gPaper AR04

Good Statistical Monitoring {gsm}: An R Package for Risk-Based Monitoring and Clinical Trial Analytics

Jeremy Wildfire, Gilead Sciences, Durham, NC, United States
Matt Roumaya, Atorus Research, Philadelphia, PA, United States

ABSTRACT

Risk-based quality management (RBQM) is a regulatory-recommended approach to manage risk in a clinical trial. While there is a significant body of literature describing RBQM implementation and best practices[1,2], there are few publicly available open-source tools for RBQM available.

The {gsm} R package provides a robust and open-source solution for evaluating risk signals at the site-level. RBQM monitoring can be a costly endeavor, and the {gsm} package is a fundamental component of a growing framework that allows for efficient, accurate, and timely assessment, visualization, and reporting of differences in quality across sites in a clinical trial.

INTRODUCTION

The advent of risk-based quality management (RBQM) in clinical trials marks a regulatory pivot towards more efficient and targeted oversight practices, emphasizing the early detection and mitigation of risks to critical data and processes. Despite RBQM's recognized benefits for trial integrity and patient safety, its uptake has been hindered by the scarcity of accessible and cost-effective analytical tools.

The Good Statistical Monitoring, or {gsm}, R package provides a standardized RBQM framework for clinical trials that pairs a flexible data pipeline with robust data checking, interactive data visualization, and reporting capabilities. It includes metadata-driven workflows that can be customized by choosing different statistical methods, data domains, and filtering subject-level data based on various criteria. By providing an extensible, open-source RBQM framework, {gsm} provides a valuable new platform for robust pre-competitive collaboration for RBQM analytics. Source code and documentation is available on GitHub: https://github.com/Gilead-BioStats/gsm.

CORE {GSM} FUNCTIONALITY

At its core, {gsm} evaluates Key Risk Indicators (KRIs) and other metrics by combining a robust data pipeline with interactive R Markdown/HTML reports, which are summarized below. Detailed documentation of {gsm} functionality is available on the {pkgdown} site: https://gilead-biostats.github.io/gsm/.

KRI DATA PIPELINE

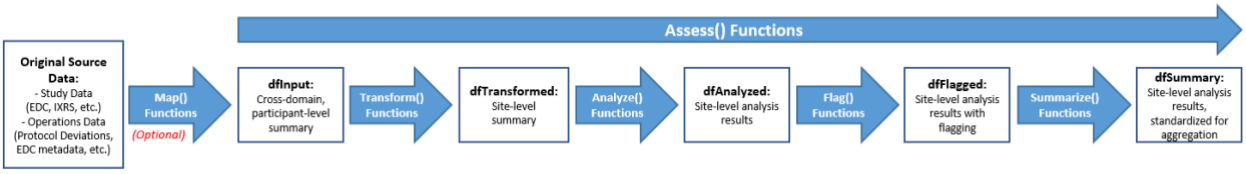
In the context of clinical research, a KRI is a measure of risk associated with the conduct of a clinical trial. Examples of KRIs include the rate of adverse events or amount of missing data at a site or across sites. Defining and deploying KRIs during study start-up allows sponsors to continually monitor risks to the integrity of the trial and take corrective actions accordingly. Currently, {gsm} is designed to generate the 12 KRIs listed below:

1. Adverse Event Reporting Rate
2. Serious Adverse Event Reporting Rate
3. Non-important Protocol Deviation Rate
4. Important Protocol Deviation Rate
5. Grade 3+ Lab Abnormality Rate
6. Study Discontinuation Rate
7. Treatment Discontinuation Rate
8. Query Rate
9. Outstanding Query Rate
10. Outstanding Data Entry Rate
11. Data Change Rate
12. Screen Failure Rate

Additional details about the list of KRIs can be found by viewing a sample report, available here.

A standardized "assessment pipeline" is used to generate all KRI results in {gsm} (Figure 1). The pipeline is a standardized process starting with clinical data and outputting a standardized site-level summary of model results. The data pipeline is designed to be flexible enough to allow for the use of multiple standard clinical datasets such as ADaM, SDTM, or datasets that were derived using custom specifications. The process is also modular, allowing for custom data mapping or analysis methods to be applied as needed.

FIGURE 1 – STANDARDIZED {GSM} ASSESSMENT PIPELINE



dfInput: Input data; Cross-domain participant-level input data with all needed data for KRI derivation. Created by `Map()` functions as needed.

dfTransformed: Transformed data; Site-level transformed data including KRI calculation. Created by `Transform()` functions.

dfAnalyzed: Analyzed data; Site-level analysis results data. Created by `Analyze()` functions.

dfFlagged: Flagged data; Site-level analysis results with flags added to indicate potential statistical outliers. Created by passing numeric thresholds to a `Flag()` function.

dfSummary: Summary data; Standardized subset of the flagged data. This summary data has the same structure for all assessments and always includes both KRI and Flag values so that a user can easily look at trends for any given site across multiple assessments. Created using the `Summarize()` function.

STUDY ASSESSMENTS AND REPORTS

Multiple instances of the KRI workflow can easily be aggregated into a study-level RBQM assessment covering multiple clinical domains. The `Study_Assess()` function allows users to easily conduct multiple KRI assessments using shared data and specifications and saves aggregate results as an R object utilizing a well-defined data model. The output of `Study_Assess()` can then be passed to `Study_Report()` to generate a R Markdown/HTML report that summarizes all KRI findings (Figures 2).

Extensive documentation of the KRI workflow, study assessment process and reporting framework are included on GitHub as vingettes:

- Data Pipeline – KRI analysis framework including detailed technical specifications.
- Step-by-Step Analysis Workflow – Deep-dive for a single KRI assessment.
- Cookbook – Concise examples with common customizations.
- KRI Method – Overview of statistical methods.
- Sample KRI Report – Example site-level KRI report. A country-level report is also available.

FIGURE 2A

Site	Country	Status	Subjects	Red KRIs	Amber KRIs	AE	SAE	PD	IPD	LB	SDSC	TDSC	QRY	OQRY	ODAT	CDAT	SF
28	US	Active	5	4	0	✓	⌃⌃	✓	✓	⌃⌃	⌃⌃	⌃⌃	✓	✓	✓	✓	✓
173	US	Active	27	2	1	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	⌄
43	US	Active	33	2	1	⌃⌃	✓	✓	✓	✓	✓	✓	⌄	✓	⌃⌃	✓	✓
75	China	Active	10	2	1	⌃⌃	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
83	Japan	Active	7	2	1	⌃⌃	✓	✓	✓	⌃⌃	✓	✓	✓	✓	✓	⌃	✓
161	Japan	Active	5	2	0	✓	✓	✓	✓	✓	⌃⌃	⌃⌃	✓	✓	✓	✓	✓
114	US	Active	7	1	1	✓	✓	⌃⌃	⌃	✓	✓	✓	✓	✓	✓	✓	✓
186	US	Active	5	1	1	✓	✓	⌃	⌃⌃	✓	✓	✓	✓	✓	✓	✓	✓
20	US	Active	1	1	1	✓	✓	✓	⌃⌃	✓	–	–	✓	–	✓	✓	⌃
60	US	Active	4	1	1	✓	✓	✓	✓	✓	⌃⌃	⌃	✓	✓	✓	✓	✓

GroupID: 28
SAEs: 10
Days on Study: 2286
Metric: 0.004
Score: 10.097
Flag: 2

FIGURE 2B

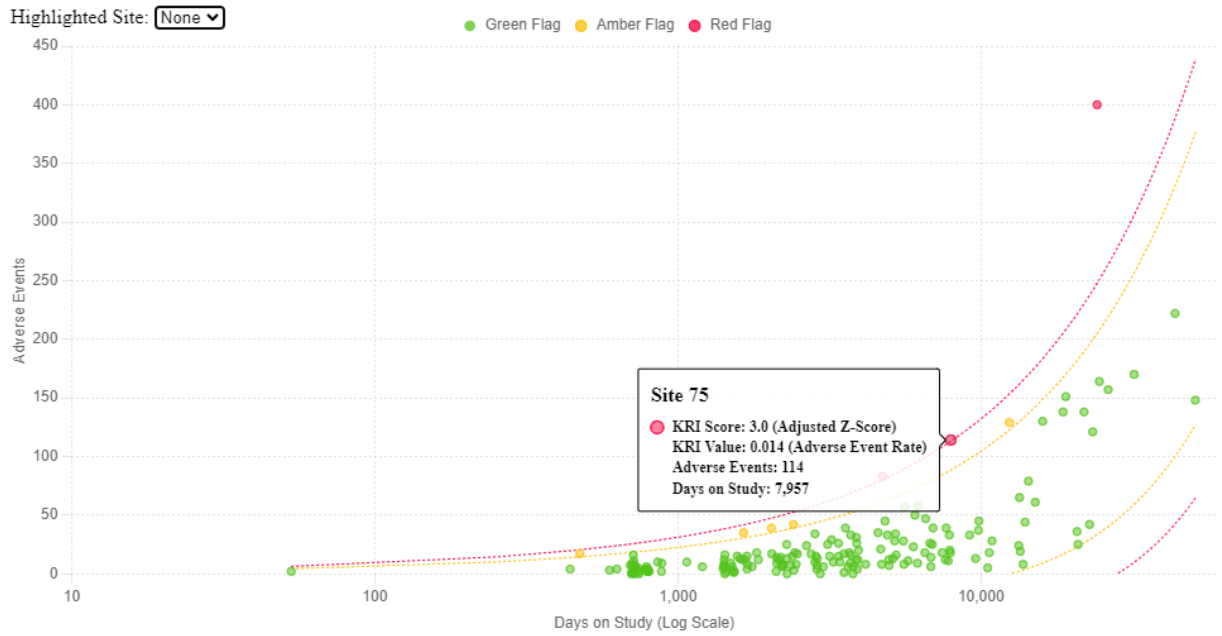


FIGURE 2C

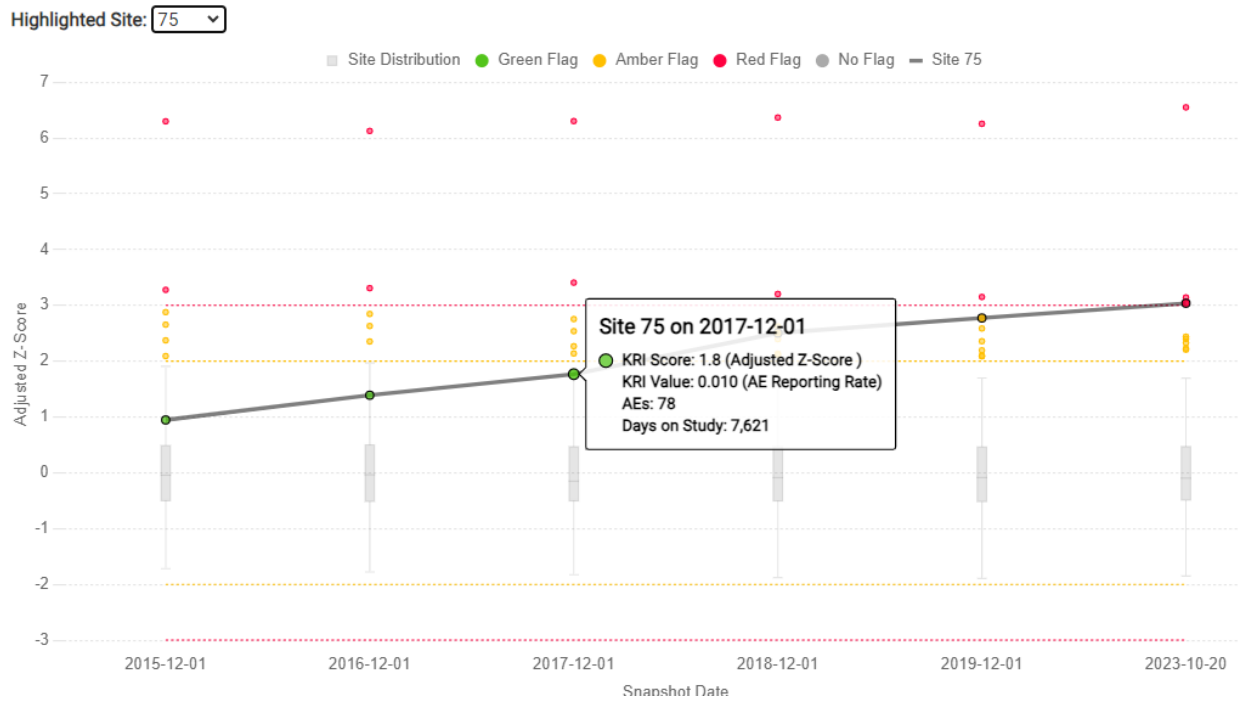


Figure 2: Panel A shows a table summarizing the finding for each KRI (column) by site (row). Green, Amber, and Red arrows are used to indicate risk status for each KRI, with arrow direction indicating over/under reporting of a metric relative to other sites in the study. Users can mouse-over individual flags to see additional information as shown.

Panel B shows a scatter plot of adverse events by days on study on the log scale is shown, where each point is a site. Users can mouse-over individual sites to see additional. Red, amber, and green dotted lines correspond to the user-specified thresholds and point color indicates risk status.

Panel C shows a longitudinal plot of adjusted risk scores (y-axis) over repeated analysis at different snapshot dates (x-axis). Users can click a point to see metric details and a trend line for the selected site. Boxplots depict the distribution of scores for each snapshot. Points are plotted for sites with red or amber flags.

QUALITY FRAMEWORK

Since {gsm} is designed for use in a GCP framework, we have conducted extensive quality control as part of our development process. In particular, {gsm} includes the following:

- **Qualification Workflow** - All assessments have been Qualified as described in the Qualification Workflow Vignette. A Qualification Report Vignette is generated and attached to each release. A separate PHUSE 2024 presentation titled *Leveraging GitHub Actions and Continuous Integration in R Package Qualification* covers {gsm}'s qualification framework in greater detail.
- **Unit Tests** - Unit tests are written for all core functions.
- **Contributor Guidelines** - Detailed contributor guidelines including step-by-step processes for code development and releases are provided as a vignette.
- **Data Model** - Vignettes providing detailed descriptions of the data model.
- **Code Examples** - The Cookbook Vignette provides a series of simple examples, and all functions include examples as part of roxygen2 documentation.
- **Code Review** - Code review is conducted using GitHub Pull Requests (PRs), and a log of all PRs is included in the Qualification Report Vignette.
- **Function Documentation** - Detailed documentation for each function is maintained with roxygen2.
- **Package Checks** - Standard package checks are run using GitHub Actions and must be passing before PRs are merged.
- **Data Specifications** - Machine-readable data specifications are maintained for all KRIs. Specifications are automatically added to relevant function documentation.
- **Continuous Integration** - Continuous integration is provided via GitHub Actions.
- **Regression Testing** - Extensive QC and testing is done before each release.
- **Code Formatting** - Code is formatted with {styler} before each release.

For more details see the package website, which includes a Qualification Workflow vignette.

CONCLUSION

The {gsm} package aims to provide a GCP-compliant open-source framework for RBQM in a cost-effective and statistically sound manner. The package was developed at Gilead by a diverse team including RBQM subject-matter experts, risk advisors, biostatisticians, software developers, data scientists, and other stakeholders. The package has been fully qualified for use at Gilead and has been used on more than a dozen active studies. A phased deployment to all studies is underway.

The package was released publicly in September 2024 with external demonstrations and collaborations starting shortly thereafter. The significance of {gsm} as an open-source solution extends beyond its immediate application as a RBQM tool, as it actively encourages pre-competitive collaboration within the open-source community and pharmaceutical industry. Ideally, this will foster and encourage teamwork and collaboration, and lead to an advanced analytics tool that will enhance patient safety and improve outcomes in clinical trials on a broader scale.

Future development plans include the incorporation of additional qualified Key Risk Indicators (KRIs), refining and expanding reporting and visualization capabilities, integrating centralized statistical monitoring analyses to complement RBQM efforts, and fostering engagement with the open-source community.

REFERENCES

1. https://www.transceleratebiopharmainc.com/wp-content/uploads/2017/09/Risk-Based-Quality-Managment.pdf
2. https://www.acrohealth.org/wp-content/uploads/2019/10/CRO-Forum-RBQM-Oversight-Paper-FINAL-Oct-2019.pdf

CONTACT INFORMATION (HEADER 1)

Your comments and questions are valued and encouraged. Contact the author at:

Author Name: Jeremy Wildfire
Company: Gilead Sciences
Address: 333 Lakeside Drive
Foster City, CA 94404
Work Phone: +1 650 574 3000

Email: jeremy.wildfire@gilead.com
Website: https://www.gilead.com/

Author Name: Matt Roumaya
Company: Atorus Research
Email: matt.roumaya@atorusresearch.com
Website: www.mattroumaya.com