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The Implementation of {teal} Shiny Apps in DMC Activity

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ABSTRACT

The integration of R Shiny applications into regulatory submission processes has gained attention through recent pilot studies, highlighting their potential to facilitate efficient and interactive reviews by regulatory authorities such as the FDA. While R Shiny applications have primarily been used for internal reviews within organizations, there is growing interest in leveraging these tools for Data Monitoring Committee (DMC) activities. Interactive dashboards built with R enable customized, study-specific analyses and endpoint evaluations, supporting more dynamic and responsive monitoring. Tools like {teal}[1], {rtables}[2], and {tern}[3] further enhance the creation of portable and downloadable files, ensuring that critical information remains accessible for ongoing reference and decision-making. This paper focuses on the practical aspects and advantages of deploying R Shiny applications in DMC activities, with an emphasis on improving the overall efficiency and effectiveness of clinical study monitoring.

INTRODUCTION

R Shiny has become more popular in recent years, especially in the context of regulatory submissions. Some pilot projects have shown that interactive applications can help reviewers, like those from the FDA, to better understand the data. Although Shiny is mostly used internally within companies, we believe it can also be useful for Data Monitoring Committee (DMC) meetings.

The DMC is an independent group that reviews the safety and progress of clinical trials. Their meetings are important for protecting participants and ensuring the trial is on the right track. Usually, DMC meetings include both open and closed sessions, with different levels of data being shared.

This paper gives an overview of how R Shiny tools can support DMC activities. We also introduce some useful packages, such as {teal}, {rtables}, and {tern}, that can help create interactive and downloadable reports.

DMC AND DMC MEETING

Data Monitoring Committee (DMC) is an independent group of highly qualified experts established to oversee the progress of a clinical trial. The DMC is responsible for a wide range of critical tasks, beginning with the ongoing evaluation of participant safety through meticulous reviews of adverse events, side effects, and other safety signals that may arise during the trial. By identifying potential risks early, the DMC helps ensure that participants are not exposed to unnecessary harm. In addition to monitoring safety, the DMC assesses interim results to determine whether the treatment is achieving its intended efficacy. This involves analyzing data to evaluate whether the treatment shows promising results or lacks effectiveness, enabling the committee to make evidence-based recommendations.

DMC meetings are formal gatherings designed to review ongoing trial data. These meetings play a central role in ensuring the trial is conducted with scientific rigor and that participant safety and well-being remain the top priorities. Typically, a DMC meeting consists of two sessions: an open session and a closed session, each serving distinct purposes in the review process.

- The open session, generally lasting 30 minutes to 1 hour, provides a forum where the sponsor and DMC members discuss general study updates. These updates often include patient enrollment, protocol adherence, and any identified safety concerns. Importantly, the open session is conducted in a blinded format, meaning no unblinded data revealing treatment assignments or outcomes are shared. This ensures that discussions remain objective and do not inadvertently bias the trial.

- The closed session, lasting between 30 minutes and 2 hours, offers a confidential setting for the DMC to conduct an in-depth analysis of unblinded materials, such as interim reports, safety data, and efficacy data provided by the sponsor or investigators. An independent statistician often plays a key role in this session, presenting unblinded documents or slides to facilitate discussions. The closed session allows the DMC to thoroughly examine the trial's progress, identify emerging risks or trends, and evaluate the treatment's effectiveness. This comprehensive analysis is crucial for determining the trial's future course of action.

- Following the closed session, the DMC reconvenes with the sponsor in the open session to discuss findings, express concerns, and request additional materials if needed. Based on their evaluations, the DMC provides formal recommendations regarding the trial's continuation, potential protocol modifications, or, in some cases, early termination due to safety concerns, overwhelming efficacy, or lack of potential benefit (futility). Throughout this process, strict confidentiality is maintained to protect the trial's integrity and prevent inadvertent disclosure of unblinded information.

CURRENT CHALLENGES

Based on CIMS Global's participation in several DMC meetings as independent statisticians, we have observed significant challenges in the current DMC meeting process that impact the efficiency and effectiveness of decision-making.

1. **Multiple Parties:** A single DMC meeting often involves multiple parties collaborating. The blinded statistical team must develop a robust programming package and deliver it to the unblinded independent statistician. Upon receiving the unblinded randomization code and programming package, the independent statistician tests the data, generates unblinded results, and prepares a summarized executive report or closed session slides. The unblinded materials are then delivered to the DMC for review. This multi-step process increases complexity and the risk of inefficiencies.

2. **Large Volume of Pages:** One major challenge is the sheer size of DMC reports, which often range from 1,000 to 10,000 pages. This extensive volume makes it difficult for DMC members to conduct a thorough review within the typical one-week timeframe before meetings. The overwhelming amount of data increases the likelihood of critical insights or trends being overlooked. Additionally, the limited time available for review raises the risk of missing key patterns or safety signals, leading to delays and inefficiencies in decision-making.

3. **Inefficient Static Output:** DMC reports are primarily static, requiring members to manually search through lengthy documents for specific keywords or parameters. This process is not only time-consuming but also prone to human error. Given the complexity of clinical trial data, relying on manual searches increases the risk of overlooking important findings necessary for an accurate assessment of trial safety and efficacy. Moreover, the time spent searching detracts from deeper analysis, reducing the time available for meaningful discussions during meetings. Consequently, the review process becomes less efficient, slowing down the committee's ability to make well-informed decisions.

4. **Insufficient Information:** Some reports lack critical information, such as subgroup analyses for different patient populations. Evaluating clinical trial results requires assessing both overall outcomes and subgroup-specific data, such as age, gender, or preexisting conditions. Subgroup analyses help determine treatment safety and efficacy across diverse populations, allowing the DMC to identify potential risks or benefits that may not be evident in aggregate data. The absence of this granular information limits the committee's ability to make fully informed decisions, potentially leading to misinterpretations about treatment effectiveness and safety.

5. **Time-Consuming Follow-Up:** Follow-up requests for additional data or analyses further exacerbate these challenges. When gaps or ambiguities are identified during meetings, requests for clarifications or further analyses are made. However, these requests often cause delays of several days or even up to a week, disrupting the DMC's workflow and prolonging the decision-making process. Such delays can have serious consequences, postponing key decisions on whether to continue, modify, or halt a trial. Additionally, prolonged timelines increase the risk of making decisions based on outdated or incomplete data, which can compromise participant safety and trial integrity.

These inefficiencies underscore the critical need for more streamlined reporting processes and tools that can facilitate faster, more accurate, and comprehensive review of clinical trial data. The current manual review process is outdated and burdensome, and it does not adequately support the needs of a data-driven, high-stakes environment like clinical trial monitoring.

OPEN-SOURCE SOLUTION

Implementing more interactive and dynamic tools could significantly enhance the speed and accuracy of the current review process. These improvements would not only increase the DMC's efficiency but also strengthen its ability to make timely, informed decisions, ensuring that clinical trials proceed with the highest levels of safety and scientific integrity. Before moving forward, we recommend the following steps as a starting point to familiarize yourself with the potential structure.

To address current challenges in DMC activities, we propose leveraging the open-source R Shiny solution {teal} to streamline the review process. {teal} is an interactive framework designed for data exploration, enabling the efficient analysis of clinical trial data. Internally, we have developed an application called {interactive.stats} specifically for DMC use.

UNDERSTANDING THE COMPONENTS OF THE {TEAL} SERIES

While numerous public resources illustrate the {teal} structure, we want to highlight key utility packages essential for developing a Shiny application tailored for DMC use:

- **{teal.data}[4]:** Facilitates data creation and loading. The {teal} framework treats the entire combination of ADaM datasets as an object within its modules using an object-oriented programming (OOP) methodology. It provides a basic merging rule for combining different ADaM datasets, enabling seamless integration for further analysis. An example is illustrated in Figure 1.

```
> teal.data::default_cdisc_join_keys
A join_keys object containing foreign keys between 19 datasets:
ADSL: [STUDYID, USUBJID]
  <-- ADAE: [STUDYID, USUBJID]
  <-- ADEG: [STUDYID, USUBJID]
  <-- ADTTE: [STUDYID, USUBJID]
  <-- ADAETTE: [STUDYID, USUBJID]
  <-- ADCM: [STUDYID, USUBJID]
  <-- ADEX: [STUDYID, USUBJID]
  <-- ADLB: [STUDYID, USUBJID]
  <-- ADMH: [STUDYID, USUBJID]
  <-- ADQS: [STUDYID, USUBJID]
  <-- ADRS: [STUDYID, USUBJID]
  <-- ADSAFTTE: [STUDYID, USUBJID]
  <-- ADVS: [STUDYID, USUBJID]
  <-- ADDV: [STUDYID, USUBJID]
  <-- ADSUB: [STUDYID, USUBJID]
  <-- ADHY: [STUDYID, USUBJID]
  <-- ADQLQC: [STUDYID, USUBJID]
  <-- ADCSSRS: [STUDYID, USUBJID]
  <-- ADEQ5D5L: [STUDYID, USUBJID]
ADAE: [STUDYID, USUBJID, ASTDTM, AETERM, AESEQ]
  --> ADSL: [STUDYID, USUBJID]
```

Figure 1. Example of Join Keys Provided by {teal.data}.

- **{teal.slice}**[5]: Provides a filtering panel for data subset exploration. This module is particularly useful in clinical reviews, where similar analyses are often conducted across different populations or subgroups. When switching between populations, multiple filters can be applied to all ADaM datasets while maintaining the predefined merging rules. A UI example is shown in Figure 2.

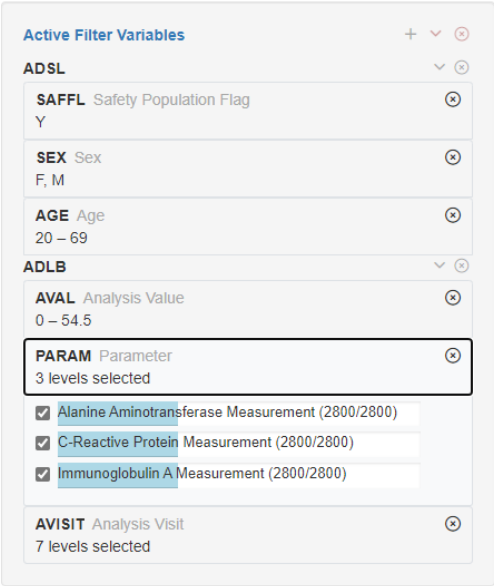

Figure 2. Example UI of {teal.slice}.

- **{teal.reporter}**[6]**:** Supports the generation of reports from {teal} applications. Since DMC meetings require documentation of discussions and evidence for session minutes, {teal.reporter} can automatically generate outputs based on the materials reviewed. An example UI is shown in Figure 3.

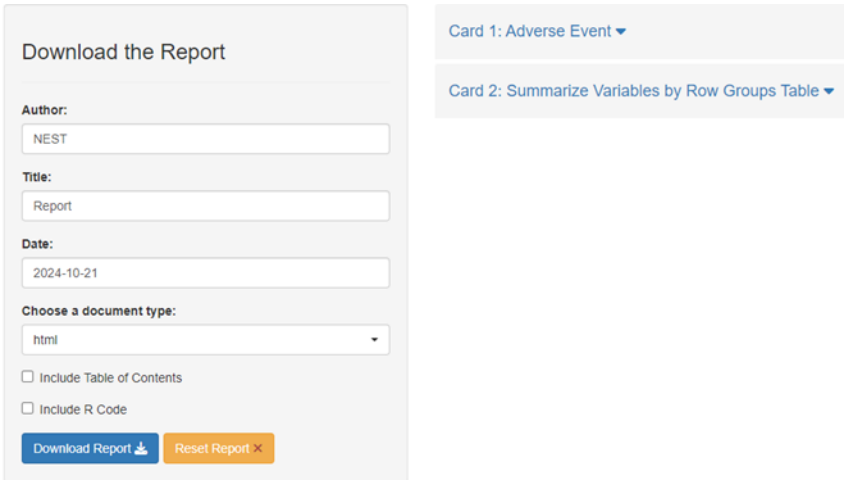

Figure 3. Example UI of {teal.reporter}.

IDENTIFYING AVAILABLE {TEAL} MODULES

One of the key features of {teal} is the availability of modules from the gallery that users can directly apply. Several useful modules in {teal} for DMC activities include:

- **{teal.modules.general}**[7]: These modules work with CDISC data, independent datasets, and general relational data to view data, visualize data, understand missing values and outliers, and perform simple data analysis.
- **{teal.modules.clinical}**[8]: These modules leverage functions from the {tern} package and focus on CDISC data to perform data visualizations, statistical model fitting, table summaries, and patient-level profiling.

We have identified several TLG-generating functions from the {teal.modules.general} and {teal.modules.clinical} module packages:

- **tm_t_summary()**: Summarizes variables and generates tables for disposition and demographics.
- **tm_t_events()**: Displays events by term and generates tables for concomitant medications, medical history, protocol deviations, and adverse events.
- **tm_t_summary_by()**: Summarizes variables by row groups, ideal for creating tables of lab values and vital signs.
- **tm_t_tte()**: Generates tables related to time-to-event data.
- **tm_g_km()**: Produces ggplot-style Kaplan-Meier plots for ADaM-structured data.
- **tm_t_pp_xx() and tm_g_pp_xx()**: Provide versatile module options for subject-level data display.
- **tm_data_table()**: Enables interactive dataset review, ensuring a flexible and efficient approach to clinical trial data analysis

CATEGORIZING MODULES FOR THE DMC CONTEXT

With the wide range of available modules, it can be beneficial to categorize them for a more efficient review from a DMC perspective. To enable both group-level and subject-level data review, we propose that each main module contain several potential submodules, organized as follows:

- **Baseline Information Module**: Disposition Table, Demographic Table, Major Protocol Deviation Table, Medical History Table, Concomitant Medication Table.
- **Safety Information Module**: Adverse Event Table, Lab Test Results Table, Vital Sign Results Table.
- **Efficacy Review Module**: Time to Event Table, Kaplan-Meier (KM) Plot.
- **Patient Profile Listing Module**: Basic Patient Information, Patient Vitals, Patient Lab Values, Patient Timeline.

CONNECTING TO EXTERNAL DATA

One challenge we've encountered is that {teal} is developed specifically for a single application per study. {interactive.stats} will only be deployed on one server but should work for multiple studies. To address this, a data connection/upload to the {teal} structure is required so that it can read the data. The good news is that {teal} provides a function called teal_data_module(), which enables users to upload data, as shown in Figure 4.

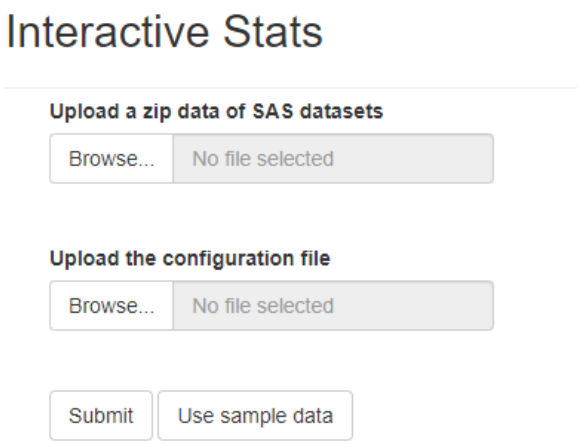

Figure 4. The Data-Import Page of the {interactive.stats} Shiny App.

COMPATIBILITY OF DATA CONNECTION

While users can upload data from different studies or sponsors to the server, one concern is ensuring that {interactive.stats} can read the data correctly. Even with the CDISC standard for ADaM datasets, different conventions can exist across sponsors. We propose using a configuration file to connect the ADaM data to the application, specifying which modules and variables should be used. The configuration file serves as a mapping method to ensure that the uploaded ADaM datasets are properly loaded into the application. It contains information such as the arm variable, analysis variable, required modules for the study, and more. An example is shown in Figure 5.

Description	Variable	Value
Baseline Module	check_mod_baseline	Y
Baseline Analysis: Planned Treatment Variable	base_trt	TRT01P
Baseline Analysis: Planned Treatment Variable choices	base_trt_option	TRT01P|TRT01A
Disposition	check_disp	Y
Disposition: Reason of Study Discontinuation	disp_anal_var	DSTRREAS
Demographic	check_dm	Y
Demographic: Variables	dm_anal_var	AGE|SEX|COUNTRY|RACE
Protocol Deviation	check_pd	Y
Protocol Deviation: Primary protocol deviation variable	pd_anal_var	DVDECOD
Medical History	check_mh	Y
Medical History: Level 1 variable options	mh_anal_var_option_1	MHBODSYS|MHCAT
Medical History: Level 1 variable	mh_anal_var_1	MHBODSYS
Medical History: Level 2 variable options	mh_anal_var_option_2	MHTERM|MHDECOD
Medical History: Level 2 variable	mh_anal_var_2	MHDECOD

Figure 5. An Example of the Configuration File.

DASHBOARD LAYOUT AND INTERACTIVE FEATURES

Upon importing data and configuration file, users are directed to a new page where they can review the dashboard populated with the imported data in a preferred format.

Figure 6 below illustrates the layout of the module dashboard. Each module follows a consistent design, featuring left panels for Reporter and Encodings, a middle panel for TFL Output, and right panels for Variable Filters. The Reporter panel allows users to add a card of the current TFL output, which can later be previewed and downloaded in the Report Previewer module. The Encodings panel enables users to select input variables—such as treatment variables, arm variables, summary variables, and more—for generating the TFL output. Based on these inputs, the corresponding outputs are displayed in the middle panel under calculations. Lastly, the Variable Filter panel provides information about the selected data, observations, and active filter variables, enabling users to apply desired filtering criteria to the current datasets.

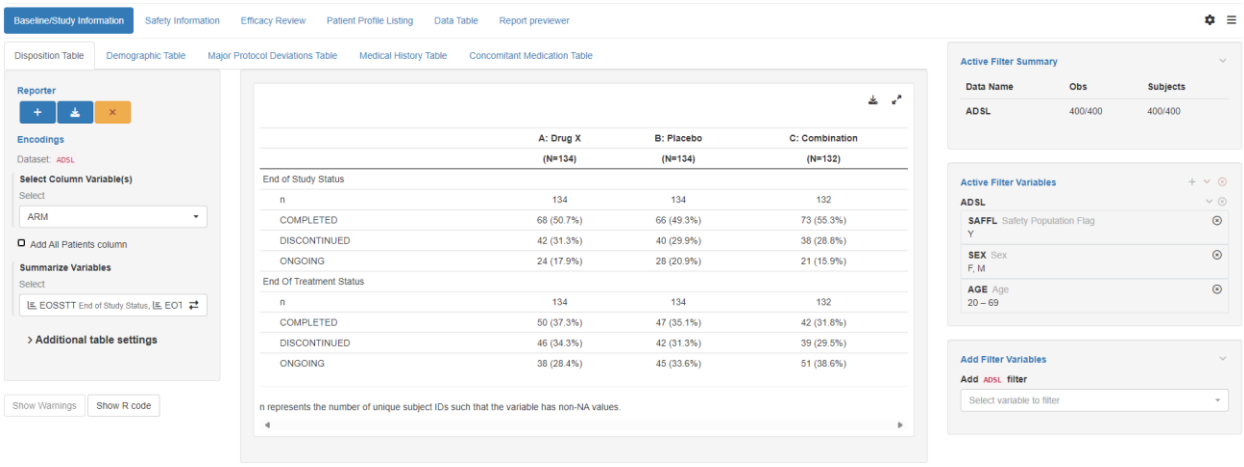

Figure 6. The Module Dashboard Layout of {interactive.stats} Shiny App.

DISCUSSION

We recognize that {teal} is primarily designed for study-specific use, meaning it is most effective when configured with multiple server addresses, each dedicated to a specific study. This allows users to tailor the tool to the unique data structures and requirements of individual clinical trials, maximizing its utility and precision in monitoring and analyzing trial data. However, at the vendor level, where there is often a need to support multiple studies simultaneously, it becomes crucial to explore strategies for hosting a single server that can efficiently accommodate and manage data.

Staying aligned with current trends in open-source development, especially within the pharmaceutical industry, is essential for maintaining a competitive edge and addressing the evolving needs of clinical trial monitoring. Open-source initiatives like {pharmaverse} have become central to fostering innovation and collaboration in industry. For those seeking further insights into these trends and their practical applications, detailed discussions can be found in CIMS's PharmaSUG 2024 Paper ST-381[9], which explores how open-source solutions are reshaping data management and analysis in clinical trials.

CONCLUSION

An abundance of open-source tools is available for clinical data analysis, and while identifying the most suitable solutions can be time-consuming, {teal} stands out as a particularly robust and reliable option. Developed and refined over several years, it has gained recognition for its efficiency and effectiveness in handling complex clinical trial data. This tool provides an interactive dashboard with a user-friendly interface designed specifically for DMC members. The dashboard enables users to focus on specific parameters, visits, or subjects by directly interacting with the visual components, eliminating the need to manually search through extensive documents for relevant keywords. This interactivity streamlines the workflow and saves valuable time.

One of {teal}'s key advantages is its flexibility in handling different populations. DMC members can easily update analyses for various subgroups or patient cohorts without relying on external statistical or programming teams, whether from sponsor or independent analysis centers. This capability allows for rapid adjustments to meet the evolving needs of the trial, ensuring that DMC members have up-to-date results. The ability to obtain instant insights enhances decision-making efficiency, eliminating delays associated with lengthy data processing or report generation.

Furthermore, {teal} facilitates seamless documentation of results discussed during meetings. DMC members can download results directly from the dashboard for reference and inclusion in meeting minutes. This feature ensures accurate data capture, simplifies the follow-up process, and enhances traceability. By integrating results into meeting documentation, {teal} supports well-documented, transparent, and easily accessible records for future meetings or audits. The ability to efficiently track, document, and share results improves transparency, accountability, and communication within the DMC, ultimately strengthening the integrity of the clinical trial monitoring process.

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