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Breaking the Shell: Validated R Workflows To Meet FDA Standards

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ABSTRACT

For years, open-source programming in clinical research has hovered on the edge of regulatory workflow: admired for its flexibility, yet questioned for its reliability. Atorus set out to challenge that perception by building the tables and listings specified in the FDA's 'Standard Safety Tables and Figures: Integrated Guide" entirely in R using rigorously validated open-source tools. By tapping into the {pharmaverse} ecosystem, our team developed a complete set of reproducible template table and listing programs that align with FDA expectations. In addition to adopting community-driven standards, we also created a set of internal R-based templates to support consistency and efficiency across projects. With these internal templates, we expanded beyond the scope of the FDA templates by constructing additional template programs for figures and efficacy outputs. This paper outlines our approach, validation strategy, and lessons learned from this process. Our team is demonstrating that R can produce submission-ready outputs for all core safety and efficacy study deliverables. We highlight how an open-source framework can combine validation, standardization, and automation to enable a transparent, collaborative future in regulatory programming. Our results position R not just as a viable alternative to traditional tools, but as a foundation for the next wave of compliant, innovative clinical reporting.

INTRODUCTION

Tables, listings, and figures are critical components of FDA submissions, as clinical reviewers utilize these outputs to interpret clinical trial data included in marketing applications. Historically, TFL outputs were developed using established statistical programming software, like SAS, that required significant manual labor to compare outputs, and programming. Recently the pharmaceutical industry has begun adapting to open-source technologies within R; however, doubts remain about its reliability and ability to comply with community standards.

With this shift in mind, our team set out to develop a collection of template programs, a twofold initiative that aimed to replicate the FDA's standard tables and figures and produce a set of standard outputs for internal use. These templates were built to:

1) Prove that R can be used to generate submission-ready outputs; and
2) Reduce development time, standardize our approach in programming, and create consistency across outputs.

This paper outlines our approach, validation strategy, and lessons learned from this process.

INTRODUCTION TO FDA'S "STANDARD SAFETY TABLES AND FIGURES: INTEGRATED GUIDE"

The main goals of the FDA's "Standard Safety Tables and Figures: Integrated Guide" are to "establish a standard set of safety analytic tables and figures" and "create an integrated guide containing associated instructions to support clinical reviewers in their use of the ST&F outputs during safety data review" (FDA, 2025). This provides a consistent format for safety tables and figures and optimizes efficiency in the application review process.

The Integrated Guide contains 55 safety tables, including 6 listings, and 22 safety figures. They are organized into the following sections: General, Adverse Event, Subgroup Analyses by Baseline, Laboratory, and Vital Signs. Within each section, they are further split into Core, Expanded, or Optional grouped analyses. All tables and figures found in the Core and Expanded sections are expected to be present in every ST&F package. Tables and figures found in the Optional section are not initially provided but can be requested.

Overall, the Integrated Guide acts as a crucial frame of reference for both clinical programmers and clinical reviewers, representing the standard with which safety tables and figures should be programmed and evaluated for a streamlined FDA application review.

INTRODUCTION TO CREATED FDA TABLES AND LISTINGS/SHELLS

The purpose of building the tables and listings specified in the FDA's "Standard Safety Tables and Figures: Integrated Guide" was to verify that it is possible to generate confirmed submission-ready outputs via open-source programming. By successfully replicating the standard safety tables and figures in R, we were able to accomplish this goal.

Out of all the FDA Standard Safety Tables and Figures, we designed shells for 54 of the tables and included all 6 listings. The shells were developed to coincide with the FDA's standard outputs, with minor adjustments made to align with company standards and the mock study data.

From these shells, we constructed R-based template programs for 37 tables and 6 listings using CDISC Pilot ADaMs. In selecting the CDISC Pilot ADaMs as our test data, we ensured that each element of the initiative was FDA-compliant and validated for reproducibility. Not all tables included in the integrated guide were programmed due to data constraints, but the final set of template programs represents a diversity of foundational safety outputs that are ready to be submitted to the FDA.

INTRODUCTION TO CREATED ATORUS TABLES, FIGURES, AND LISTINGS/SHELLS

In addition to creating template programs rooted in community-driven standards, we built another suite of R-based templates to bolster consistency and efficiency across internal projects. This initiative focused on not only safety tables, but also efficacy tables and figures, expanding standardization and automation to a larger scale of study deliverables.

The internal template programs were derived from a set of standard mocks outlining 32 safety tables, 24 efficacy tables, and 32 figures. These tables and figures represent some of the most commonly created deliverables in their respective categories, such as summary and change from baseline tables, as well as box plot and bar chart figures. The standard mocks also account for different variations of table structures. For instance, two tables were generated in different formats: one including event counts, the other excluding them. While the visual differences are subtle, clients have the ability to request either version depending on their study. Considering each of these popular variations and pairing them with their own template program facilitates a streamlined programming approach and ultimately promotes increased productivity and performance.

From these shells, we crafted template programs for all the mock safety tables, 22 of the mock efficacy tables, and 29 of the mock figures. However, the outputs that we could produce with these templates are not restricted by these numbers. In fact, since so many tables follow a standard programming structure, one template can unlock several different deliverables with simple modifications. During the initial programming phase, 2 efficacy tables and 3 figures were not programmed because they involve complex statistical methods that require additional research. We do plan to move forward with these displays in the future phase of this ongoing project.

INTRODUCTION TO R SOFTWARE

All programs were created in RStudio Pro with Posit Workbench and executed inside Atorus' validated data analytics platform. In addition to the working environment, the programming team utilized a rigorously validated package system. While these programs were developed using R version 4.4.2, they are confirmed to individually run successfully with R version 4.5.0, allowing them to run seamlessly in future project workflows.

INTRODUCTION TO {PHARMAVERSE} PACKAGES AND OTHER VALIDATED PACKAGES USED

Recreating the FDA Standard Safety Tables and Figures in R was never going to be about a single package or a clever script. It required a full, validated ecosystem built specifically for clinical reporting.

The {pharmaverse} is a coordinated collection of open-source R packages built specifically for clinical reporting workflows. These are not general-purpose tools awkwardly adapted for our needs. These packages are designed with ADaM structures, metadata-driven programming, and regulatory-style outputs in mind. They support everything from derivations to table construction in a way that feels surprisingly natural to clinical programmers, just expressed in R rather than SAS.

For this project, our central question was straightforward:
Can validated open-source packages generate every foundational safety output described in the FDA guide?

Before incorporating any package into our template framework, it underwent extensive validation to confirm that it behaved as expected within a controlled environment. Our team at Atorus takes the good aspects of the open-source world and systematically validates the packages needed, many of which are sourced from the {pharmaverse}. Packages are validated using careful risk assessments, ensuring accuracy within functions.

In addition, we gave ourselves the freedom to be the opinionated programmers that we are, and we picked among the many excellent packages from our validation team. This allowed us to define standardized tools for our templates and within the department moving forward.

What emerged from this project was not a fragile proof-of-concept, but a cohesive and scalable framework capable of supporting a complete safety reporting workflow.

APPROACH TO CREATING R TEMPLATE PROGRAMS

Our goal was not simply to reproduce the FDA sample shells in R; it was to build a reusable architecture that once built correctly, we could reuse in future projects.

Instead of simply developing individual programs for each table or listing, we focused on architectural standardization. Each template was designed as part of a cohesive framework with consistent structure, naming conventions, input expectations, and output behavior. The goal was predictability. If you understand one template, you understand them all. Additionally, a controlled .Rprofile was implemented for default environment options and predefined settings for output production, ensuring consistency across generated .docx output files.

Templates were parameterized wherever possible to accept standardized inputs and metadata, allowing the same structural code to be reused across studies with minimal modification. Rather than expecting to copy and modify legacy programs, we defined a repeatable pattern that can be easily applied in future studies.

The result was not just a set of programs that recreate FDA shells, but an extensible framework capable of supporting additional safety, efficacy, and figure outputs using the same architectural principles.

APPROACH TO VALIDATING R PROGRAM OUTPUTS

Validation was not an afterthought in this project.

To establish confidence in the R-based templates, all outputs were validated directly against independently produced SAS reproductions of the same tables and listings. The goal was not simply structural similarity, but numerical equivalence and consistent handling.

Validation occurred at two levels.

First, as mentioned, the R packages incorporated into the workflow were internally validated prior to use. This ensured that their functionality performed as expected within a controlled computational environment.

Second, each template output was compared to a SAS-generated version of the same shell. We evaluated layout structure, row and column definitions, labeling conventions, and most importantly, cell-level numerical results. Any discrepancies were investigated, resolved, and documented before finalizing the template.

This parallel reproduction approach allowed us to separate two questions:

Is the R implementation correct?

And does it reproduce established regulatory-standard results?

By answering both affirmatively, we were able to think deeply about statistical and computational decisions that are often handled automatically in SAS. We discussed as a team how we were going to define and produce specific numbers and statistics moving forward, ensuring there were no hidden assumptions in our approach. One example of this involved numeric rounding. R and SAS have different methods of rounding which can lead to discrepancies within our data. To ensure consistency, we implemented a rounding function that produced the same rounding behavior as SAS.

Another important consideration was consistency across deliverables. If a statistical value was calculated within a table program, we ensured that any corresponding figure program calculated that same statistic using the same logic and function. By defining these calculations one time, and applying them consistently across programs, we avoided discrepancies between tables and figures.

The result was not just confidence in individual programs, but confidence in the framework as a whole.

CONCLUSION

This project set out to answer a practical question: can R produce submission-ready outputs for the core safety and efficacy deliverables outlined in the FDA Standard Safety Tables and Figures guide?

Based on our experience, the answer is yes.

Validated open-source packages are capable of generating every foundational table and listing required. Architectural standardization enabled reuse and consistency across outputs. Parallel validation against SAS ensured numerical equivalence and regulatory alignment.

Perhaps most importantly, this work demonstrated that open-source adoption in clinical programming does not require sacrificing control. With thoughtful validation, structured templates, and disciplined development practices, R can operate within the expectations of reproducibility and rigor that regulatory work demands.

We view this effort not as a replacement of existing tools, but as an expansion of what is possible. Open-source ecosystems continue to evolve, supported by an active and collaborative community. As these tools mature, they offer increasing opportunities for transparency, efficiency, and innovation in clinical reporting.

Our next steps include expanding template coverage, enhancing automation of validation checks, and continuing to contribute to and learn from the broader open-source clinical programming community.

The technical barriers are lower than many assume. The opportunity now lies in thoughtful implementation.

REFERENCES

U.S. Food & Drug Administration. “Standard Safety Tables and Figures: Integrated Guide.” Retrieved February 23, 2025, from https://www.fda.gov/drugs/development-resources/standard-safety-tables-and-figures-stfs

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