Paper ET11

An RShiny App for Real-Time Continuous Safety Monitoring in Post-POC Trials: A Bayesian Approach to Decision-Making

Jinquan Wu, Pfizer, Collegeville, PA, USA
Xiao Huang, Pfizer, Cambridge, MA, USA
Kevin Roberts, Pfizer, Cambridge, MA, USA
Ping Mahling, Pfizer, Cambridge, MA, USA

ABSTRACT

This paper presents an interactive RShiny application purpose-built for real-time, continuous safety monitoring in post-POC clinical trials. The app empowers clinical and statistical teams to conduct timely, data-driven safety assessments through an intuitive interface—eliminating the need for extensive coding or ad-hoc analyses. Key innovations include flexible data input, robust model configuration, and dynamic visualizations (text summaries, density plots, forest plots) that streamline the safety review process. Developed in accordance with FDA guidance [1], the application operationalizes Bayesian statistical methods [2,5] in a user-friendly environment, making advanced analytics accessible to trial teams and supporting proactive decision-making.

Keywords: RShiny application, Continuous safety monitoring, Bayesian analysis, Real-time data visualization, post-POC trials, Decision support.

INTRODUCTION

In the landscape of clinical development, particularly after **proof-of-concept (POC)** has been established, the focus shifts from demonstrating preliminary efficacy to confirming and characterizing both efficacy and safety in larger, more heterogeneous patient populations. *Post-POC trials*—typically encompassing later-stage Phase II and Phase III studies—are designed to evaluate treatment effects under conditions that more closely resemble real-world clinical use. These trials often involve longer durations of exposure, broader eligibility criteria, and increased patient numbers, thereby generating more complex and voluminous safety data.

As a result, post-POC clinical trials produce substantial amounts of safety information, including adverse events (AEs) and serious adverse events (SAEs). The scale and complexity of these data can make it challenging for clinical teams to promptly identify emerging safety signals—defined as patterns or trends that may suggest previously unrecognized or evolving risks associated with the investigational treatment.

Traditionally, safety monitoring in clinical trials relies on periodic, static reports, typically generated at predefined intervals (e.g., monthly or quarterly). While these reports provide valuable aggregated summaries, they inherently introduce delays between the occurrence of safety events and their review by the trial team. Such delays may result in missed opportunities for early intervention, potentially affecting patient safety and the overall integrity of the trial.

Moreover, regulatory agencies, including the U.S. Food and Drug Administration (FDA) [1], have increasingly emphasized that **continuous and proactive safety surveillance** is both a scientific and operational priority. Recent regulatory guidance encourages sponsors to adopt data-driven approaches that enable ongoing evaluation of safety data as it accrues, rather than relying solely on retrospective summaries. However, implementing continuous safety monitoring in practice is often constrained by limitations of existing tools, which may require advanced statistical expertise or substantial programming effort, limiting accessibility for non-statistical stakeholders.

To address these challenges, we have explored innovative approaches and developed an interactive application built on the RShiny platform [4]. The tool is designed to democratize access to advanced analytical methods, enabling statisticians, clinicians, and trial managers to actively participate in safety monitoring. By integrating Bayesian statistical methodologies [2,5] with dynamic visualizations within an intuitive interface, the application supports near–real-time detection of safety signals, facilitates proactive decision-making, and helps ensure that emerging risks are identified and managed in a timely manner. In doing so, it enhances the ability of trial teams to protect patient safety, align with regulatory expectations, and make informed decisions based on the most current available data.

BACKGROUND AND MOTIVATION

Despite regulatory guidance emphasizing the importance of continuous safety surveillance in clinical trials [1], practical implementation remains challenging for many study teams. Existing safety monitoring tools often require advanced statistical programming or lack intuitive interfaces, limiting their effective use to a small group of specialists and reducing broader team engagement in ongoing safety oversight.

To address this gap, we developed an interactive RShiny application that combines analytical rigor with accessibility. The tool enables clinicians, statisticians, and trial managers to engage directly with safety data through an intuitive interface and clear visualizations, without requiring programming or in-depth statistical expertise. Advanced Bayesian models are implemented transparently within the application to support continuous safety evaluation in alignment with FDA recommendations [1], while results are presented in an interpretable and actionable manner.

Simulated data are used to demonstrate the application’s functionality and workflow, ensuring compliance with data privacy requirements. Overall, the application is intended to facilitate practical, efficient, and accessible continuous safety monitoring for multidisciplinary clinical trial teams.

METHODS

App Design and Workflow

The RShiny application provides an accessible, interactive platform for continuous safety monitoring. Its design prioritizes usability for both statisticians and non-programmers, while offering robust analytical capabilities.

- **Flexible Data Input:** Users can upload trial datasets, specify external placebo prior information (MAP), define randomization ratios, and select the serious adverse event (SAE) of interest, adapting to various trial designs.
- **Robustification:** Users can adjust the placebo prior weight for sensitivity analyses, improving model robustness.
- **Customizable Model Configuration**: Parameters such as random seed, number of Markov Chain Monte Carlo (MCMC) chains, warmup, and sampling iterations are easily set through the interface, ensuring reproducibility and flexibility.
- **Real-Time Analysis:** Bayesian sampling is performed using cmdstanr[3], with real-time progress feedback.
- **Comprehensive Visualization:** Results are presented in multiple formats to facilitate interpretation:
    - **Text Summaries:** Key metrics such as the probability that experimental treatment has a higher SAE incidence rate than control ($P(\theta_e > \theta_c)$), incidence rates (IR), IR differences, and relative risk (RR) are clearly displayed.
    - **Density Plots:** Posterior distributions for incidence rates, IR differences, and relative risk are visualized, helping users understand the range and likelihood of possible outcomes.
    - **Forest Plots:** Summarize interval estimates and credible intervals, enabling direct comparison between treatment groups and clear visualization of uncertainty.

Statistical Methods

The app implements a Bayesian hierarchical model [5] for safety signal detection, modeling adverse event counts using a Poisson likelihood with exposure time to estimate incidence rates in both experimental and control arms. Prior information is incorporated through meta-analytic-predictive (MAP) priors on the control incidence rate, which can be robustified via a weighted mixture with weakly informative priors to mitigate prior–data conflict. Posterior estimates are dynamically updated as new data accrue, and Bayesian inference supports continuous safety monitoring and real-time decision-making [6] by providing posterior probabilities for key safety metrics, including the likelihood of elevated risk in the experimental arm. All statistical complexity is handled within the app's backend, making advanced analytics practical and accessible.

Analysis Pipeline

The analysis process includes:

1. **Data Preprocessing:** Calculates event rates and exposure to compute incidence rates for both experimental treatment group and control group.
2. **Bayesian Inference:** Runs Bayesian analysis with cmdstanr [3], producing posterior distributions for incidence rates, IR difference, relative risk, and the probability that experimental treatment has a higher SAE incidence rate than control, denoted as $P(\theta_e > \theta_c)$.
3. **Result Visualization:** Displays posterior distributions in density plots and summarizes results with credible intervals in forest plots.

RESULTS

User Interface:

The app's interface (Figure 1) is designed for clarity and ease of use, guiding users from data upload through model configuration to results interpretation. Features include dynamic progress indicators, clearly labeled input fields, and interactive output panels for text summaries, density plots, and forest plots. This intuitive layout ensures that both statisticians and non-programmers can efficiently navigate the safety monitoring process and access actionable insights in real time.

Case Study:

Simulated Clinical Trial

A simulation-based case study mimicking a clinical trial with 100 patients (focused on depression-related safety outcomes) demonstrates the app's functionality:

- **Data Upload and Preprocessing:**Users upload synthetic SAE records, which are then automatically processed for analysis.
- **Configuring Analysis Parameters:**Users specify placebo prior information, randomization ratios, and the SAE of interest. Robustification options enable sensitivity analyses by adjusting the placebo prior weight.
- **Interactive Bayesian Analysis:** Users configure model parameters, and the app performs real-time Bayesian inference, estimating incidence rates, incidence rate differences, relative risk, and the posterior probability that the experimental treatment has a higher SAE incidence rate than control ($P(\theta_e > \theta c)$). In this simulation, $P(\theta_e > \theta c) = 0.95195$, indicating strong evidence of a potential safety signal associated with the experimental treatment.
- **Real-Time Monitoring and Feedback:** The app dynamically updates all posterior distributions as new data accumulates, providing immediate feedback.
- **Visualization and Interpretation:** After Bayesian sampling, the app presented results in both text summaries and interactive visualizations:
  - **Text Summaries:** Key safety metrics—including the posterior probability that the experimental treatment has a higher SAE incidence rate than control, incidence rates, IR differences, and relative risk—are displayed for rapid assessment (see Figure 2).
  - **Density Plots:** Posterior distributions for incidence rates, IR differences, and relative risk provide intuitive visualizations of uncertainty and treatment effects (see Figures 3–5).
  - **Forest Plots:** Posterior estimates and credible intervals are summarized in forest plots, enabling direct comparison between treatment groups (see Figures 6–8).

Key Findings:

In the simulated trial, the experimental arm showed a mean incidence rate of 5.55 compared to 2.51 for the control group, with a relative risk of 3.28 and an incidence rate difference of 3.04. The posterior probability that the experimental treatment has a higher SAE incidence rate than control ($P(\theta_e > \theta_c)$)reached 0.95195, exceeding the predefined unblinding threshold of 0.9355. These results, supported by credible intervals whose lower bounds excluded zero or unity, indicate strong evidence of a potential safety signal associated with the experimental treatment and demonstrate the app's ability to support timely safety decision-making.

DISCUSSION

The RShiny application demonstrated strong potential as a practical and accessible tool for continuous safety monitoring in post-POC clinical trials. By integrating advanced Bayesian modeling with real-time visualization, the app enables dynamic safety assessments and operational decision-making earlier than traditional, static methods. The intuitive interface (Figure 1) lowers the barrier for both statisticians and non-programmers, allowing clinical teams to upload trial data, configure priors, and run analyses without programming expertise.

The simulation-based case study illustrates the app's effectiveness in a realistic trial scenario. The posterior probability that the experimental treatment has a higher SAE incidence rate than control ($P(\theta_e > \theta_c) = 0.95195$) exceeded the predefined unblinding threshold, demonstrating how the app can operationalize Bayesian decision rules and link statistical evidence directly to trial management actions focused on safety oversight. Numeric summaries and visual outputs (Figures 2–8) provided clear, actionable insights, showing a higher mean incidence rate and relative risk in the experimental arm, with credible intervals supporting the identification of a potential safety signal.

A key strength of the application is its ability to combine numeric and graphical evidence for Bayesian decision-making. The dynamic progress bar, interactive output panels, and real-time updates facilitate rapid interpretation and support adaptive trial strategies. The app's design ensures that advanced analytics are accessible to all members of the trial team, regardless of programming background.

Building on these strengths, several enhancements could further extend the application's functionality and applicability.

Potential enhancements include

- **System Integration:** Linking with platforms could automate data flow and further streamline trial operations.
- **Expanded Validation:** Extending validation efforts across a broader range of study designs would enhance confidence in methodology's robustness and support its applicability to diverse clinical trial settings.
- **Additional Safety Metrics:** Incorporating severity grading and other clinical endpoints could broaden the app's applicability and provide more comprehensive safety assessments.
- **Expanded Customization:** While the current application allows users to define custom prior distributions and configure key model parameters (such as random seed, number of chains, and sampling iterations), future enhancements could offer even greater flexibility—such as advanced options for model structure or integration of user-defined statistical methods—to support a wider range of trial designs.

CONCLUSION

Developed collaboratively by the statistical data science programming team and the statistical team, the RShiny application marks a significant advancement in continuous safety monitoring for post-POC clinical trials. By translating advanced statistical methods into an accessible, interactive platform, the app's user-friendly interface and dynamic visual outputs (Figures 1–8) empower clinical and statistical teams to conduct real-time safety assessments and make data-driven decisions without the need for specialized programming expertise.

The simulation-based case study demonstrated the app's effectiveness for continuous safety monitoring, with a posterior probability of 95.2% indicating an elevated incidence rate of the selected safety event in the experimental arm relative to control. The integration of text summaries, density plots, and forest plots provides clear, actionable insights, streamlining the safety review process and supporting timely, data-driven decision-making for trial teams.

Looking ahead, validating the application with real-world clinical trial data, and integrating it with enterprise systems will further enhance its value and operational impact. In summary, this RShiny tool offers a practical, regulatory-compliant framework for continuous safety evaluation, making advanced analytics accessible and actionable for modern clinical development.

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ACKNOWLEDGEMENTS

The authors would like to express their sincere appreciation to **LiFeng Good** and **Ajay Aiyer** for their thoughtful review of this paper and for providing constructive critiques and helpful suggestions that significantly strengthened the quality of the work.

CONTACT INFORMATION

Your comments and questions are valued and encouraged. Please contact the authors:

Jinquan Wu
Pfizer, Inc.
500 Arcola Rd, Collegeville, PA 19426
Email: jinquan.wu@pfizer.com
Website: https://www.pfizer.com

Appendices:

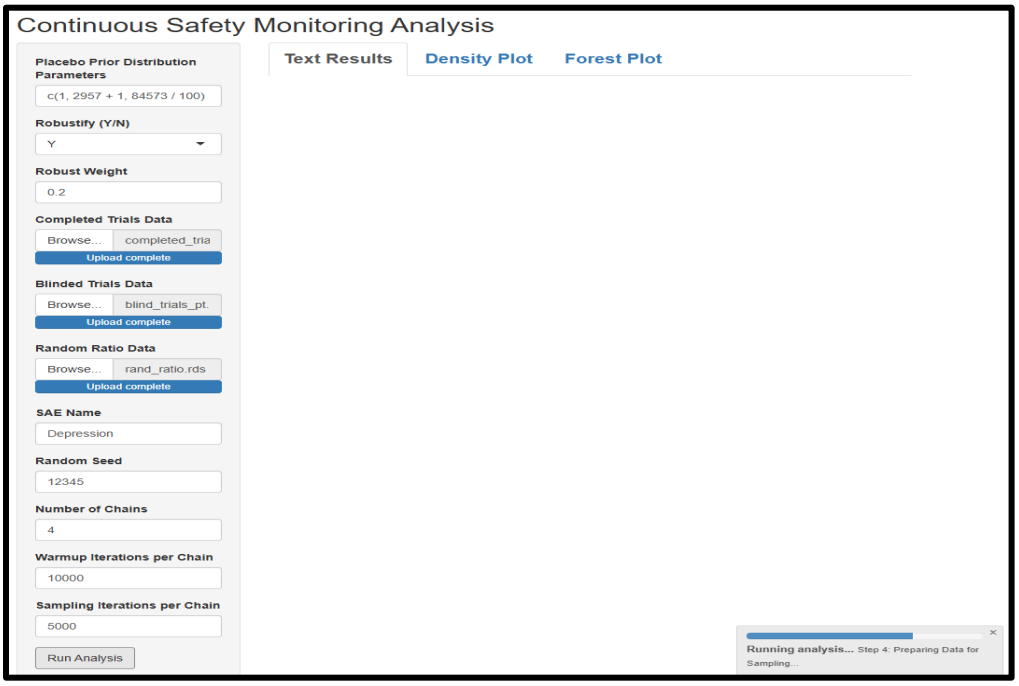

Figure 1. User Interface of the Continuous Safety Monitoring RShiny App

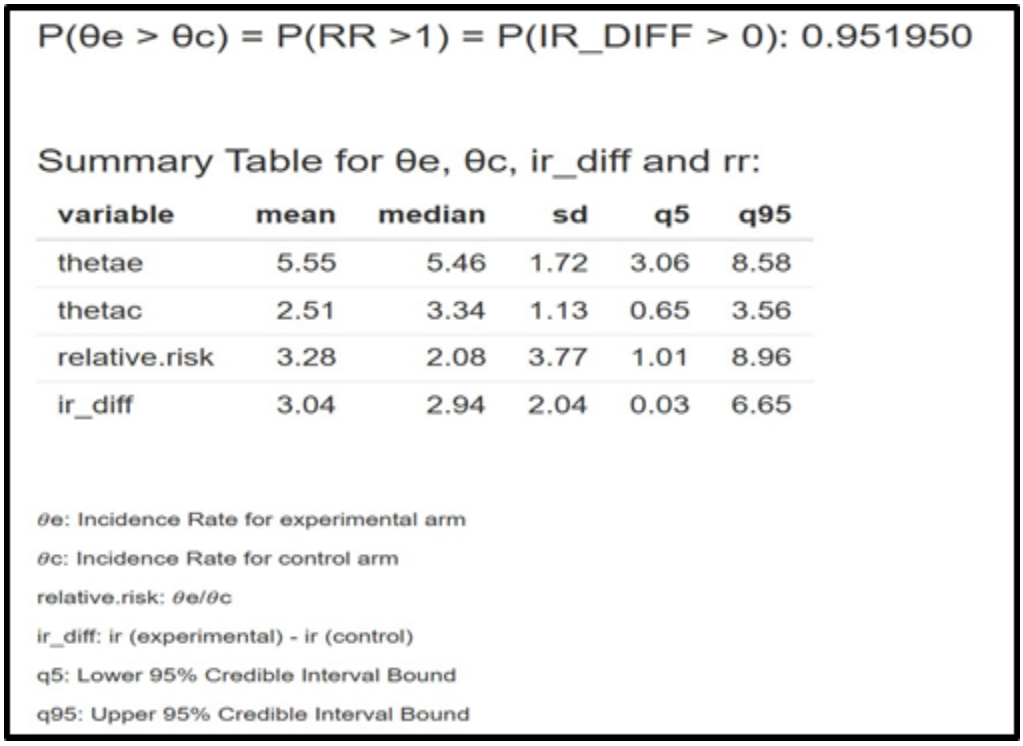

Figure 2. Text Results

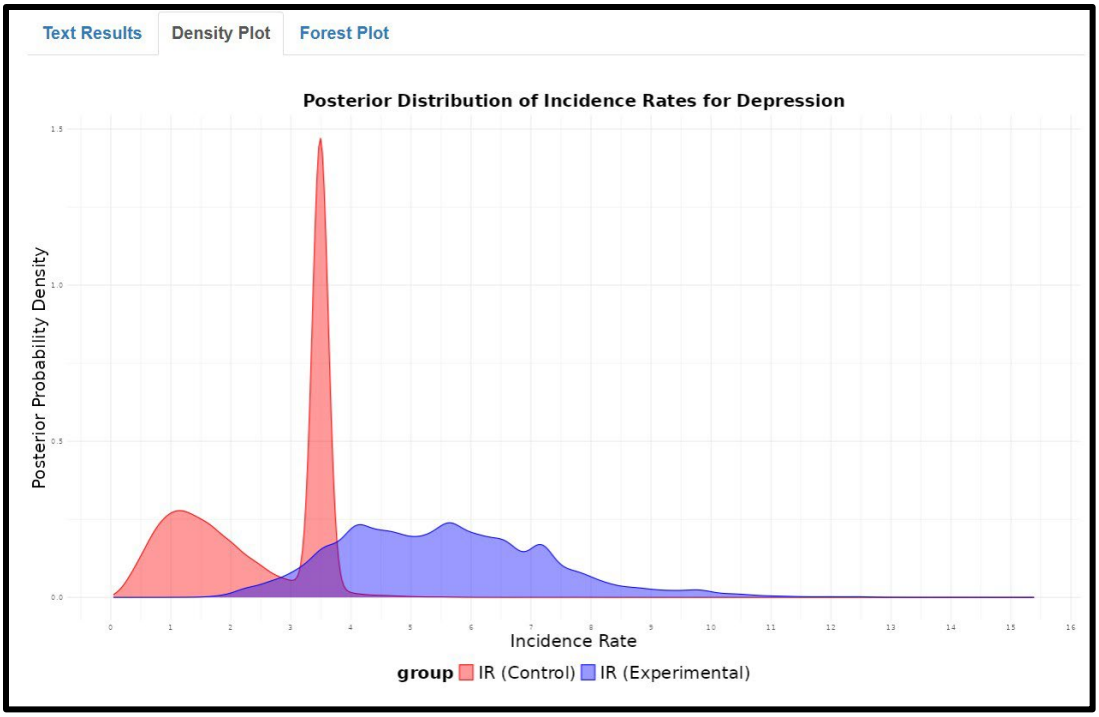

Figure 3. Posterior Probability Density Plot of Incidence Rates

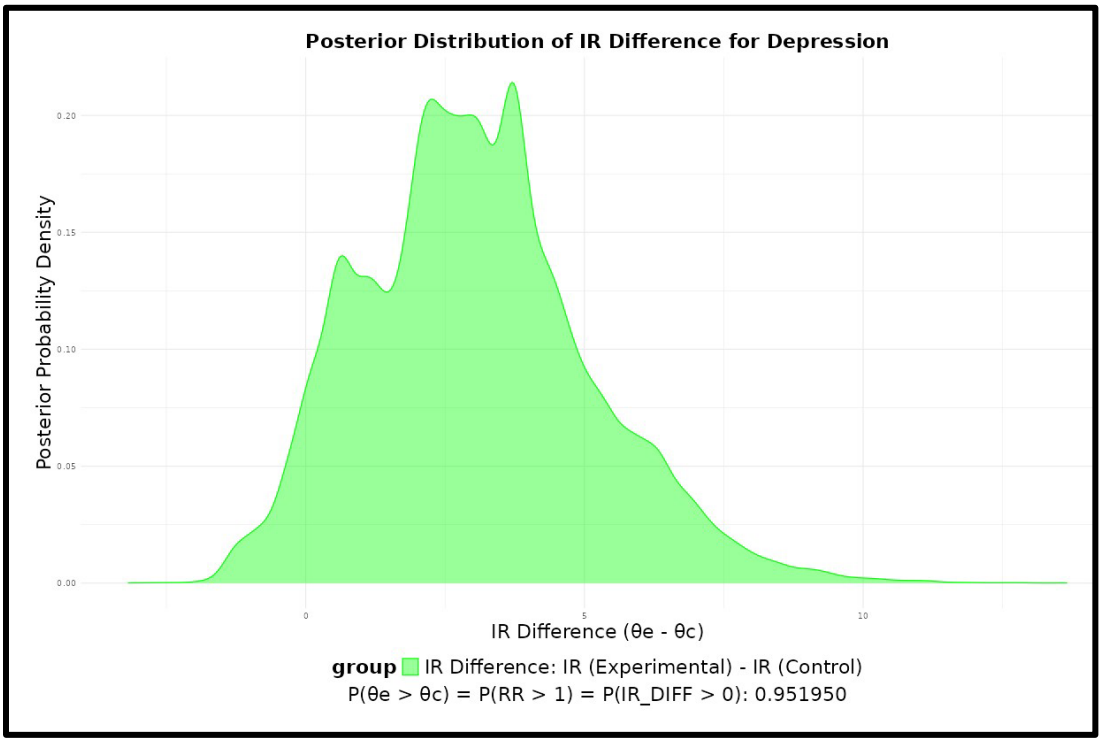

Figure 4. Posterior Probability Density Plot of IR Difference

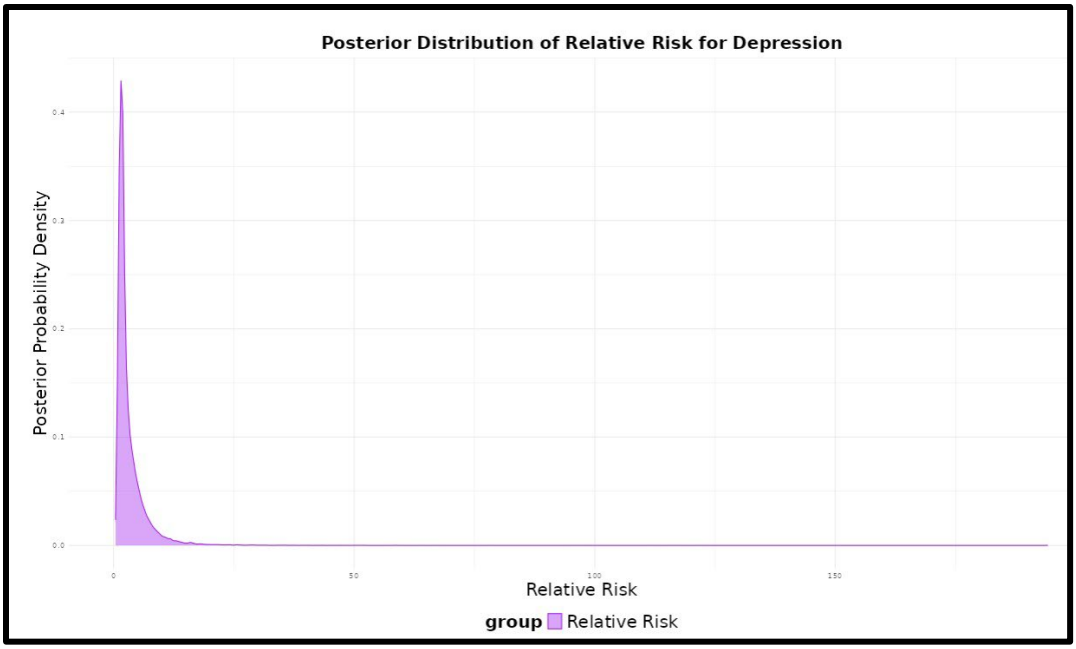

Figure 5. Posterior Probability Density Plot of Relative Risk

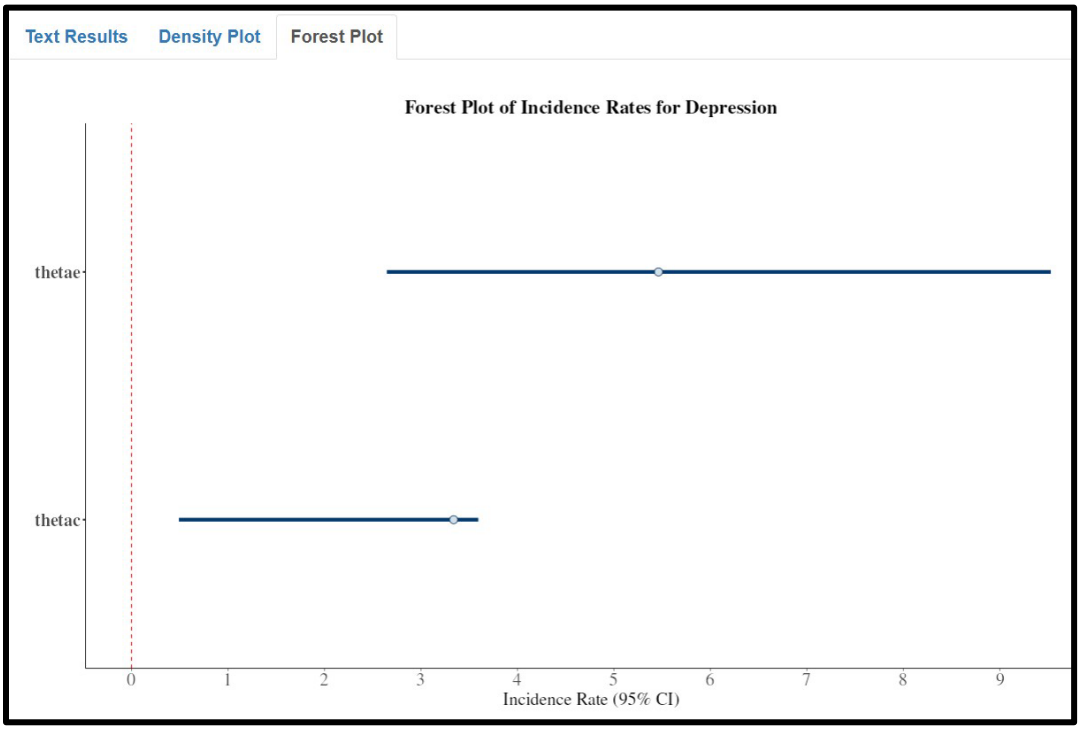

Figure 6. Forest Plot of Incidence Rates

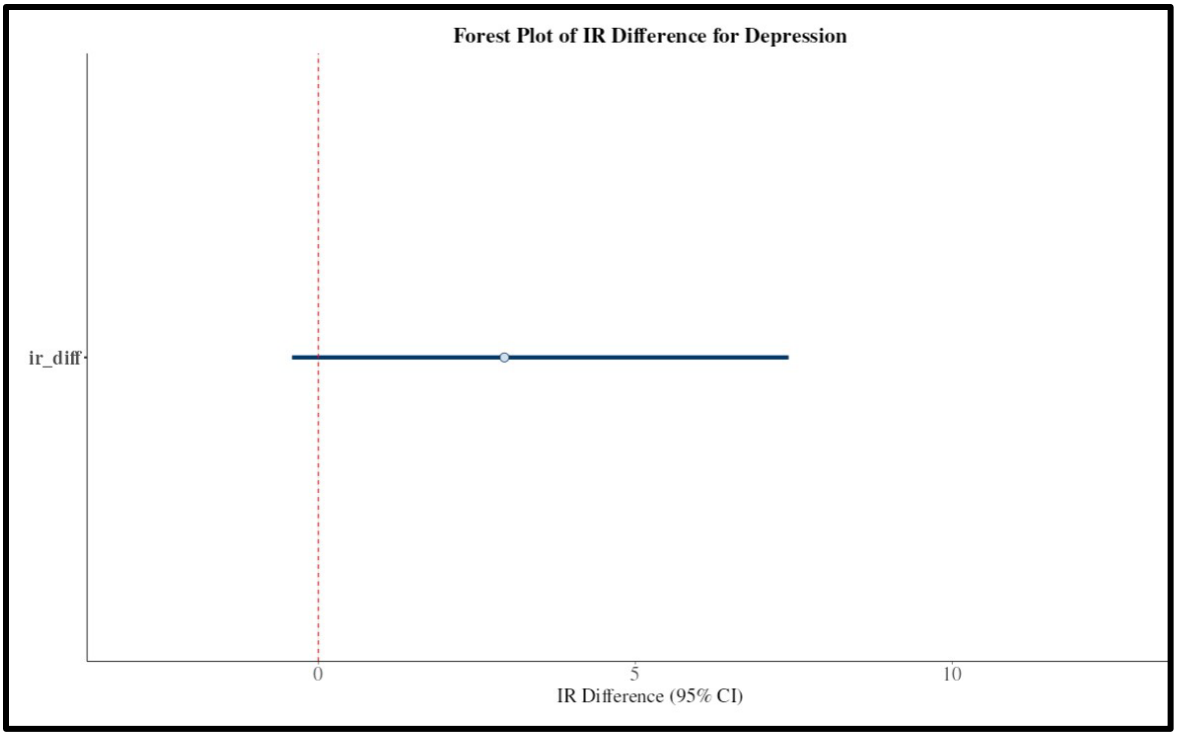

Figure 7. Forest Plot of IR Difference

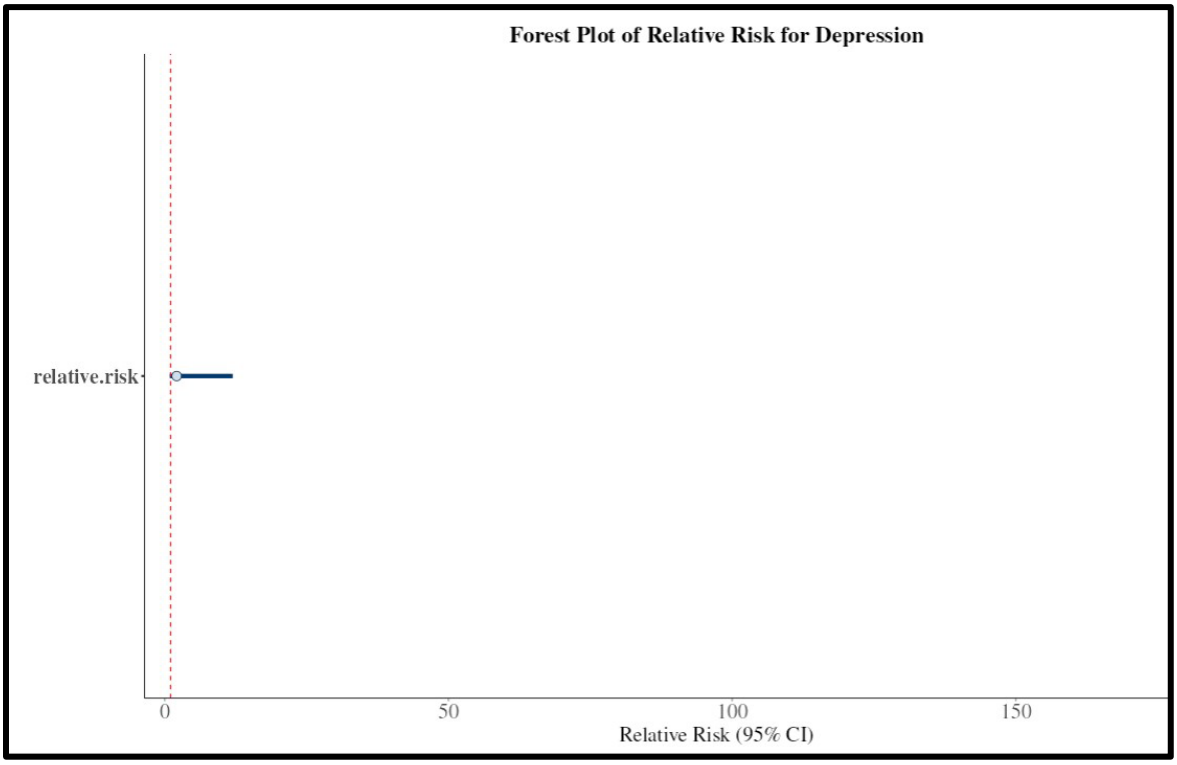

Figure 8. Forest Plot of Relative Risk