Paper SM11

Automation and Macros in Clinical Submissions: Challenges, Limits and the Path Forward

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ABSTRACT

As automation and macros increasingly streamline clinical data workflows, their limitations in regulatory submissions remain evident. While these tools enhance efficiency, they often struggle with unstructured data, evolving standards, and complex submission requirements. Structured data plays a pivotal role in enabling scalable, reproducible automation, yet inconsistencies across studies hinder full automation potential. Current practices rely heavily on manual oversight, especially in submission-ready deliverables like SDTM, ADaM, and Define.xml. Looking ahead, the integration of metadata-driven frameworks, AI-assisted validation, and standardized data models promises to reshape automation capabilities. However, regulatory expectations and data variability will continue to challenge full automation. This abstract explores the current landscape, identifies key limitations, and envisions a future where structured data and intelligent systems drive compliant, efficient submissions.

INTRODUCTION

Over two decades, clinical data automation has progressed from ad-hoc SAS macros to global macro libraries, standards toolkits, and metadata-driven engines tightly aligned to CDISC standards and regulatory expectations. "Automation success depends on stable standards, uniform data, and complete metadata," which enables consistent templates and high reusability across studies for standardized deliverables.

This paper distills practical insights from such work and frames a forward path: from macros → to metadata-first automation → to AI-assisted and agentic systems, underpinned by rigorous standards governance and human oversight.

Foundational Efficiency in Clinical – Summary

Clinical macros (using tools like SAS and R) allow teams to reuse standardized code and automate repetitive tasks. Clinical automations, built using technologies such as Python, .NET, and Excel, help manage complex data flows, perform batch processing, and detect discrepancies through intelligent systems.

Across the industry, these capabilities have led to measurable efficiency gains, including a 40% reduction in data processing time, 30% fewer errors, 50% improvements in statistical programming productivity, and 15% savings in operational costs. Automation is widely used in SDTM/ADaM mapping, medical coding, risk-based monitoring, and automated quality control—making clinical workflows faster, more accurate, and more cost-effective.

Evolution of Standards, Automation, and AI

- **CDISC & submission models:** From SDS 1.1 (2000) to SDTM 3.1 (2004) becoming the foundation for regulatory submissions; ADaM 1.0 (2006); Define-XML 1.0 (2005); CDASH 1.1 (2009). Later expansions include SDTM 1.7 (2018) and initiatives such as Digital Data Flow (2022).
- **Automation trajectory**: Early reliance on custom SAS macros evolved to centralized macro frameworks (e.g., SAS Clinical Standards Toolkit, 2009), then to standardized libraries and metadata-driven engines. Automation can replace "up to 50% of manual mapping tasks" under the right conditions.
- **AI milestones**: From early academic systems to deep learning breakthroughs (2012), through generative AI (2023) enabling assisted CSR drafting, toward "agentic AI" for real-time design and risk monitoring concepts.

Problem Statement

Despite clear benefits, automation often encounters limits when exposed to unstructured sources, heterogeneous sponsor conventions, evolving rules, and complex/adaptive trial designs. The result: frequent exceptions, the need for manual intervention, and a persistent requirement for expert review to ensure accuracy, traceability, and regulatory defensibility.

Current Methods and Approach

Our approach draws on three complementary elements:

1. Template- and macro-driven automation for repeatable tasks (e.g., SDTM mapping, ADaM derivations, and templated output generation). This layer optimizes well-structured, high-volume deliverables.
2. Metadata-first design: Shift transformation logic (e.g., variable derivations, mappings, controlled terminology alignments) into versioned metadata definitions. This makes logic "machine-readable, auditable, and easier to modify," with lineage preserved from collection through submission (TLFs, eCTD).

3. Human-in-the-loop governance: Standards committees, medical monitors, statisticians, and data managers provide expert oversight for exceptions, evolving rules, and study-specific adaptations—particularly for complex designs and non-traditional endpoints.

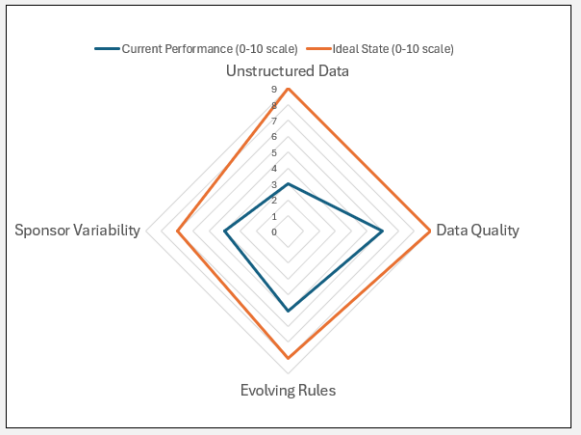
Results and Observations

What Works Well (Today)

- Efficient automation of repetitive tasks: Macros and engines reduce cycle time on standardized mapping/derivation work.
- Template-driven consistency: Study-agnostic templates enhance reusability and uniformity across deliverables.
- When the data are structured: Predictable schemas, controlled terminology, and well-maintained metadata unlock scalable, reproducible automation.

Current Limitations

- Unstructured/heterogeneous inputs: Textual, imaging, and irregular EHR sources introduce variability macros cannot robustly handle.
- Scalability constraints: Study-specific exceptions and sponsor variations stress generic macro logic and metadata coverage.
- Regulatory nuance and change: Evolving expectations necessitate “expert oversight” and “manual validation” to remain compliant and inspection-ready.



A representative internal benchmark (0–10 scale) illustrates a performance gap between the current state and an ideal target across unstructured data, data quality, evolving rules, and sponsor variability, reinforcing where investments should focus.

Discussion

- **Why Structured Data and Metadata Matter**
  Structured datasets and centralized, versioned metadata serve as the substrate for scalable automation. They provide predictable mappings and standardized derivations, reduce variance through controlled terminology, and enable transparent lineage from source to submission. Conversely, inconsistent standards, stale metadata, and sponsor-specific coding create barriers to uniform automation.

- **Regulatory Realities**
  Regulatory submissions demand precision and traceability. Even with advanced automation, “human expertise is essential for defensible metadata and auditable derivations,” particularly in adaptive designs and unconventional endpoints. A hybrid automation model—automation plus targeted expert review—best aligns with current expectations.

Roadmap: From Macros to Agentic Automation

- **Stabilize the foundation:**
  - Harden templates and macro libraries against common variability patterns.
  - Elevate metadata governance (definitions, derivation catalogs, CT alignment, change control).
- **Operationalize metadata-first pipelines**:
  - Express transformation logic in machine-readable metadata so programs “understand and

transform data as needed," simplifying audits and updates.
    - Preserve end-to-end lineage through SDTM → ADaM → TLFs → eCTD.
- **Augment with AI responsibly**:
    - Use AI to assist anomaly detection, mapping suggestions, issue triage, and documentation drafting—under human supervision.
    - Explore agentic patterns (goal-directed, tool-using systems) to support real-time design checks and risk monitoring—again with human-in-the-loop controls.

Limitations

This paper focuses on operating models and practical experience rather than controlled comparative trials of automation vs. manual processes. Results may vary by therapeutic area, data landscape, and sponsor conventions; the hybrid model is intended to be adapted rather than prescriptive.

CONCLUSION

- **Automation is reliable where work is structured and repeatable;** it measurably reduces cycle times and improves consistency.
- **Human expertise remains critical** for regulatory nuance, complex designs, and exceptions. A hybrid model delivers the best quality and defensibility.
- **Metadata-first design is the bridge** to future-ready pipelines and smoother audits/inspections.
- **AI and agentic systems will amplify impact** when layered responsibly atop strong standards and governance

REFERENCES

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RECOMMENDED READING

- CDISC 360i : https://www.cdisc.org/cdisc-360i
- 360i Program Kickoff: Enabling Standards Driven Automation from Study Design Through Results:
- https://www.cdisc.org/sites/default/files/pdf/360i-Program-Kickoff20250218.pdf

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