

“CONNECT and CREATE” Connect Standards and Enable Protocol Authoring

Mr. Abi Velurethu, Bayer HealthCare, Whippany, U.S.A
Mrs. Susanne Pangritz, Bayer HealthCare, Leverkusen, Germany

ABSTRACT

At Bayer HealthCare, the initial idea behind the Global Medical Standards toolset (Metadata Registry and supporting systems) was to implement a tool set, which allow to develop, maintain, re-use and track clinical standards for the organization. Post-release of the initial rollout and many lessons learned later, Bayer has realized that we can expand the use case and reduce the ambiguity during study standards definition and setup cycle time.

The idea is to link the standards at various levels (e.g., global, therapeutic) internally within the standards management tool. After that, make the standards available within the protocol authoring tool to enable a Standards driven authoring process.

To achieve this idea, Bayer HealthCare is going to adapt to new processes (business and system) for the Phase 2 and Phase 3 rollouts of the Global Medical Standards and Protocol Designer tools. This paper details the idea, the approach we have taken and a data flow process overview.

INTRODUCTION

The overall vision of the system is to provide related Medical Standards for every Protocol Activity that must be executed in a study. In other words, the selection of Protocol Activities in the Protocol Designer tool (also known as Structured Study Design Tool – SSD) will automatically drive the study standards setup in the Global Medical Standards tool (known as PULSE internally at Bayer). The study standards structure will include:

- Protocol Activities
- EDC forms and items (eCRF)
- Data Structures
- Codelists with subsets
- Edit Checks
- Table, Lists, and Figures
- Mapping and derivations
- Clinical Study Report

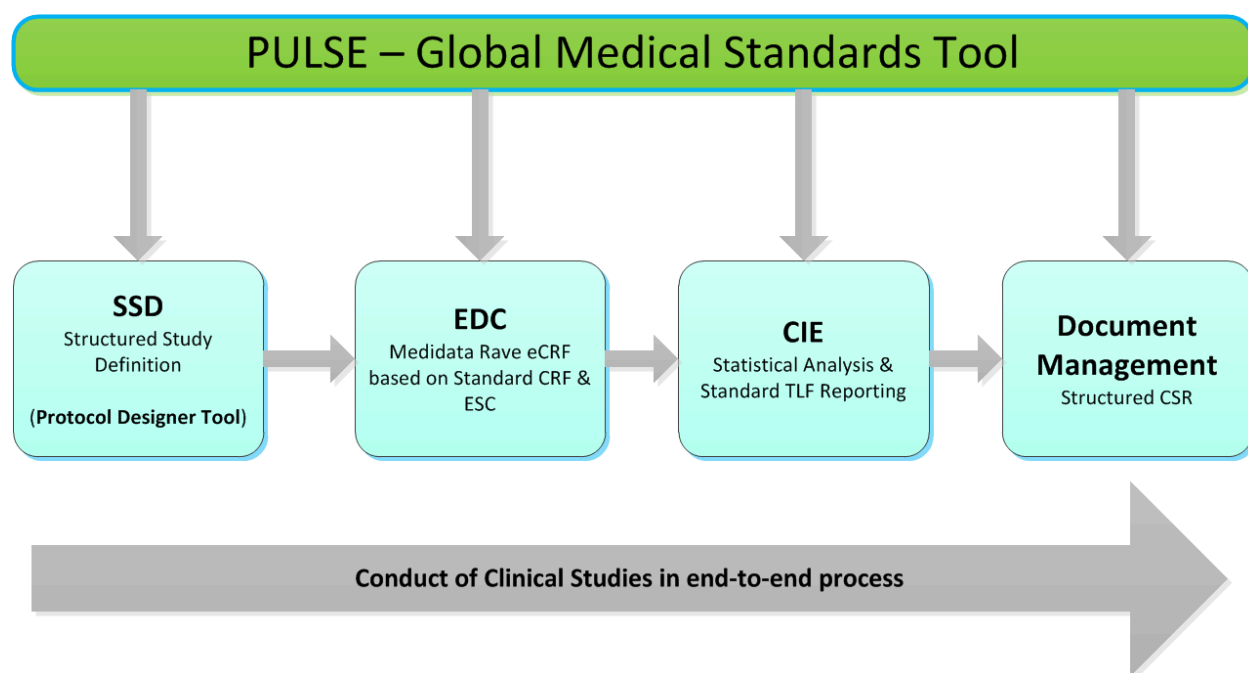


Figure 1: This image depicts the overall vision of standards implementation at Bayer HealthCare.

To achieve this vision, Bayer focused on two key areas within the Global Medical Standards toolset initiative:

- **Standards Management System**
 - Standards Taxonomy (directory) setup
 - Standards Data Flow
 - Standards Visualization and Reporting
- **Standards Content**
 - Create Standards Content Structure
 - Connect Standards

To fully realize the benefits of each area, we have adopted a phased approach for implementation as seen in Figure 2.

Phased Approach

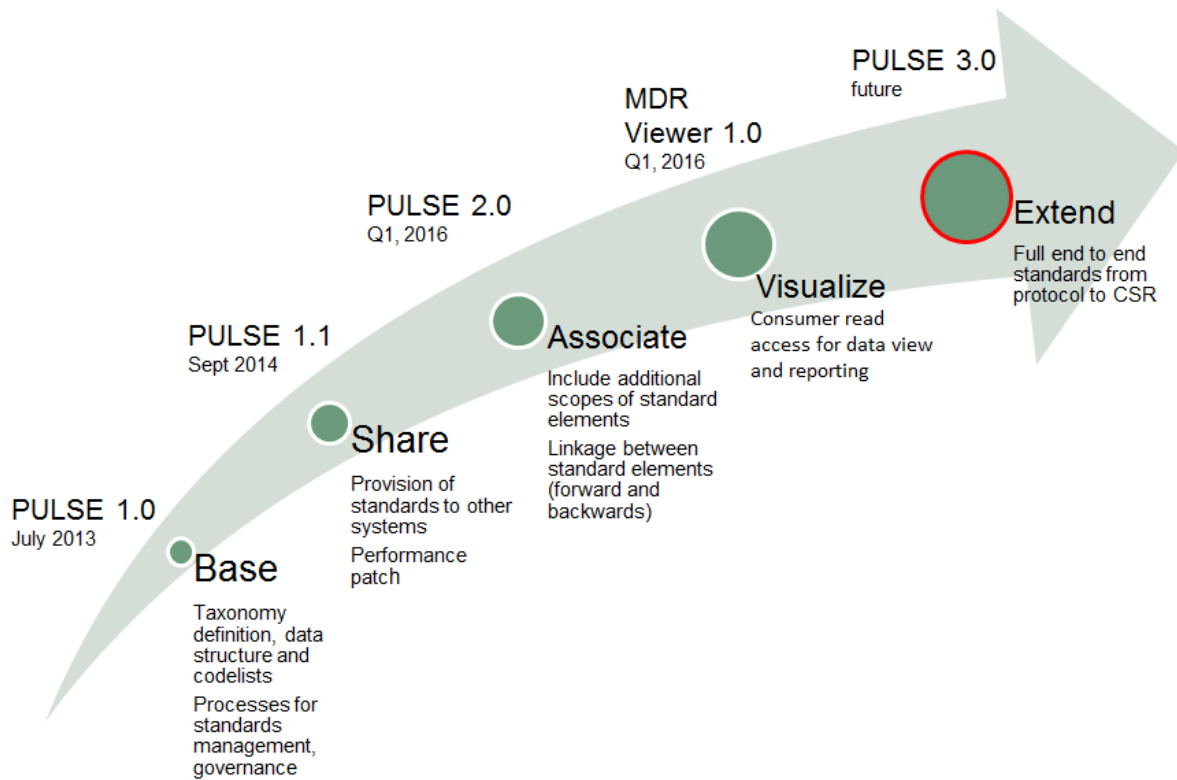


Figure 2: This image depicts Bayer HealthCare's phased approach and timeline for the Standards implementation initiative.

The primary focus of this paper is to discuss and detail the two key areas as stated above, Standards Management System and Standards Content. Our goal is to share the knowledge that we have gained thus far and to obtain better understanding from the industry. Ultimately, establish good standards utilization practice to improve the quality of the Conduct of Clinical Studies.

STANDARDS MANAGEMENT SYSTEM

To address the standards management business needs, Bayer implemented a solution that is capable of storing and maintaining standards in a repository with the ability to execute and track workflows. It was imperative that the solution must be able to support the creation of new standards, update existing standards and conduct impact analysis due to changes of standards tracked within the system.

Also, we have realized a need for supporting tools that are required to complete the overall Global Standards Management vision, primarily to help our standards consumer community. In doing so, we have introduced the concept of 'MDR Viewer'. The MDR Viewer would enable users to visualize, report and extract the data from a lightweight web interface that interfaces with the Global Medical Standards toolset.

In the following sections, we will detail the standards taxonomy, standards data flow and visualization that enable the upstream and downstream usage of medical standards.

STANDARDS TAXONOMY

In order streamline the maintenance and the usage of Standards, Bayer implemented a structure that enables the grouping of standards into Global, Therapeutic Areas, Compounds and then Studies. A user who handles the setup of study specific Standards may choose from Global, the specific Therapeutic Area or the particular Compound. Subsequent details are described in the Standards Content section of this paper.

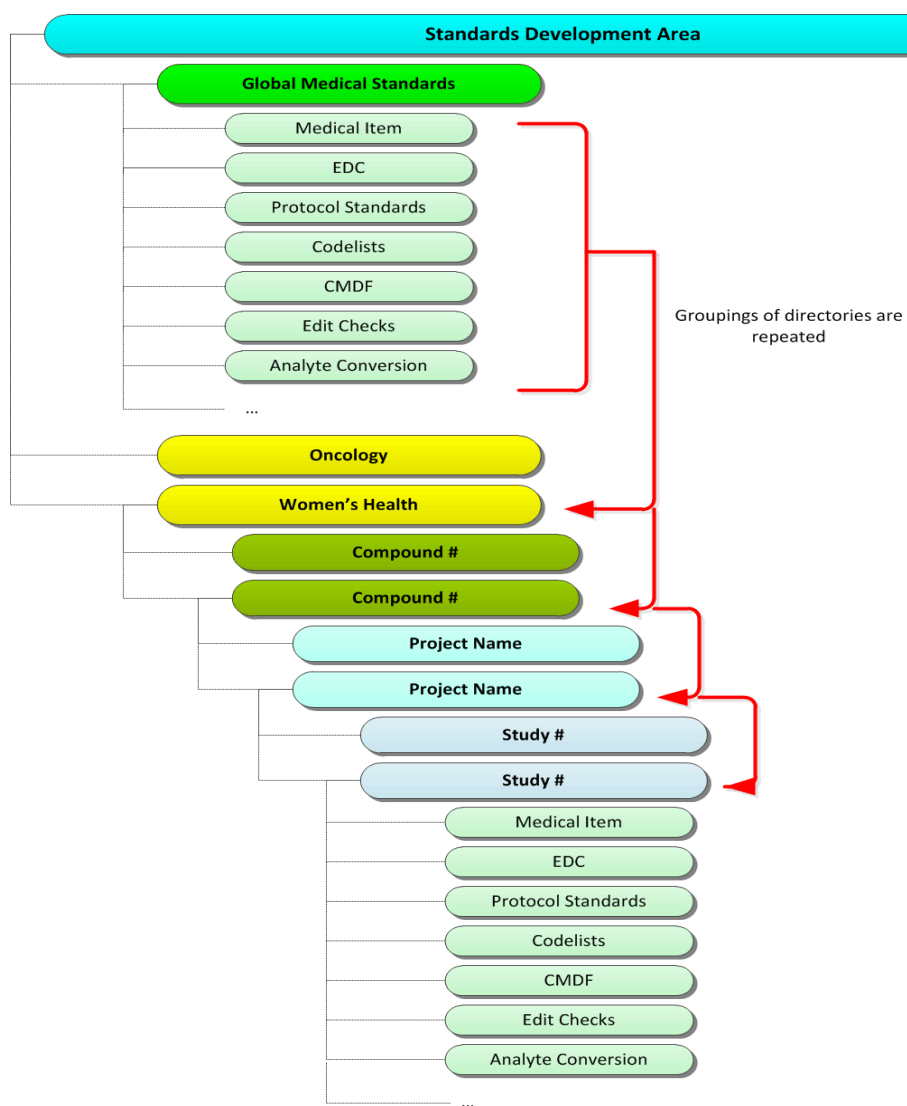


Figure 3: This image depicts the current Standards grouping and hierarchy.

STANDARDS DATA FLOW

Once the standards are linked with the protocol activities in the Standards Management tool, a new process is required to surface the particular standard in the Protocol Designer tool. In the case of Bayer, this standard is an Activity. In other words, Activity is maintained as a Standard in the Standards Management tool, and then exposed in the Protocol Designer tool. The linking and association details within the Standards implementation process are described in subsequent sections of this paper.

The following process is in consideration to connect the protocol authoring process to the standards implementation process.

Future State : Connect Activity to Protocol Authoring

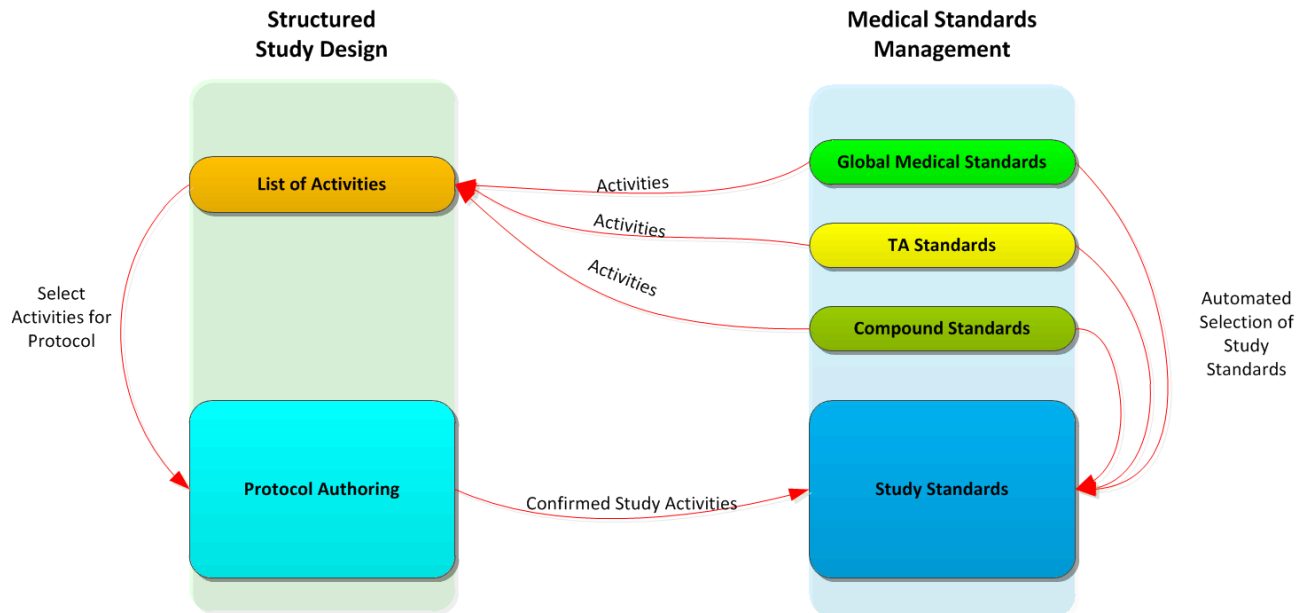


Figure 4: This image depicts the various Standards flow within the Global Medical Standards Tool (GMST) and Protocol Designer Tool (SSD).

STANDARDS VISULIZATION AND REPORTS

The Standards Management tool is designed and organized to ensure the most effective management of standards with an appropriate taxonomy and processes. Since such Standards organization is the most effective for management, it is not necessarily the most effective for users to browse, evaluate and consume the Standards.

Therefore, we have employed an auxiliary system that will enable us to present the Standards in the most effective way for different use cases for downstream use. This auxiliary system is termed the MDR Viewer and it enables, for example, a Protocol authoring user to gain an efficient access to Standards presented via the Protocol Activity context in which it is obvious which Medical Items (Concepts) belong to assigned activities and with them the data structures needed to collect the data for that activity.

In a similar way, the Standards consumers from other functional areas like EDC are able to view the Standards from the context of EDC forms (eCRF) and relevant Edit Checks.

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The MDR Viewer achieves the above-mentioned capabilities through a developed Business Data Model. Such model has the following advantages:

- Well known by the business users and can adapt to any related operational use case
- Optimized for data browsing, searching and reporting
- Enables dedicated views that users can adapt, filter and change through the user interface and thereby enabling them to get access to appropriate data subsets
- Links relevant standards together
- Gives a clear indication in all standards dependencies and it enables 360 degrees impact analysis
- Provides the value-level metadata for all the activities used in the protocol

STANDARDS CONTENT

Current situation:

The Clinical Standards at Bayer include Case Report Form representation of Medical Items, Database structure for SDTM based operational acquisition dataset and ADAM based Analysis Datasets, Codelists, Edit Checks and TLF specification.

The Standards Elements are provided in documents such as Word or Excel and stored in a document repository. Database structures and Codelists are implemented in a data management system.

Currently, the Standards Elements are not linked to each other; a user has to search for single standard elements on its own. For example, if a user selects one CRF, the corresponding database structure, applicable Codelists, Edit Checks and TLF specification needs to be identified separately.

This situation leads to Activities not being in sync with the Standards during the Protocol development process.

Future situation:

All Standard Elements will be made available in a consumable format to enable the provision of Standards to other operational systems. The Standards Elements will also be linked, enabling:

- Automated population of studies with Standards
- Supporting downstream processes of Standards provision to other operational systems such as Protocol authoring or Data Management/Statistical Systems
- Automated Impact Analysis during Standards updates
- Automated workflow-driven Standards maintenance and governance

CREATE STANDARDS CONTENT STRUCTURE

The Standards Elements are grouped into Functional Areas, then structured and specified according to the requirements for these areas:

- Protocol Standards
- Medical items
- Clinical Metadata Foundation
- Codelist
- Edit checks

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- EDC
- Analyte Conversion

Functional Areas for Protocol Standards, Medical items, Codelist and Clinical Metadata Foundation are described in more detail below.

Protocol Standards:

Protocol Standards are divided into two areas:

- Activities
- Trial Design

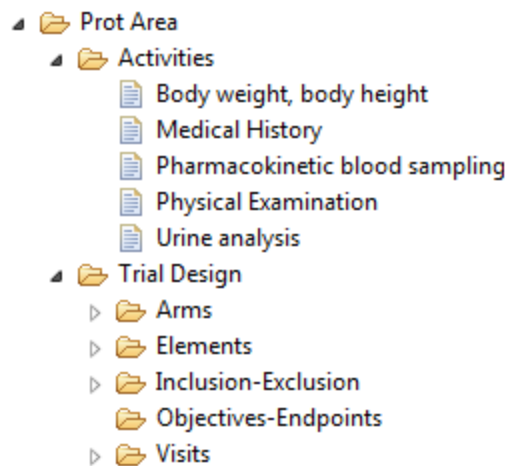


Figure 5: This image depicts the Protocol Standards Area with Activities and Trial Design Elements.

Activities

The Standard Element Activity describes the activity in a protocol such as the procedure or the measurement performed at the Clinical Research Site to obtain clinical data for the study result.

Activities are represented hierarchically in two levels:

- Grouping level
- Activity level

The **Grouping** level is used to group Activities with similar purpose, and as such is not affected by the maintenance process, Grouping level contains Activity objects.

Activity level contains the activity objects which have attributes to identify activity for downstream processes and to define the activity that can be used by a Protocol Designer tool to create the Clinical protocol. Change requests may be raised at this level to provide a maintenance mechanism on the Activity level. On the Activity object, the association to the Activity related Medical Items are enabled.

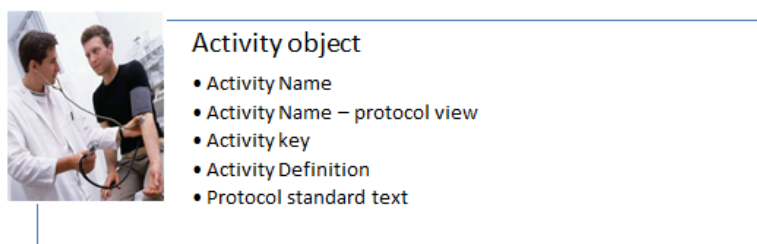


Figure 6: This image depicts the Activity Standard Element object and its attributes.

Trial Design

The Trial Design folder contains sub-folders for management of different aspects of the trial design:

- Arms
- Elements
- Visits
- Inclusion-Exclusion Criteria
- Trial Summary

Conceptual representation of the Trial Design folder is shown in Figure 7. The implementation of the Trial Design representation can be realized by using sub-folders.

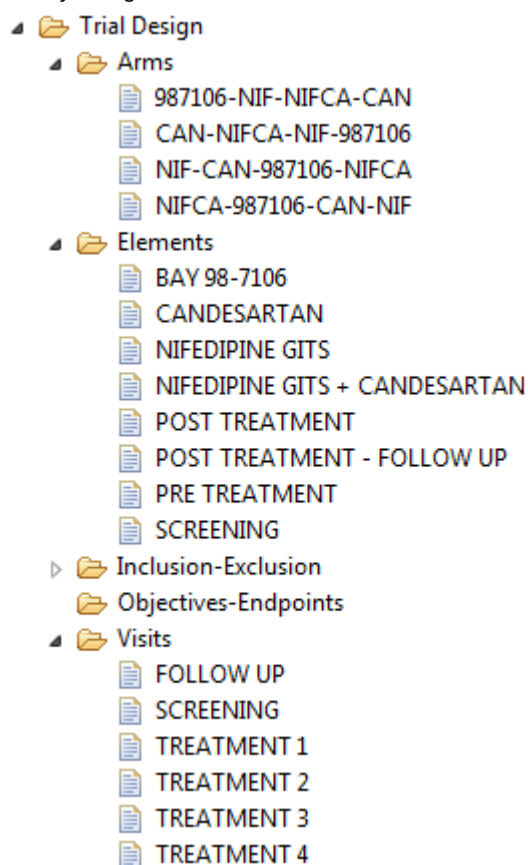


Figure 7: This image depicts the Structure of Trial Design folder and its sub-folders.

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Arms sub-folder contains the Standard Definitions of the Trial Arm which are used by the Protocol Designer tool to define study design. In order to support the Structured Study Design (SSD) process, the Arms contain identification attributes and overview of the sequence and the content of the trial elements and epochs.

Elements sub-folder contains the Standard Definitions of the Trial Elements. The Trial Elements are used by the Protocol Design tool to setup periods/sub-periods for the Study Flowchart. In order to support SSD, the element contains identification attributes and start/end rules for the element, which may be defined as the permissible changes for given clinical project/study.

Visits sub-folder contains the Standard Definitions of the Trial Visits, which are used in the Study Flowchart of the SSD Tool. Similar to the elements, the visit contains the identification attributes and start/end rules for the visit. The start/end rules may be defined as the permissible changes for given clinical project/study.

Inclusion-Exclusion sub-folder contains the Inclusion and Exclusion criterion for the given project/study. These criteria will include classification to indicate why this particular inclusion/exclusion is relevant for the particular project/study.

Trial Objective-Endpoints sub-folder contains the Protocol-specified Objective and Endpoints for the given project/study.

Medical item

Medical Items consists of two-level hierarchy:

- Item Grouping
- Medical Items

Item Grouping level is used to organize or group individual Medical Items.

The **Medical Item** level contains all Medical Items relevant for the given grouping level. Each Medical Item is a standard object and as such, it can undergo the maintenance process. The content of the Medical Item standard object are stored in the attributes of the Medical Item. In addition, it has references to CMDF variables and their respective Codelists. The Medical item defines the relevant subset of the Codelist.

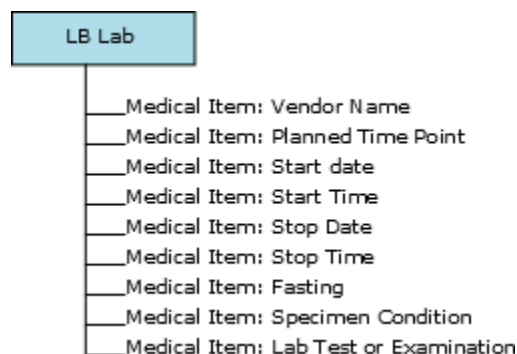


Figure 8: This image depicts an Example of the Medical Item grouping and the Medical Item objects.

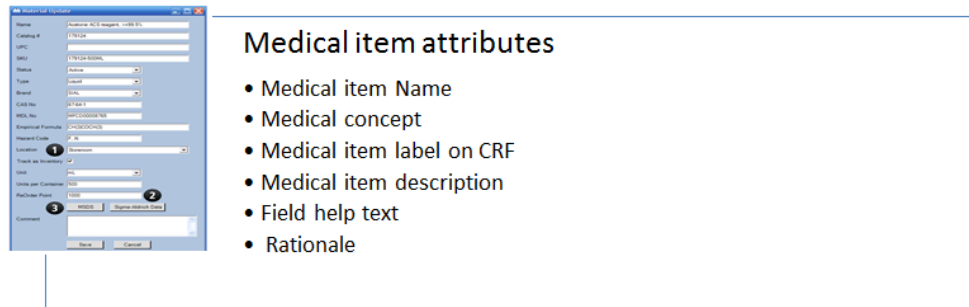


Figure 9: This image depicts the Medical Item Standard Element object and its attributes.

Codelists

Codelists consists of a three-level hierarchy:

- Codelists Folder
- Codelists Name
- Decode levels

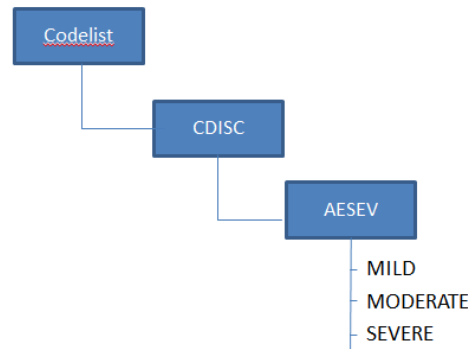


Figure 10: This image depicts the Codelists structure.

Codelists Folder level is used to group Codelists according to their use, origin or similar (e.g., CDISC or BHC Codelists). The folder level is only used to group the Codelists (by storing specific Codelists) and is not affected by the maintenance process or versioning. In other words, it is a container and changes cannot be raised at the Codelists folder level.

Codelist Name level contains metadata that are used to describe the complete Codelists. Therefore, it can undergo the maintenance process, i.e., changes can be requested for this level. Any change to the Codelists Name level does not affect the Decode level. Complete Codelists can also be retired by retiring it at the Codelists name level, e.g., by retiring a Codelists all corresponding decodes will be retired as well.

Decode Level contains the full description (metadata) of the codes/decodes that form a particular Codelists. Maintenance process applies, and one or more decodes can be requested by raising a new standard request at this level. In case of a change request at this level, it affects only the given decode for which the change has been raised. When items at this level are retired, it only affects those codes/decodes for which the retirement has been requested.

Clinical Metadata foundation (CMDf)

The CMDf Functional Area represents a model incorporating a unified view of the data structure standards. This model will contain a superset of all attributes required by the different type of datasets. Based on consumer requirement, various views on the standards data structure can be achieved. Also, the maintenance of the data structure Standards will be significantly reduced as the Standards are managed and maintained in one place and then provided in different view for multiple purposes.

Currently, the PULSE tool will provide the CMDf structure that is capable to maintain and provide standards for the following data structures:

- Source Plus
- Foundation Sets
- OAD (for backward compatibility)
- ADS
- SDTM (including different SDTM versions)

CMDf Functional Area consists of two level hierarchies:

- Variable Grouping
- Variable

An example of the CMDf hierarchy is shown in Figure: Example of CMDf hierarchy

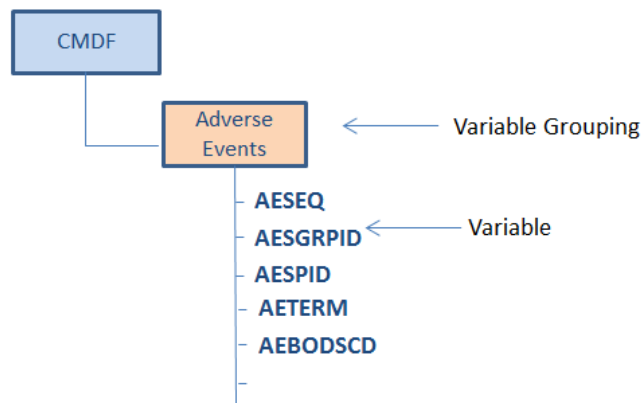


Figure 11: This image depicts an example of CMDf hierarchy.

In addition to the two-level hierarchy structure, CMDf Functional Area contains Standard objects called Dataset Name which will provide metadata relevant for datasets of different scopes (SDTM, ADS, etc.).

Variables are presented in their separate grouping; they will have attributes that provide the reference to the particular dataset that they belong to (variables can belong to one or many dataset names).

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Depending on the need of the operational system (standard consumer), the Standards Management tool will be able to provide relevant attributes to fulfil the need. For example, if SDTM 'view' of the Variable Grouping is required by the standards consumer system; the Standards Management tool will provide all SDTM relevant attributes and provide an SDTM domain view of the **Variable Grouping**, including the relevant variables (Figure: CMDF standard variables exported for different views, e.g., SDTM, ADS).

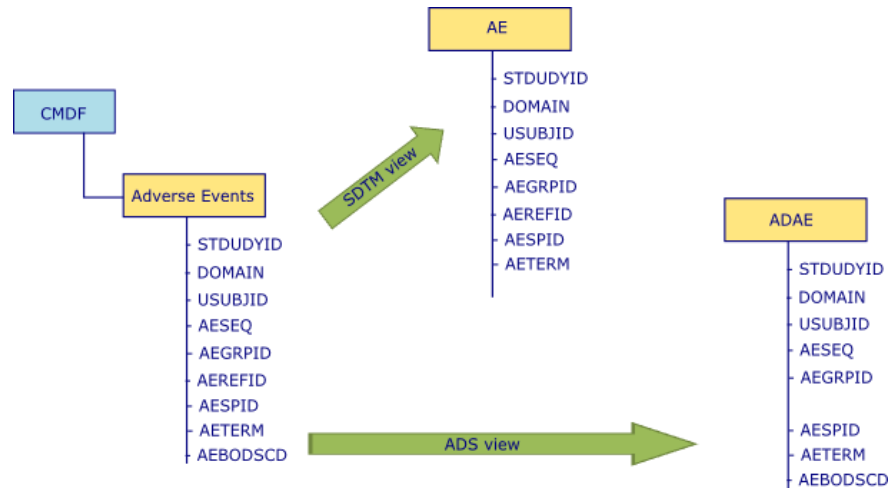


Figure 12: This image depicts the CMDF Standard Variables export for different views, e.g., SDTM, ADS

Each Variable in a Variable Grouping contains all attributes that enable the unified representation of that variable. For example, attributes relevant for SDTM view are grouped under 'SDTM' grouping, while all attributes common to all views could be grouped under the 'Main' grouping. Attributes relevant for different representation of the CMDF may be grouped according to their representation (e.g., SDTM or ADS views). Primary attributes of CMDF variables are Variable name, Variable Label, Type, Format Length, and Codelist Name.

Each Variable in the CMDF, which are a part of one, many or all CMDF Views, may be mapped to another CMDF View. This mapping functionality is managed and maintained on the Variable itself; using attribute grouping and relevant attributes within the mapping grouping. These mapping attributes may contain:

- Mapping Sources
- Mapping Type
- Method

Standard Attributes on Standard Objects

The metadata structure of the Standard Elements has attributes for the standard content, linkage to other Standard Elements as well as for the standards maintenance.

Every Standard Element has the same set of attributes for versioning and maintenance information for the particular object.

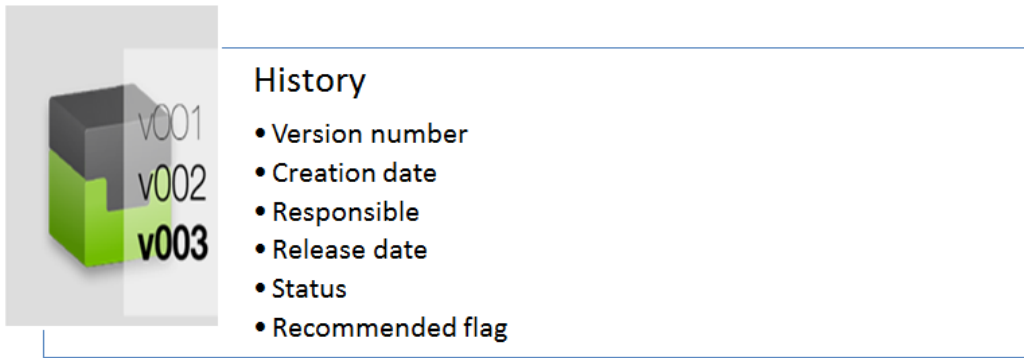


Figure 13: This image depicts History attribute grouping for every standard objects.

CONNECT STANDARDS

The Bayer Global Medical Standards Tool will be able to provide all related Medical Standards for every Protocol Activity that will be executed in a study.

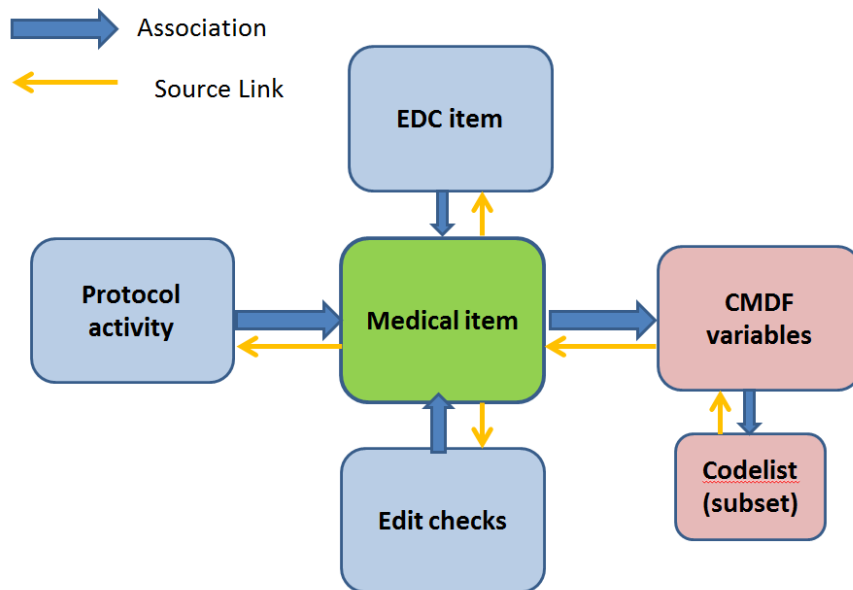


Figure 14: This image depicts the linkage connections of Medical Items to other Standard Element Objects.

The details of the Medical Item Associations and Source Links are as following:

- The Medical Item is the central standard object to provide linkages between the other Standard Elements.
- The Medical Item contains association to the related CMDf Variables and their related Codelists with the possibility of subsetting.
- The Source Link attribute in CMDf provide all medical items using the Variables.
- The Activity contains associations to the related Medical Items including their associated CMDf Variables and Codelists.

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- Source Link table in Medical Items provide all Activities using the Medical Item, as well as Edit Checks and EDC Items which are associate to the Medical Item.
- EDC Fields contains associations to the related Medical Items in order to build the Medical Concept for data capture.
- Edit Checks contains associations to the related Medical Items where the Edit Check is defined for.

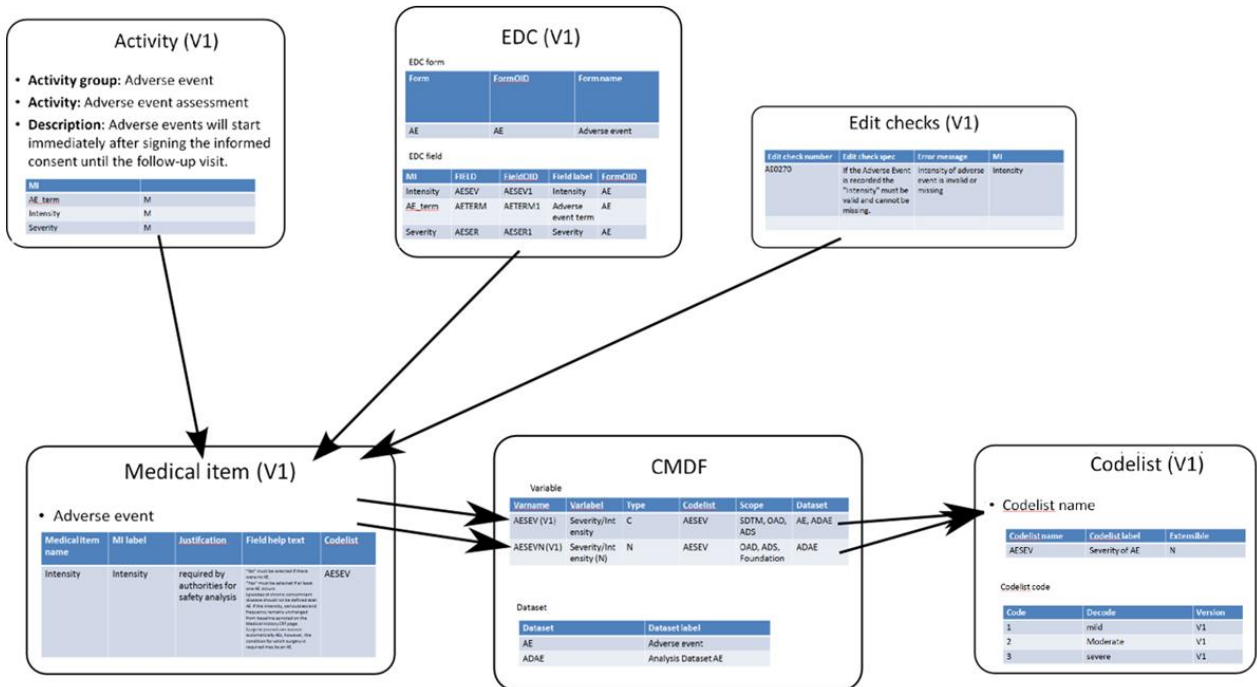


Figure 15: This image depicts an example of Activity with Medical Item association and linkages to other standard elements.

When a Medical Item is used in a study area (by referencing a given medical item or an activity that Medical Item belongs to), then the relevant other standard objects will also become available (referenced) in that study area through the Medical Items associations.

If a Protocol Activity is referenced to study area to be used, it will also make all associated Medical Items and its standard objects automatically available in that study area. The example of Medical Item associations for protocol activity and EDC form is shown in Figure 15: Example of Activity with medical item association and linkages to other standard elements.

When a change request is performed on a Medical Item (or any other standard element) the association and source links allow for an impact analysis of all related standards elements that may be affected by the change request. All related standard elements will be listed in a report for evaluation and consistency.

CONCLUSION

In our journey, we have realized that the implementation of the Standards Management toolset is not as difficult as the setup and utilization of the Standards; which is a cumbersome and time-consuming effort. Regardless of the toolset, it was imperative for us to Create and Connect the Standards for proper usage and adaptation.

Although, our initial focus was to implement a solution for standards management, our focus has shifted to creating and connecting Standards at various levels within the system. Thereafter, surface them for upstream and downstream usages, in particular for the Standards Management and Protocol Designer tools.

Our journey is not complete, but the vision realization is close.

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TERMS AND ABBREVIATIONS

SSD	Structured Study Design , used for the protocol Designer tool
CIE	Clinical information environment for all systems used for the data management and statistical analysis
CSR	Clinical Study report
CMDF	Clinical Metadata foundation, a superset of variables for SDTM, ADS, and operational database
Analyte conversion	Contains conversion factors, standard units and standard analyte names, to be used for converting original values into standardized values
OAD	Operational acquisition database , SDTM plus operational variables
ADS	Analysis data sets
Source plus	Operational data sets from the electronic data capture system plus some derived variables
Foundation	Different views on operational datasets plus all derived variables required for medical review

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CONTACT INFORMATION

Abi Velurethu
Bayer HealthCare Pharmaceuticals
100 Bayer Boulevard, PO Box 915
Whippany, NJ 07981-0915
Office Phone: + 1 862 404 3883
Mobile Phone: + 1 215 622 1524
Email: abi.velurethu@bayer.com
Web: <https://pharma.bayer.com>

Susanne Pangritz
Bayer Vital GmbH
BV-PH-MED-GDS&A-GMS
Leverkusen, K 9, 442
Phone: +49 214 30 51626
Fax: +49 214 30 51285
Cell: +49 175 3051626
E-mail: susanne.pangritz@bayer.com
Web: <http://www.bayervital.com>

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