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Utilizing Data Visualization for Continuous Safety and Efficacy Monitoring within Early Development

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ABSTRACT

Early Development (ED) clinical research requires substantial ongoing data monitoring due to the complexity of patient safety, risk of drug toxicity, and variability of first-in-human (FIH) trials. Historically, clinical decisions were made throughout a drug development life cycle utilizing static statistical tables, data listings, and graphs. Though these outputs offer valuable statistical findings, the cadence of the data presentation is contingent on milestone deliveries.

Within the industry, there is a shift to introduce interactive visualizations used for dynamic data review. Data Visualization (DV) is a solution to bridge the gap for the need of Near Real-Time (NRT) data review between major milestones to proactively empower informed data driven decision-making. Throughout this paper we will highlight the impact of a harmonious partnership cultivated by continued collaboration between DV and ED to allow for active safety and efficacy surveillance.

INTRODUCTION

The goal of safety monitoring in clinical trials is to identify, evaluate, minimize, and appropriately manage risks. While Data Visualization (DV) is a tool to represent complex information in a digestible format. Within Early Development, the two worlds of safety and efficacy surveillance along with data integration and visualization have collided to utilize Near Real-Time (NRT) data for continuous review.

OVERVIEW

Data visualization helps to tell stories by curating data into a form easier to understand, highlighting the trends and outliers. A good visualization tells a story, removing the noise from data and highlighting useful information. At Bristol Myers Squibb the Global Biometric and Data Science division is motivated by the mission, *every drug development decision optimized by the power of data*. Providing an in-house solution to data visualization allows for tools and outputs to be customizable to targeted end users. In the creation of this solution, a comprehensive approach has been utilized, by highlighting all areas to increase efficiency through the life of the clinical trial driving major decisions. Pivoting away from static outputs to interactive visualizations is a bold and innovative solution to provide stakeholders access to Near Real-Time (NRT) data for informed decision making. As technology grows and rapidly advances, there is a commitment to keep pace, providing study teams with the best possible resources, enabling them to address the unmet medical needs of patients with serious diseases.

Developing and evaluating Tables, Listings and Graphics (TLG(s)) is a necessity throughout clinical trials. Historically, these are delivered as static outputs. The slow cadence of these outputs diminishes the value of data review. TLG(s) integrated with interactive visualizations allow for stakeholders to not only review the data at a faster rate but also visualize an abondance of different outputs due to its dynamic nature. To reduce the time in delivering these outputs a solution has been identified to produce these applications at a faster rate. A user interface for personnel to quickly select outputs and map the respective data, allows for a turnover time of deployed application containing interactive TLGs within hours. This application provides study teams with the ability to further explore the data by creating the option to change between certain variables such as subgroups and populations. This tool addresses past pain points including speed, cost, and efficiency.

HOW DOES EARLY DEVELOPMENT PLAY A ROLE IN THIS SCENARIO?

Early Development (ED) clinical research primarily focuses on safety and tolerability. ED is an essential step within drug development to allow a new drug or treatment to come to market. For clinicians to make well informed data-driven decisions, it is key to equipment stakeholders with an innovative approach for on-going patient surveillance. The reality is within ED, if failure of a drug or treatment is to occur then the hope is to “fail fast”. “Fail fast” does not imply lack of commitment to a mission or goal, but to the contrary, indicates a willingness to experiment in the process, learn quickly from the results, and adjust to achieve the mission and vision. Failing fast does not downplay the value of a well-thought-out plan, but rather facilitates continuous quality improvement. Ultimately, fast failures allow patients more options to pursue alternative clinical trials or treatments. Through ongoing safety and efficacy monitoring, clinicians are better equipped for active patient surveillance.

The challenges of early drug development are lengthy, complex, and costly processes, entrenched with a high degree of uncertainty that a drug will succeed. For a drug to succeed and receive regulatory approval, the therapeutic benefit of a drug must outweigh the clinical safety concerns for patients. Most of these efforts are directed in early detection and prevention of serious events. The goal is enhancing the speed and rigor of decision-making, and influence better data-driven decisions, through active monitoring the risks can be minimized, and the success of therapies and treatments can continue to rapidly advance towards revolutionizing early development and healthcare.

PARTNERSHIP: THE NEED

The purpose of Global Biometrics and Data Sciences at Bristol Myers Squibb is embedded quantitative rigor and strategic insight throughout the drug development lifecycle by solving complex problems through collaboration and operational excellence to advance the science that transforms patients’ lives. To serve the quick turnaround need within Early Development, a partnership with Data Visualization was created to provide study teams with a means to perform scientific analytical review between the major milestones. Developing Core TLG(s) and On Demand TLG(s) fill in major gaps, enabling Statistical Programming and Biostatistics to help address exploratory needs for their Clinical Science partners throughout a study.

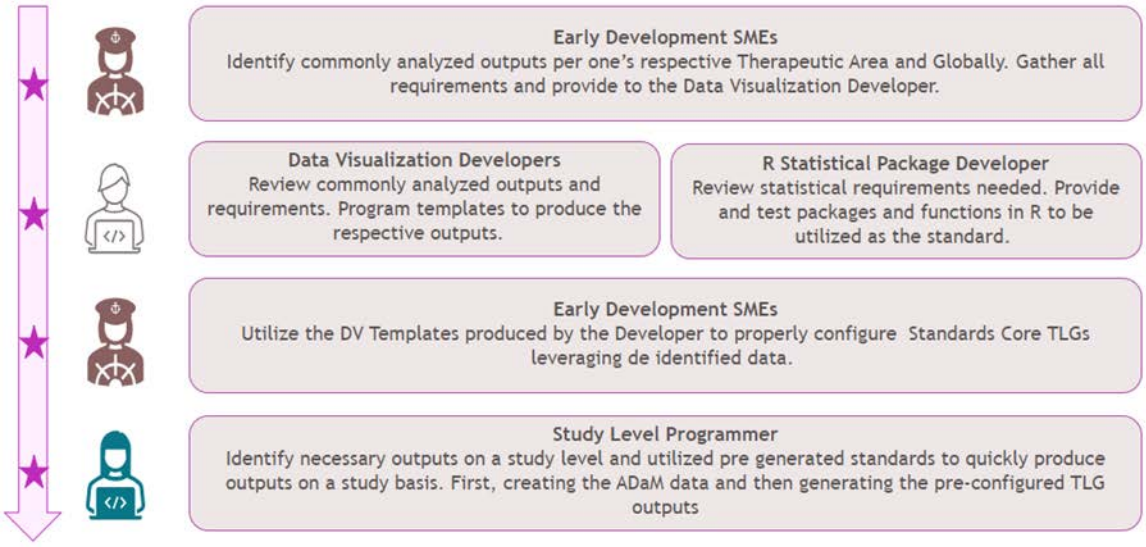
This capability formalizes ED-specific and Therapeutic Area (TA) specific analyses and TLG outputs to serve the requirements of ED, minimizing the number of study-specific deviations and adhoc Event Based Request (EBR) to vendors. Having a cohesive set of standards allows for resources to be used for more value-added tasks.

TECHNICAL IMPLEMENTATION

Subject Matter Experts (SMEs) from statistical programming and biostatistics within the Early Development team were identified. These experts have a deep understanding of the study objectives, analysis plans, and regulatory requirements. The identified SMEs collaborate to define a standard set of Core TLGs that are applicable across Early Development focusing on Study Design, Therapeutic Area, and indicated major endpoints. These TLGs serve as the foundation for generating the desired outputs. The Core TLGs were then provided to the Data Visualization team. This team is responsible for generating the underlying DV Templates using the R programming language. The DV Templates are designed to be flexible and customizable for each output and the parameters passed.

DV Templates are composed of shiny modules, which are interactive components in R that allow for customization and parameterization. These modules enable the SMEs to easily customize the outputs based on the specific requirements of the study. The SMEs utilize the DV Templates and shiny modules to provide the appropriate parameters for displaying the standard Core TLGs. The user will input the necessary information, such as variables, filters, formatting options, and any other relevant parameters, to generate the desired TLGs. Once the parameters are provided, the DV Templates generate the TLGs according to the specified requirements. These TLGs are then made available to the study team for their

use and analysis. By following this implementation process, the tool enables the SMEs to easily generate and customize TLGs based on the standard Core TLGs. The use of DV Templates and shiny modules facilitates efficient parameterization and customization, ensuring that the generated TLGs meet the specific needs of the study team.



Display 1. Implementation Process for Interactive TLGs

USE CASES

CORE TLG(S)

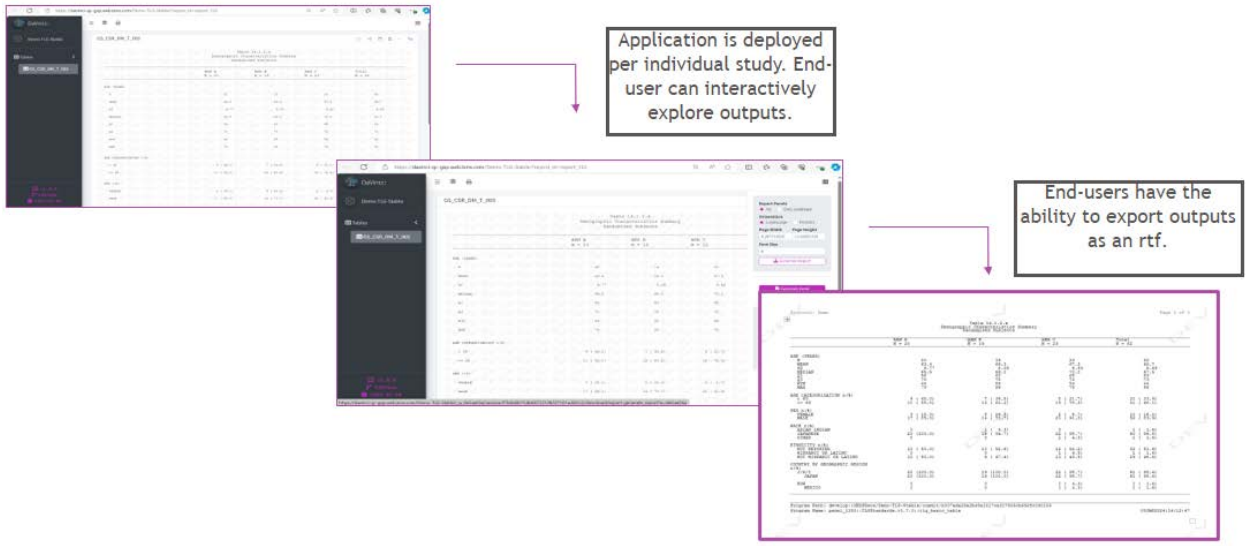
The Core TLG package includes a subset of study-specific outputs that are essentially a subgroup of the final CSR package, these outputs follow the Core TLG template framework set in place by DV and the ED SMEs. The package allows end users to interactively view different versions of the outputs, which allow users to explore the data and customize their viewing experience based on their specific needs and preferences. Users can easily navigate through tables, listings, and graphs to gain insights and extract relevant information. The package leverages the tool's interactive features to enhance the user experience. Users can dynamically filter, sort, and manipulate the data within the TLGs, enabling them to focus on specific subsets or variables of interest. This interactivity promotes a deeper understanding of the data and facilitates more efficient analysis.

The Core TLGs are designed to have a faster data refresh cadence. This means that any updates or changes to the underlying data source are automatically reflected in the outputs without any downtime or waiting period. Users can access the most up-to-date information, ensuring they have the latest insights for decision-making and analysis. The interactive nature of the TLGs and the faster data refresh contribute to improved efficiency. Users can quickly access the information they need, perform ad-hoc analyses, and make informed decisions in a timely manner. This saves valuable time and resources, allowing for more productive workflows and faster response to evolving needs. With the ability to interactively view and manipulate the TLGs, users can delve deeper into the data and uncover hidden patterns or trends. They can drill down into specific subsets, compare different variables, and generate custom views, enabling comprehensive data exploration and facilitating more robust insights. Overall, the Core TLGs package provides a user-friendly and efficient way to interact with data, empowering users to gain valuable insights and make informed decisions.

ON DEMAND TLG(S)

Core TLGs provide a solid framework for On Demand TLGs by offering readily available outputs that can be quickly configured using a point-and-click user interface. The Core TLGs package includes a subset of study-specific outputs that are essentially a subgroup of the final CSR package, these outputs follow the Core TLG template framework set in place by DV and the ED SMEs. These templates serve as a starting point and provide a consistent structure for generating TLGs. When an event-based or urgent request arises, users can leverage these templates to quickly create the desired TLGs without starting from scratch. The point-and-click user interface allows users to easily configure the TLGs based on their specific requirements. They can select the variables, filters, and formatting options using intuitive controls, eliminating the need for complex programming or scripting. This configurability enables users to tailor the TLGs to the specific event or request, ensuring the outputs are relevant and meaningful. With the Core TLG framework in place, generating the On Demand TLGs is a streamlined process. Users can simply select the desired template, make the necessary configurations, and trigger the generation process. The tool automatically applies the defined settings to the underlying data, generating the TLGs in a matter of minutes or even seconds. This rapid generation ensures quick turnaround times for urgent requests. The Core TLGs framework offers flexibility in terms of output formats and delivery options. The Core TLGs framework seamlessly integrates with the existing data infrastructure and analysis tools. It can pull data from multiple sources, including all relevant statistical computing environments, ensuring that the On Demand TLGs are based on the most up-to-date and relevant data. This integration eliminates the need for manual data extraction and manipulation, further speeding up the process of generating the TLGs.

In summary, the Core TLGs provide a robust framework that enables the quick and efficient generation of On Demand TLGs. The predefined templates, configurability, rapid generation, flexibility, and seamless integration contribute to a user-friendly experience, allowing users to respond promptly to event-based or urgent requests with high-quality TLGs.



Display 2. The comprehensive process of navigating interactive TLGs and exporting them into a suitable format.

REAL WORLD USE-CASE

PROOF OF CONCEPT

The implementation of these tool is suggested for all Early Development studies following the same model. The process begins with the generation of data in the Study Data Tabulation Model (SDTM) format. SDTM is a standard format for organizing and structuring clinical trial data. The data is then transformed into the Analysis Data Model (ADaM) format, which is optimized for statistical analysis. Once the ADaM data is available, the study team members, including statistical programmers, and

biostatisticians, collaborate to identify a subset of study-specific outputs that are essentially a subgroup of the final CSR package. The team considers the study objectives, analysis plans, and regulatory requirements to identify the relevant TLGs from the standard set.

The programmers work together to generate the TLGs based on the ADaM data. They utilize the existing standards and defined data mapping provided to generate the request core TLGs. Once the outputs are created, they are provided to their biostatistician counterparts for review. Once the outputs have been reviewed and the verification has been complete the TLGs are then provided to the clinical stakeholders for use.

In the event a specific request arises, the study team reconvenes to discuss the necessary outputs and TLGs. This request could be driven by new analysis needs, regulatory queries, safety concerns, or any other study-related requirements. The team evaluates the existing outputs and standards to determine if they can fulfill the request or if modifications are needed.

Using the existing TLGs and standards as a starting point, the team makes the necessary adjustments or configurations to generate the requested TLGs. This may involve modifying the variables, filters, or formatting options to meet the specific requirements of the request. The team ensures that the generated TLGs align with the study objectives, regulatory guidelines, and any other relevant considerations. Once the TLGs are generated, they are provided to the stakeholders who requested them. These stakeholders can then utilize the TLGs for their analysis, decision-making, or any other purposes as needed.

Overall, the flow involves the generation of data in SDTM and ADaM formats, the creation of Core TLGs through collaboration between study team members, and the generation of TLGs based on event-based requests using existing outputs and standards. This iterative process ensures that the TLGs are tailored to the study objectives and meet the specific needs of the stakeholders.

CONCLUSION

In conclusion, the use of this tool for generating TLGs streamlines processes and puts critical data at stakeholders' fingertips, enabling urgent decisions with direct impacts on clinical trials and patient lives. By providing a user-friendly interface, predefined templates, and rapid generation capabilities, the tool facilitates quick access to relevant TLGs, contributing to improved study management, enhanced patient safety, and more efficient regulatory interactions. Overall, the tool empowers stakeholders to take timely actions that positively influence trial outcomes and benefit patients' lives.

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