDTM standards
  - Training on Merck Serono standards
  - Representation of Merck Serono interests in CDISC world
- Controlled Terminology Librarian
  - Maintenance of Controlled Terminology (SDTM and ADaM)

The SDTM Governance Team consists of all SDTM librarians plus delegates from the General Data Standards Team and the ADaM Standards Team.

STANDARDS GOVERNANCE PROCESS

A Merck Serono Working Instruction is in place which describes the management of the General (DST) and Therapeutic Area (TA) data modules, SDTM and ADaM standards in relation to the creation, use, maintenance and documentation of the standards to ensure data consistency and to facilitate regulatory submissions.

EXEMPTION FORM (EF)

The governance process is applicable for all interventional Phase I to IV clinical trials carried out by Merck Serono's Global Research and Development and Contract Research Organizations (CRO). If the current clinical data standards do not cover all the requirements for setting up any of the trial specifications (e.g. eCRF, SDTM annotated CRF and data sets, ADaM data sets) or anything which does not comply with or requires an amendment to an existing standard then a "Clinical Data Standards New, Change or Exemption Request Form" (also referenced as EF=Exemption Form) must be completed and sent to the appropriate Clinical Data Standards Librarian. The wording "Clinical Data Standards Librarian" summarizes all types of librarians: DST, SDTM and ADaM librarians.
In all cases where

- a new study specific form/module is created because a standard doesn't exist
- a standard exists, but the Trial Team requires a change, deletion of a mandatory field or the addition of a new field

the EF must be completed according to a template.
This process applies to the General and Therapeutic Area Data Standards Collection Modules, Merck Serono SDTM Standards, ADaM Standards, Controlled Terminology (CT) and Value Level Metadata (VLM).

WORKFLOW

Once the (CRO) Project Team identifies that the current version of a standard is not covering trial/project needs, the (CRO) Project Team Requestor discusses the exemption with the other (CRO) Project Team members to ensure it is required. The core reviewers for the EF, changes in data standards, CT, VLM and SDTM standards are the Program Data Manager, Project Biostatistician/Project Statistical Programmer and the SDTM Independent Expert. The core reviewers for changes in ADaM standards are the Project Biostatistician, Project Programmer and if applicable, the ADaM Team Lead.

If it is agreed that the EF is needed, it is completed and sent to the Global Clinical Data Sciences (GCDS, formerly Global Data Management) or Global Biostatistics (GBS) Trial Team Contact at Merck Serono, depending on the type of request. The Trial Team Contact in GCDS (Program Data Manager) or GBS (Trial Statistical Programmer/Biostatistician) reviews the exemption and checks to ensure that it is correct and is needed. If for any reason the Merck Serono contact does not think it is needed and the standards can be followed instead, the request should be sent back to the CRO and should not be sent to the Standards Librarian to go through the governance process. If the form is not complete, it is returned to the requestor for the additional information. It is important that the date of the request on the form is the date it is sent to the Clinical Data Standards Librarian. This date is used to track the turnaround time of the responses (which is a performance indicator for the librarians).

If the request is acceptable, the form is sent to the appropriate Clinical Data Standards Librarian to go through the governance process.

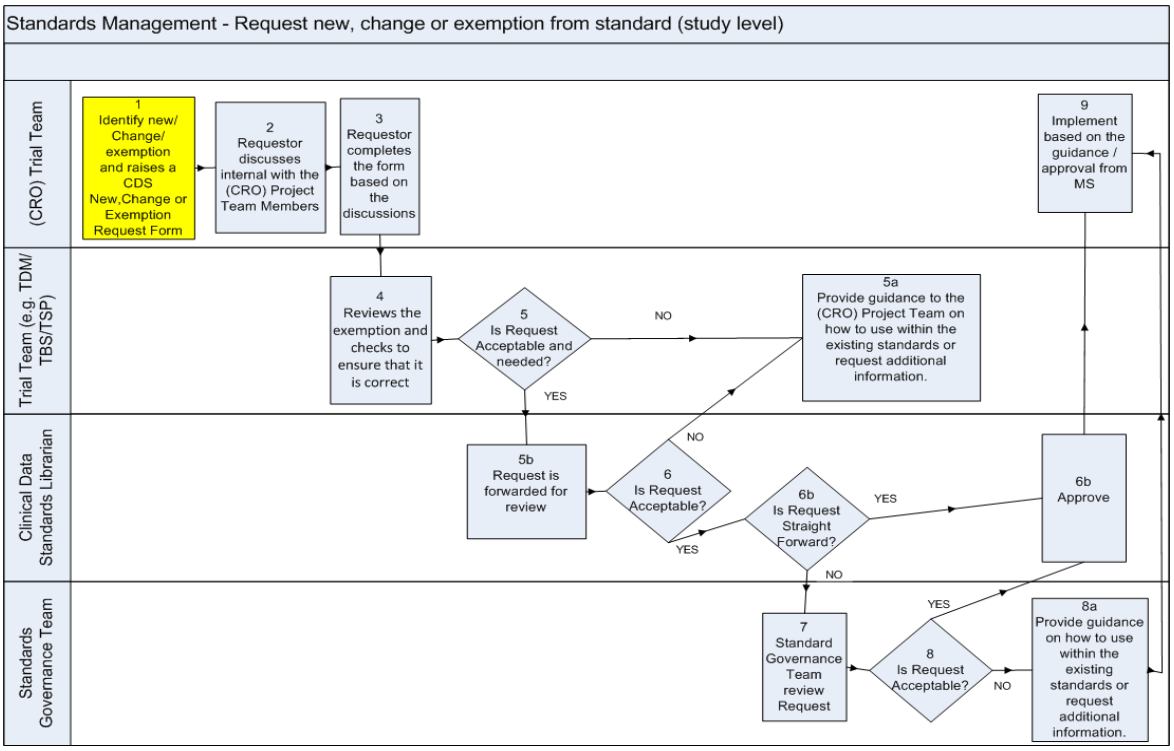
The request is forwarded to the relevant Clinical Data Standards Librarian for review and approval.

A general tracking sheet for all 'Clinical Data Standards New, Change or Exemption' forms is completed by the librarian and a reference number is provided.

Then the Clinical Data Standards Librarian evaluates the request. The previous requests outcome should be also considered to ensure consistency in responses from the librarians.

- If the request is rejected then guidance should be provided on how to use the existing standards and communicated to the Merck Serono Trial Team Contact and (CRO) Project Team via email and no further action is required by the Clinical Data Standards Librarian.
- If the request is straightforward (i.e. typos) or changes had been previously discussed with the appropriate team and require no input from the other Standards Team leads, then the librarian can approve as a trial-specific exemption from the standards.
- If additional information is needed, the librarian should request this information before asking for input from other Standards Team members and/or other librarians.
- If the request is not straightforward, other Standards Team members should be asked for input on the request.
- If the request is approved, an email confirming approval will be sent to the requestor and should be retained in the trial master file by the (CRO) Project Team as evidence of approval.

The (CRO) Project Team implements the exemption based on the guidance/approval from the appropriate Standards Governance Team.



All decisions on requests (approval or rejection) should always be communicated among the different types of librarians in the respective Standards Teams.
The following outcomes can occur from the review:

- Approve or partially approve as a trial-specific exemption from the standards (including partly rejected issues)
- Reject with a proposal of how to handle within the current clinical data standards
- Request additional information

If a request is partially accepted it is documented in an email as to what is accepted and what is rejected. This may be done by sending a document with the SDTM and/or ADaM metadata sheets attached and the approval or rejection on each row.

GENERAL REMARKS

The information in the EF tracking sheet is used to calculate Key Performance Indicators (KPIs). The agreed KPIs for the General and Therapeutic Data Standards will be "Average compliant rate in % on the mandatory general data standards for phase I-III studies" and "Average compliant rate in % on the mandatory oncology data standards for phase I-III studies". This is done for the General Data Standards by taking the number of Phase I-III studies and counting the number of approved exemptions (not new forms) on thirteen mandatory modules. For the Oncology Data Standards it is done by taking the four mandatory oncology modules. Another KPI used for all Merck Serono standards is the turnaround time. It is the goal of the Standards Teams to provide an initial response to EF as quickly as possible.

MANAGEMENT OF MERCK SERONO SDTM STANDARDS

The SDTM Governance Team keeps all versions of Merck Serono SDTM standards. Each Project Team decides which version of the Merck Serono SDTM standard shall be used for a respective trial; usually this is the version which was available when a trial started. Whether the project needs to be moved to a newer version of the standards is also decided by the Project Team. This may depend on project timelines and planned submission dates.
The SDTM Governance Team decides when a new Merck Serono SDTM standard will be released. This depends on the number of changes in the SDTM data model and on new updates by CDISC. Updates on Controlled Terminology are performed on a regular base, close to the releases published by the NCI. This also means that there are more frequent updates e.g. to Controlled Terminology than to other standards documents and that each part of the SDTM model may have a different version number.

CHALLENGES AND HURDLES

EXEMPTION FORM HANDLING

The working instruction for standard governance at Merck Serono has been in place for more than 1 year now. The exemption form process for SDTM started in Q1/2013. The extent of the workload for both the governance and the Trial Teams was not foreseeable. A lot of studies have deviated from the Merck Serono SDTM standards, due to in-licensed products with legacy trials, or studies set up with older versions of the Merck Serono standards.

When we started the exemption form process, the trial data managers had concerns about the work required to create exemptions for each and every new or changed item, especially for SDTM. The trial data managers need to know the Merck Serono standards very well and they also need to know which exemptions are already approved for the project to allow harmonization within the project. Moreover, they usually have not the time to deal with the details of the trial database when working on several outsourced trials in parallel.

It is also a huge amount of work for the (three) SDTM librarians working one fifth of their time on exemption forms for all trials. We received on average 4 exemption forms per month, each with 6 to 200 variables/controlled terms for approval. The decision on approval needs knowledge of the project to get a harmonized approach within the projects and the librarians have to cover the expertise for all ongoing trials at Merck Serono including consultancy on any SDTM-related questions. Therefore we assigned the SDTM librarians to certain projects. If a SDTM librarian thinks that an exemption could be relevant for the general SDTM domain model, a request is added in an issue tracking system. This is a case-by-case decision and these requests are discussed during regular TC calls within the SDTM Governance Team and then possibly implemented into the Merck Serono SDTM standard. Usually trial-specific exemptions approved for Controlled Terminology or Value Level Metadata are included in the Merck Serono SDTM CT and VLM updates.

UPDATES OF MERCK SERONO SDTM STANDARDS

The Merck Serono SDTM Governance Team maintains the global SDTM standards, but there are no resources to keep project-specific SDTM standards as well.
The number of updates of the global SDTM data model depends on

- the resources available in the SDTM Governance Team
- the number of new releases by CDISC
- the importance of new releases by CDISC

Updates of CT and VLM are made close to the updates released by the NCI.
To reduce the amount of work for exemption form handling it will be necessary to do more frequent updates on the Merck Serono SDTM data model in the future.

CONCLUSION

There is no “single” way of implementing standards in a company. The Merck Serono way of maintaining standards by using exemption forms which are completed and tracked manually turned out to be a very onerous and time-consuming option involving a lot of bureaucracy. However, the exemptions give a good indication of where our Merck Serono SDTM data model needs to be expanded and updated. In the future, a clinical data repository, which at this time is in a pilot state, will support us in handling the standard governance process for SDTM and ADaM more effectively. The exemption request and approval process will be embedded in the system and should reduce the manual work. At this time, project-specific standards (data model, CL, VLM) are not governed by the SDTM Governance Team, but this will be possible within the new system.

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