Paper DS05

# Approaching End-to-End Analysis Standardization at Global and Therapeutic Area Level

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## ABSTRACT

In the long term, standardization is expected to reduce costs and increase efficiency. The paper outlines a strategic approach for developing and implementing analysis standards end-to-end to bolster efficiency and consistency within Bristol Myers Squibb (BMS). We have devised a model that establishes a standards organization with representation from all therapeutic areas in the relevant functions and ensures resources are available to develop, maintain, implement, and govern the analysis standards. Members of the standards organization seamlessly collaborate and play a pivotal role in standardization. We crafted a streamlined process that supports and facilitates the use of these standards. We approach standardization at the global level in a way that provides the flexibility for Therapeutic Area (TA) specific customization. Each Therapeutic Area (TA) contributes to the development of global standards. Subsequently, the study leverages these standardized components to create study level documents and deliverables.

## INTRODUCTION

It is common practice to develop analysis standards that can be used across clinical trial studies. However, it is not always easy to achieve good compliance with the developed standards and assess the impact of a revised standard on other standards. BMS established a two-tier standards organization and accompanying process to develop, maintain, implement, and govern standards effectively, end-to-end (E2E) from Protocol to SDTM to Statistical Analysis Plan (SAP) to Data Presentation Plan (DPP) / TLG (Tables, Listings, and Graphs) Mock Shells to ADaM to e-submission, accounting for their dependencies, and the impact of a revised standard on other standards. The first tier comprises of standards development teams; each team is responsible for developing, maintaining, implementing, and governing one or more standards at either the global or TA level. Our process expects users of standards to comply with the standards and submit change requests when the current standard requires improvements or does not meet their needs. The second tier is established as a committee that seamlessly connects Subject Matter Experts (SMEs) across TAs from all functions who are stakeholders of E2E standards, including SMEs from the standards development teams, thus ensuring an end-to-end view of all standards. Co-chairs and facilitators of the second tier ensure the impact assessment of revised standards.

## DETERMINE SCOPE OF E2E STANDARDS

Heads of the functions involved in the design, conduct, and analysis of clinical trials decided what standards to develop within their respective function and whether to develop them only at the global level, only at the TA level, or at both levels to increase efficiency, ensure quality and consistency, and reduce cost and resources within their functions (Table 1).

When a global standard could be used directly to efficiently develop study level deliverables, a corresponding TA standard was not developed. For instance, study level SDTM specification is developed by using the Global SDTM Specification directly as a starting point and only keeping the domains and variables as per study CRF collection. The Electronic Submission Playbook is used as a reference to prepare e-submissions for all studies.

Standards that served as a model template were developed only at the global level as they could be used across TAs, such as the Statistical Analysis Plan (SAP) Model Document. We developed TA Core SAP by using the SAP Model Document as the starting point and populating the TA level contents in the required sections as per the instructions provided in the model document.

Some standards were developed at both the global and TA levels. For instance, Global CSR Data Presentation Plan (DPP) / TLG Mock Shells and Global ADaM specification were developed to standardize safety analysis such as demography, adverse events, laboratory, concomitant medications, pharmacokinetics, etc., across multiple TAs. These standards provide the flexibility to customize them based on CRF collection and analysis requirements. TA Core DPP /TLG Mock Shells and TA Core ADaM Specification were developed using the respective global standard as a foundation. This involved retaining the global content, customizing it based on the TA's CRF collection and analysis requirements, and integrating TA specific content such as efficacy, biomarkers, and exposure that could be standardized across studies within the TA.

**Table 1 Scope of Global and TA Standards**

| **Global Standards in Scope:** | **TA Standards in Scope*:** |
|---|---|
| • Protocol Model Document<br>• Case Report Forms (CRFs)<br>• SDTM Specification<br>• Non-CRF External Data Specification<br>• Statistical Analysis Plan (SAP) Model Document<br>• Data Presentation Plan (DPP) Model Document<br>• CSR Data Presentation Plan (DPP) / TLG Mock Shells<br>• ADaM Specification<br>• Programming Code and related User Requirements (e.g., SDTM, ADaM, TLGs)<br>• Electronic submission documentation - aCRF<br>• Electronic Submission Playbook | • Core Case Report Forms (CRFs)<br>• Core Statistical Analysis Plans (SAP)<br>• Core CSR Data Presentation Plans (DPP) / TLG Mock Shells<br>• Core ADaM Specification<br>• Programming Code and related User Requirements (e.g., ADaM, TLGs)<br>• Electronic submission documentation - adrg<br><br>***Note:** TA standards include compound and indication level standards |

## ESTABLISH E2E STANDARDS ORGANIZATION (FIRST TIER)

Heads of the functions involved in the design, conduct, and analysis of clinical trials sponsored the establishment of one or more standards development teams within their function, which collectively formed the first tier of the E2E Standards Organization. Each team is tasked with developing one or more standards and is comprised of SMEs who are either core members or supporting members. A core member is designated as the “standard owner”, leads the team, and facilitates the meetings. The core members do the hands-on work while the supporting members review the standard and are consulted for decision-making.

Global standards development teams usually comprise of SMEs from multiple TAs as core members, and if needed, SMEs from specific functions (e.g., clinical, medical writing) as supporting members. SMEs may vary based on the type of standard. The core members determine the content to standardize at the global level based on what can be applied across multiple TAs, and the flexibility needed in the standard to accommodate TA CRF collection and analysis requirements.

TA standards development teams usually comprise of SMEs from different compounds and indications within the TA as core members, and SMEs from specific functions within the TA (e.g., clinical, medical writing) and if needed, SMEs from other TAs as supporting members. SMEs may vary based on the type of standard. The core members determine the content to standardize at the TA, indication, or compound level based on what can be applied across studies within the TA. The feedback provided by the SMEs from other TAs during their review of the standard helps in aligning its content across TAs where applicable.

The process expects the study level deliverables to comply with global and TA level standards and users of standards to submit change requests when the current standards require improvements or do not meet their needs.

**Responsibilities:**

- Develop and maintain the standard(s) in accordance with the relevant industry guidance and health authority requirements
- Evaluate change requests submitted by users and determine if the current standard(s) should be revised to address a broader need or improvement, or should be documented as an exception
- Understand the dependencies of the E2E standards and assess the impact of other revised standards to determine if the current standard(s) should be revised
- Oversee implementation of the standard(s) by delivering training timely, encouraging feedback, and addressing questions and concerns

**Additional Responsibility of Global Standards Development Team:**

- Promote TA standard to global standard if it applies to more than one TA

**Additional Responsibility of TA Standards Development Team:**

- Ensure alignment with global standards

## ESTABLISH E2E STANDARDS ORGANIZATION (SECOND TIER)

The second tier of the E2E Standards Organization was established as a committee that seamlessly connects SMEs across TAs from all functions who are stakeholders of E2E standards (such as statistics, clinical, pharmacokinetics, biomarker, medical writing, regulatory, data management, etc.), including SMEs from the global and TA standards development teams. Two committee members, one from the statistical function and one from the clinical function, are designated as co-chairs. Two committee members are designated as facilitators of the meetings. The process expects

all development teams to present an overview of new standards and their subsequent revisions to committee members for their awareness and, if needed, to solicit feedback on specific content of the standards. This ensures an end-to-end view of all standards and enables the SMEs to learn about all the standards, provide feedback, brainstorm solutions, and assess the impact of a revised standard on their standards. Co-chairs and facilitators of the second tier ensure the impact assessment of revised standards.

**Responsibilities:**

- Provide feedback on specific content of new and revised global and TA standards when the standards development team requests review
- Bring up topics for awareness or decision-making (e.g., the impact due to the revisions in a standard or process)
- Provide guidance regarding potential issues or findings identified (e.g., challenges identified during implementation of industry standards, health authority guidance, and BMS standards, processes, and tools)

## ESTABLISH E2E STANDARDIZATION PROCESS

This section describes the process of E2E standards development, maintenance, implementation, and governance (Figure 1).

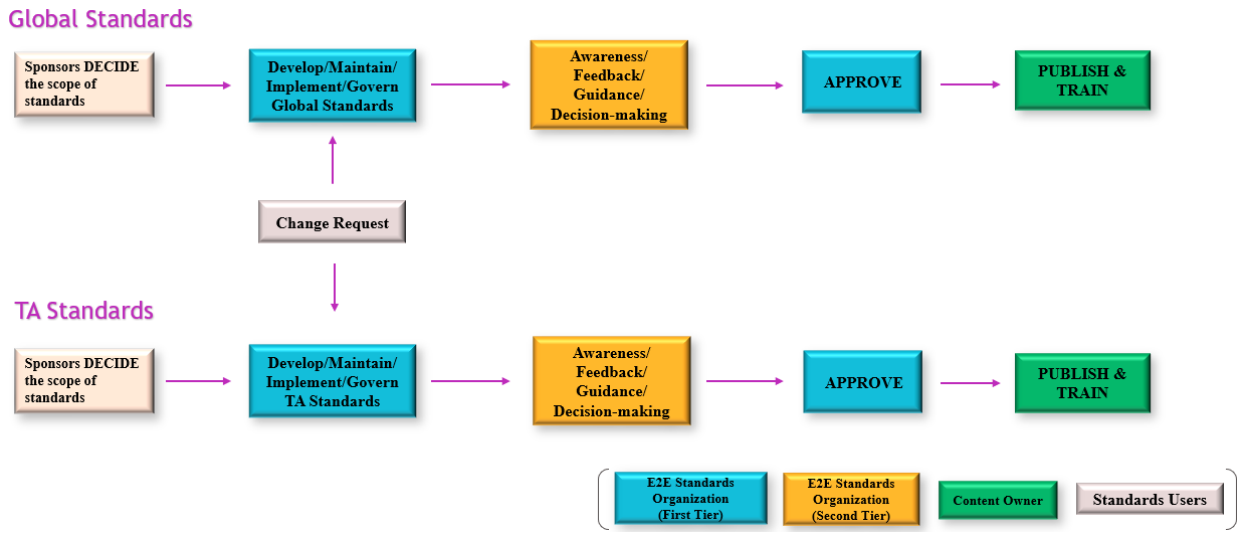


**Figure 1 E2E Standardization Process**

The process of developing new standards commences with the heads of the functions involved in the design, conduct, and analysis of clinical trials, deciding the scope, and providing sponsorship. This leads to the establishment of dedicated standards development teams in the first tier of the E2E Standards Organization, with each team comprising of SMEs who develop one or more standards and revise the standard over the course of its lifecycle.

The development team lead provides an overview of the new standard and its subsequent revisions to committee members in the second tier of the E2E Standards Organization for their awareness and, if needed, to solicit feedback on specific content of the standard. The development team may modify the standard if the committee provides feedback and, thereafter, approves it.

Upon approval, the standard is published, accompanied by comprehensive training to ensure widespread understanding and promote effective implementation.

The users of standards play a pivotal role during implementation by utilizing the established standards as a foundational starting point. They are responsible for incorporating study specific content into the standards, thereby transforming them into study level documents. They are expected to submit change requests when the existing standards do not fully align with their studies' specific requirements. These change requests will undergo evaluation by the standards development team. Approved change requests prompt revisions of existing standards, while non-approved change requests are documented as exceptions.

## CONCLUSION

The BMS two-tier standards organization model and accompanying process establish a structured and consistent approach to develop, implement, govern, and maintain analysis standards, thus ensuring timely adoption of and

alignment with relevant industry standards and health authority guidance, higher-quality analyses, and reliable outcomes. The developed standards enable the users to spend less time on established analyses and focus on other analyses, such as novel safety or efficacy analysis. The strategy of allocating dedicated SMEs to oversee standards and their implementation, along with change request facilitation and comprehensive training improves the users' awareness and understanding of and compliance with standards. The end-to-end view of standards ensures impact assessment of revised standards, fosters effective decision-making, collaboration, knowledge sharing, and a culture of continuous improvement, and eliminates redundancy.

In conclusion, the adoption of the two-tier standards organization model represents a significant step in developing E2E analysis standards. Despite initial investments in time and resources, this model has proven highly effective, yielding notable improvements in operational efficiency and the quality of deliverables.

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