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Statistical Monitoring Report: A Path Forward to Interactive Data Analysis and Quantitative Decision-Making

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ABSTRACT

Early development clinical trials warrant an agile approach of interactive data analysis for exploratory analyses that take the form of “quick insights” and lead ultimately to the generation of scientific hypotheses. The Statistical Report Tool (START) is a cross-functional collaboration to streamline the process from exploratory analyses to hypotheses generation and early decision making. The framework consists of several fit-for-purpose modules, ranging from data preparation to specific types of analyses, allowing for dynamic previews of safety and preliminary efficacy. The modules are programmed in R and the analyses are presented via a html interface that supports interactivity. In contrast to static outputs, the interactive visualizations and data tables support cross-domain data linking and multi-dimensional data analysis that could be hard to capture using static displays. This data-driven analysis supports stakeholders (clinicians, operations, global medical safety) in formulating inferential hypotheses and developing a holistic view of the benefit-risk profile of the compound.

BACKGROUND

Clinical trials in their early stages of development should adopt an agile approach to interactive data analysis for exploratory analyses that yield "quick insights" and eventually lead to the formulation of scientific hypotheses. It has been noticed that physicians and scientists often lack the ability to review and analyze clinical trial data in a comprehensive and efficient way on an ongoing basis interactively and visually. The current processes mostly rely on standard statistical analyses which include pages and pages of static tables, listings, and graphs. These processes are meant to support health authority interactions and external data publications involving rigorous validation processes. As such, it is a time-consuming task and may not be best suited for ad hoc/exploratory analysis purposes. Moreover, the inherent complexity of clinical trial data obscures important insights in numerous pages of outputs in repetitive formats; as a result, it prolongs the process in identifying relevant safety signals and early efficacy signal. The Statistical Report Tool (START) is designed to foster cross-functional collaboration to streamline the process from exploratory analyses to hypotheses generation and early decision making. This toolset facilitates ongoing clinical trial data analysis, providing quantitative evidence to formulate related hypotheses. The toolset is open source. It consists of several fit-for-purpose modules, ranging from data preparation to specific types of analyses, allowing for dynamic previews of safety and preliminary efficacy. The modules are programmed in R and the analyses are presented via a html interface that are highly interactive.

START helps facilitate cross-functional knowledge sharing. It is initiated by the statistician and efficiently enables the subsequent collaborations between cross-functional stakeholders such as clinicians, statistical programming, operations, and global safety. The data-driven analysis supports 1) clinicians and statisticians in formulating inferential hypotheses, and 2) safety management teams in developing a holistic view of the benefit-risk profile of the compound. These analyses can also be extended to support program-wide pooled safety analyses.

METHODS

the toolset was developed using static R scripts and a stand-alone interactive R-markdown interface.

The key feature of this toolset is that it enables statistical review of ongoing clinical trial data throughout the various phases of drug development. This implies the toolset will need to be implemented early in the process and makes use of the available SDTM datasets (rather than the ADaM datasets which are generated later in the process). The data preprocessing module generates ADaM analogous datasets (pseudo-ADaM) from ongoing SDTM datasets. The ADaM analogous datasets do not undergo the same level of rigorous validation as the standard ADaM datasets.

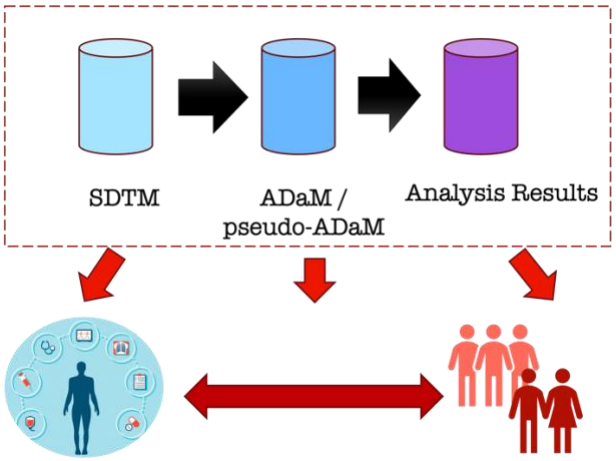

Figure 1 Schema of Statistical Report Tool

Currently, the analysis modules supported by START including: (i) preparation of analysis-ready datasets; (ii) patient demographics and baseline disease characteristics; (iii) safety analyses; and (iv) early efficacy analysis. In addition to these standard modules, study-specific patient trackers, biomarker analyses and visualizations of patient-journey are also supported. The key idea is to extend the generalized fit-for-purpose modules across various indications and therapeutic areas based on study requirements.

In contrast to static outputs, START includes a navigation bar with user-friendly options, interactive visualizations, and data tables. These interactive visualizations support cross-domain data linking and multi-dimensional data analysis that could be hard to capture using static displays. For example, the onset of adverse events and the durability of response with respect to treatment exposure, in conjunction with dose modifications, can all be visualized using an interactive swimmer plot. Interactive data tables allow for filtering, sorting, and searching, thus avoiding duplication of several static tables and listings and pages of outputs. Dynamic visualizations include an interactive evaluation of Drug-Induced Serious Hepatotoxicity (*eDISH*) plot (Patel, 2022), interactive forest plots and swimmer plots. *Plotly* (Sievert, 2020) and *Crosstalk* (Cheng, 2023) packages in R were employed, allowing for a deep dive into the data by using the interactive features. Multi-dimensional patient trackers were developed to track primary endpoints, drop-out rates, and unusual high rate of screen failures owing to inclusion/exclusion criteria, thereby helping to identify appropriate target populations for analysis.

The figure below illustrates the various modules of START.

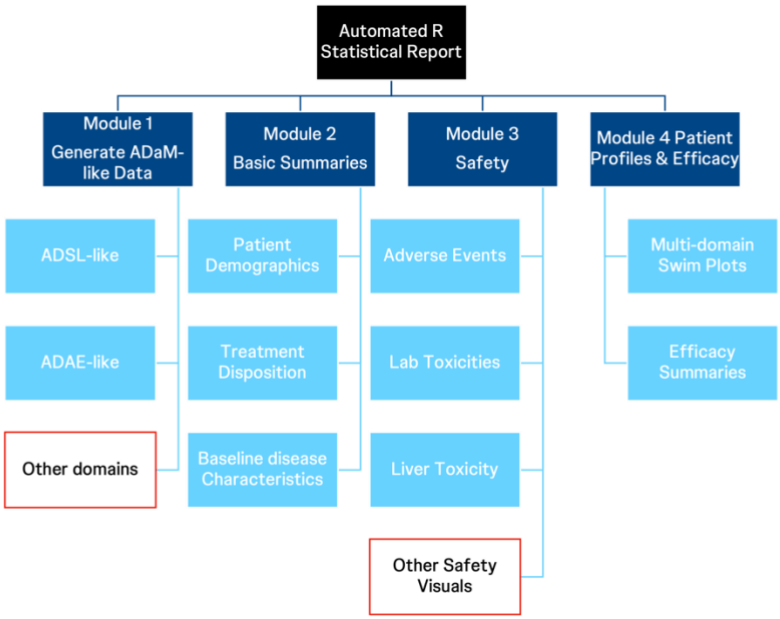

Figure 2 Modules of START

START can be useful for performing internal review of statistical analysis for Independent Data Review Committee meetings, and senior management review meetings. It can be extended to support aggregate safety data review across trials in a systematic manner and can be leveraged by the safety management team for the periodic safety review meetings.

CONCLUSION

START's primary goal is to facilitate internal data exploration and ad-hoc analysis. Its function is to complement the standardized output generation. The toolset supports the generation of scientific questions and expedites quantitative decision-making. All stakeholders are thus engaged in the formulation of hypotheses and a joint, collaborative interpretation of the data analysis results.

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