Paper DS15

Standardization of Auxiliary Medicinal Products (AxMPs) in Clinical Trials

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ABSTRACT

Auxiliary Medicinal Products (AxMPs) are essential to clinical trial integrity, serving as background treatments, rescue medications, challenge agents, or tools for endpoint assessment. Though not investigational, their accurate classification, documentation, and analysis are critical under the EU Clinical Trials Regulation (EU CTR) to ensure regulatory compliance, patient safety, and data quality.

Historically, classification and handling of AxMPs have been inconsistently applied across sponsors and trials, leading to operational inefficiencies. To address this, Novartis has developed a standardized, end-to-end framework for AxMP management - covering early classification during protocol development, followed by implementation of CDISC compliant standardized Case Report Forms (CRFs), safety monitoring, statistical analysis of AxMPs and regulatory submissions to ensure consistent and high-quality data capture.

These tools enable accurate attribution of adverse events, facilitate drug-drug interaction assessments, and support harmonized safety signal detection across studies

Standardizing AxMP CRFs ensures consistent, high-quality data capture across studies, enabling accurate safety assessments and streamlined regulatory reporting. It also supports efficient analysis of AxMP impact on trial outcomes, enhancing overall trial integrity.

INTRODUCTION

AxMPs are medicinal products required for the needs of a clinical trial but are not classified as investigational. Under EU CTR Article 2(8), an AxMP is defined as a medicinal product used for the needs of a trial as described in the protocol but not serving as the direct investigational agent. AxMPs frequently include challenge agents, background therapies, rescue medications, supportive treatments, and products required to perform assessments, such as imaging agents. Unlike ConMeds, AxMPs are protocol-specified, controlled, and essential to ensuring consistent trial execution. Their role is often underestimated, yet they can significantly influence both the scientific validity of a study and the clinical interpretability of safety events.

The lack of historical standardization led to several challenges. AxMPs were often embedded within ConMed CRFs without proper flags or identifiers. Protocols frequently lacked explicit sections defining AxMPs, leaving site personnel to interpret product roles inconsistently. Data lineage - from protocol to CRFs, EDC, SDTM, ADaM, TFLs, and ultimately the CSR - was fragmented, forcing downstream teams to infer product classification or construct post-hoc reports to meet regulatory expectations. These inconsistencies became especially problematic with the implementation of EU CTR, where regulators increasingly scrutinize medicinal products influencing trial outcomes, even when they are not investigational.

IMPORTANCE OF AxMPs

The importance of AxMPs stems from their centrality to trial integrity, safety assessment, and regulatory compliance. Incorrectly capturing or classifying AxMPs can lead to ambiguous AE causality assessments, masked safety signals, or inaccurate interpretation of efficacy endpoints due to confounding background therapies. EU CTR elevates AxMP visibility and mandates transparent justification, consistent documentation, and traceability of AxMP exposure to subject-level outcomes.

From a safety evaluation perspective, AxMPs may directly or indirectly influence adverse event patterns. Drug-drug interactions between IMPs and AxMPs can either intensify or mitigate safety signals. Background therapies may modify disease pathways or contribute to physiological changes misattributed to the investigational product. Without dedicated AxMP data structures, risk assessments lack the granularity needed for accurate interpretation.

Operationally, a standardized approach to AxMPs reduces the burden on clinical teams, minimizes rework, and supports consistent data quality across studies. Structured metadata and well-defined controlled terminology eliminate ambiguity in EDC build, support clear SDTM and ADaM mapping, and enable predefined Table, Figure,

and Listing (TFL) shells in the Statistical Analysis Plan (SAP). The downstream benefits extend to safety database reconciliation, signal detection workflows, and regulatory submissions such as SUSARs, PSURs, and ASRs.

END-TO-END FRAMEWORK FOR AxMP STANDARDIZATION

Novartis' strategic response involved developing a comprehensive E2E (end-to-end) AxMP framework to ensure consistent identification, classification, documentation, analysis, and reporting of AxMPs. The framework is grounded in the full data lifecycle, starting from protocol design and extending through CSR development and safety reporting. The framework contains several core components, each of which was refined during pilot implementations across multiple therapeutic areas.

1. Early Identification and Classification

The process begins at the protocol stage, where AxMP classification rules are explicitly outlined. Protocol templates were updated to include a dedicated AxMP section describing product roles, justification, expected dosing patterns, and links to procedures. Decision trees were developed to guide teams in distinguishing between IMPs, AxMPs, and ConMeds. This structured approach ensures that products are appropriately categorized before study startup.

2. Standardized CRF Design and Metadata

Dedicated AxMP CRFs were created using CDISC-aligned design principles. These forms capture key product attributes, including formulation, route, regimen, AxMP role (challenge, background, rescue, supportive), start/stop dates, and relationship to IMP dosing. Metadata-driven EDC implementation ensures that AxMP CRFs are reusable and governed centrally. AxMP-specific controlled terminology was integrated to support consistent downstream mapping.

3. SDTM and ADaM Mapping Strategy

Clear domain strategies were defined to ensure accurate representation of AxMPs in SDTM. In ADaM, AxMP identifiers support analysis datasets enabling linkage to AEs, vital signs, laboratory values, or endpoint-related variables. This structured lineage ensures consistency throughout the analysis workflow.

4. Analysis and Reporting

Predefined TFL shells were developed for AxMP-related AEs, exposure summaries, and listings linking AxMP usage to key safety and efficacy outcomes. These outputs ensure that AxMPs are consistently represented across programs and meet evolving regulatory expectations. Regulatory reporting structures (such as SUSAR/PSUR/ASR submissions) benefit from the clarity provided by standardized AxMP identifiers.

5. Cross-Functional Collaboration and Governance

Standardization required strong cross-functional alignment. Clinical development teams defined AxMP intent; safety teams assessed risks; biostatistics and programming ensured alignment with analysis needs; regulatory teams ensured EU CTR-compliant documentation; and clinical operations ensured site-level implementation. A governance model was established to review AxMP-related queries, maintain controlled terminology, and oversee continuous improvement.

6. Observed Benefits and Pilot Learnings

Pilot studies demonstrated reduced misclassification, minimized downstream reconciliation, improved AE causality interpretation, and smoother regulatory reviews. Metrics collected across early-adopting studies showed decreased query volume, enhanced data quality, and more efficient safety database integration.

CONCLUSION

AxMPs, although not investigational, exert significant influence on clinical trial conduct, safety assessment, and data interpretation. Without proper classification and documentation, the scientific narrative of a study becomes vulnerable to misinterpretation. By implementing a standardized E2E AxMP framework, Novartis has strengthened data integrity, improved operational efficiency, and ensured regulatory alignment under EU CTR. Clear identification, structured CRFs, metadata-driven EDC design, well-defined SDTM/ADaM mapping, and robust analysis workflows collectively transform AxMP management from an ambiguous afterthought into a strategic component of clinical development. As adoption expands, further opportunities will emerge for industry-wide alignment, cross-sponsor harmonization, and future integration into CDISC standards.

ACKNOWLEDGMENTS

We thank the cross-functional contributors across Clinical Data Standards, Clinical Development, Pharmacovigilance/Safety, Biostatistics & Programming, Regulatory Affairs, and Clinical Operations for their collaboration in developing and piloting the AxMP framework.

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