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Collaborative Industry Open Source Solutions for Clinical Trial Quality Management

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INTRODUCTION

Recent ICH guidelines require a risk-based strategy for the quality management of clinical trials in both, quality control and quality assurance. This includes areas such as risk management, centralised monitoring and auditing. Risk management frameworks such as risk-based quality management (RBQM) provide guidance on how risk-based approaches can be implemented and require some form of statistical monitoring and assurance of operational and clinical trial data. The intercompany quality analytics consortium (IMPALA) and the PHUSE Open RBQM workstream are cross-industry collaborations that promote the open source development of statistical tools and frameworks for clinical trial quality management. The good statistical monitoring {gsm} R package provides a framework for data transformation, statistical analysis and reporting. {simaerep} and the gsm extension {gsm.simaerep} use a non-parametric approach for flagging site outliers for the reporting of subject-level clinical events (e.g adverse events, protocol deviations). Statistical data monitoring and assurance can be covered using the clinical trial anomaly spotter {ctas} package. In the future we aim to extend this suite of tools to cover quality tolerance limits and standard fraud detection tools (e.g. last digit preference, patient/form duplication detection).

Cross Industry Organisation

IMPALA Intercompany Quality Analytics Consortium

- Founded 2022
- 19 industry members
- Statistical Open Source Packages
- Scientific Publications
- Quality Frameworks (RAPID, Quality Briefs)
- Joint Health Authority Engagement
- https://impala-consortium.org/

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- Founded 2024
- > 3 industry members
- RBQM focus (Critical to Quality, Centralized Monitoring, Quality Tolerance Limits)
- 6 Projects
- White Papers
- Open Source Packages

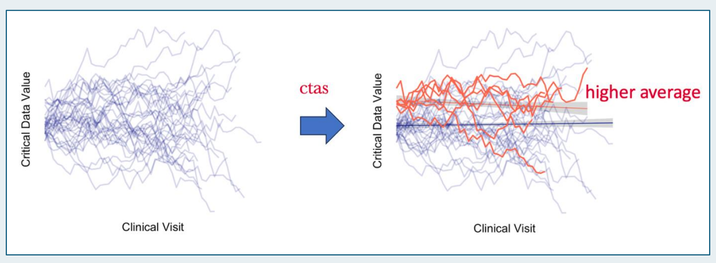
Clinical Trial Anomaly Spotter

ctas

Clinical Trial Anomaly Spotter

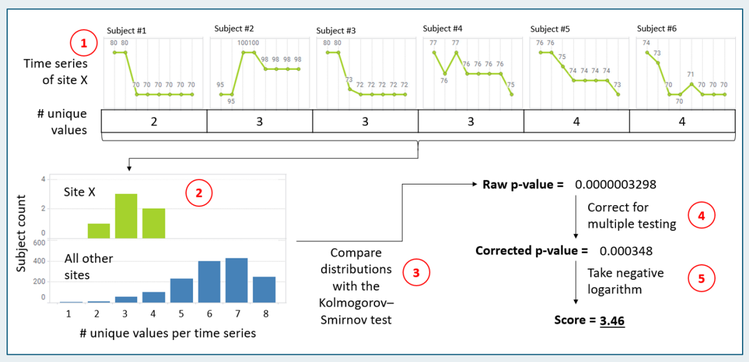
Collaborative Scientific Evaluation Within IMPALA

GitHub https://github.com/IMPALA-Consortium/ctas



- {ctas} identifies anomalous sets of time series (clinical sites) of continuous variables.

- "Unsupervised" tool which does not use pre-specified KRIs.
- Originally developed by Bayer
- Code base shared with IMPALA for co-development in July 2023



{ctas} generates summary metrics for each time series and looks for sites with anomalous summary metric distributions.

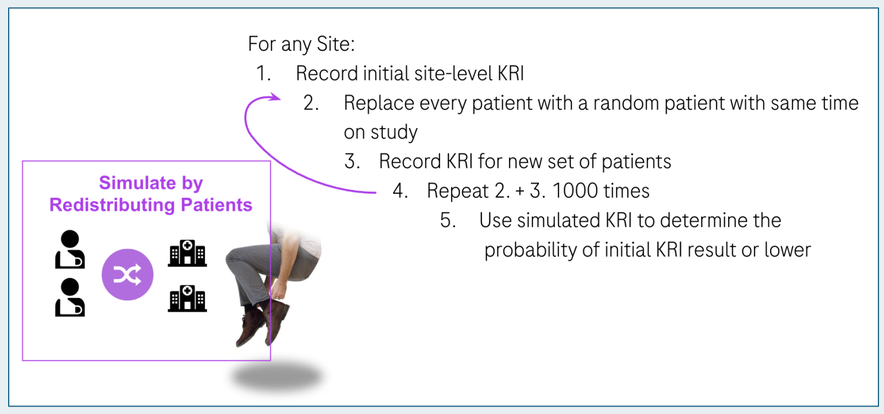
Event Reporting Probabilities

simaerep

Collaborative Evaluation Within IMPALA
https://doi.org/10.1007/s43441-024-00631-8

GitHub

- https://github.com/openpharma/simaerep
- https://github.com/IMPALA-Consortium/gsm.simaerep



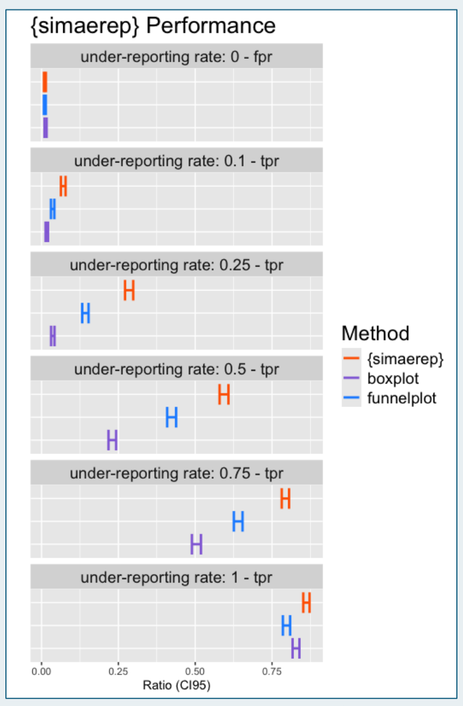
{simaerep} uses a non-parametric bootstrapping algorithm to calculate individual site-level event reporting probabilities. Typical quality relevant events e.g. Adverse Events, Protocol Deviations, … that are tracked as KRI throughout a study.

{simaerep} outperformes other KRI flagging methods.

Alternative Flagging Methods:
boxplot: uses KRI boxplot statistics

funnel plot: uses normal approximations of nominator denominator ratios.

To test performance a compliant portfolio was generated using flexible event reporting rates that adapt to the time patients spent on study. Then a fixed ratio of events was removed from each site and the relevant flagging method was applied.



True positive rate (tpr), false positive rate (fpr)

Good Statistical Monitoring

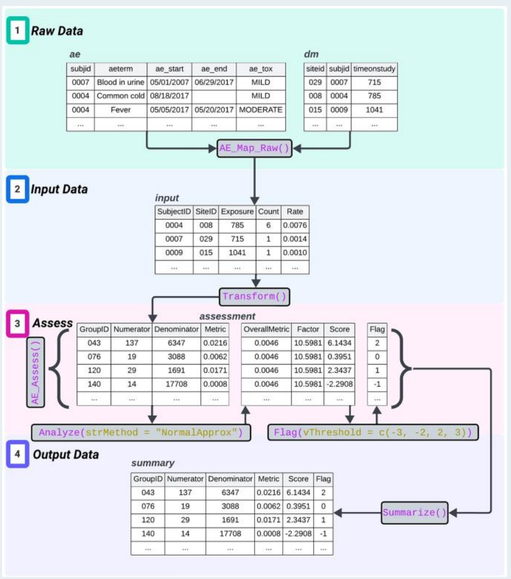
gsm

SCIENCE https://doi.org/10.1007/s43441-024-00651-4

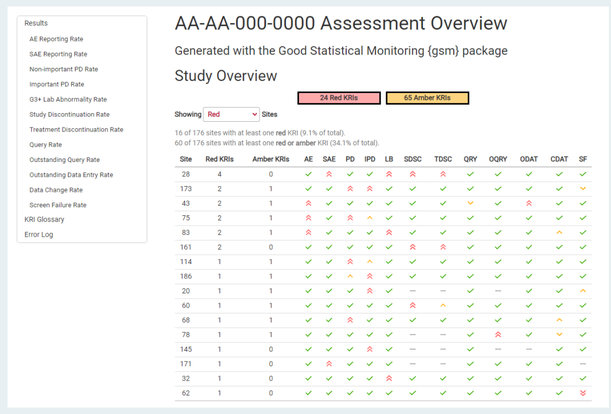
GitHub https://github.com/Gilead-BioStats/gsm.core

End to End RBQM Framework
- Mapping
- Processing
- Reporting

Originally developed by Gilead



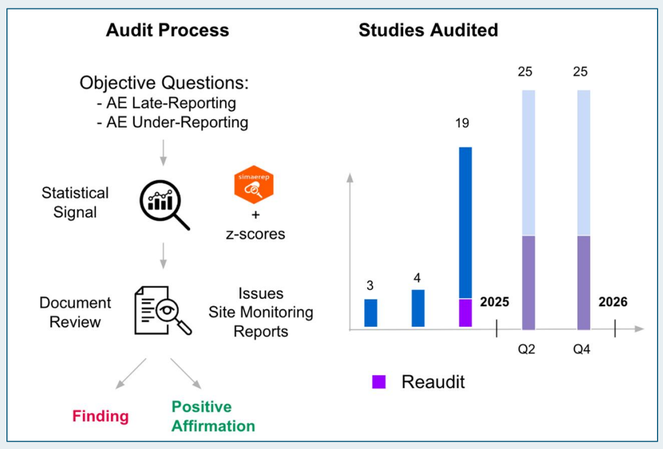
The {gsm} packages offers specialized configurable functions for the mapping, processing and quality reporting of clinical trial data. It supports the integration of modules such as {gsm.simaerep}.



RAPID Real-time Audit Package Informed by Data

RAPID audits follow a data-driven approach to answer specific objective quality questions. Instead of following a sample-based approach they can target an entire study or portfolio.

- Maintain Industry Standard (e.g Audit Report)
- Pre-Defined Methodology
- Based on Data Analytics
- High Coverage
- Minimal Preparation and Execution Time



Outlook

- RBQMverse metapackage suite similar to pharmaverse (metapackage for data submission)
- Continued development of existing packages
- Explore new packages and potential Gen-AI use cases
- Increase Inter-Operability

Contact

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