

Visualization of risk indicators using Shiny App

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Dermatology
beyond the skin



What is “Risk-Based Monitoring”?

RBM is an **adaptive approach** to clinical trial monitoring that **directs monitoring focus and activities** to the evolving areas of greatest risk which have the most potential to impact **patient safety and data quality**.

Promotes risk mitigation and early issue detection

Takes a proactive approach through Central and Remote Monitoring

Leverages technology and a risk-based approach

Focuses On-Site monitoring on the risks to critical data and processes

Guidance for Industry

Oversight of Clinical Investigations —
A Risk-Based Approach to Monitoring

 EUROPEAN MEDICINES AGENCY SCIENCE MEDICINES HEALTH	
1	4 August 2011
2	EMA/ICH/GCP/000000/2011
3	Consultation and Inspection
4	Reflection paper on risk based quality management in clinical trials
5	Draft
6	Draft Agreed by the CTG ¹ for release for consultation
7	31 May 2011
8	Draft Adopted by the GCP Inspectors Working Group for consultation
9	14 June 2011
10	End of Consultation (Deadline for Comments)
11	15 February 2012
12	Comments should be provided using this template . The completed comments form should be sent to GCP@ema.europa.eu

E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1)
Guidance for Industry

Since the development of the ICH GCP Guideline, the scale, complexity, and cost of clinical trials have increased. Evolutions in technology and risk management processes offer new opportunities to increase efficiency and focus on relevant activities. When the original ICH E6(R1) text was prepared, clinical trials were performed in a largely paper-based process. Advances in use of electronic data recording and reporting facilitate implementation of other approaches. For example, centralized monitoring can now offer a greater advantage, to a broader range of trials than is suggested in the original text. Therefore, this guideline has been amended to encourage implementation of improved and more efficient approaches to

Centralized monitoring goals

- Recommendations from FDA



Augment on-site monitoring by performing monitoring activities that can only be accomplished using centralized processes (e.g., statistical analyses to identify data trends not easily detected by on-site monitoring)



Target on-site monitoring by identifying higher risk clinical sites (e.g., sites with data anomalies or a higher frequency of errors, protocol violations, or dropouts relative to other sites)



Conduct aggregate statistical analyses of study data to identify sites that are outliers relative to others and to evaluate individual subject data for plausibility and completeness



Conduct analyses of site characteristics (e.g., high screen failure rates, eligibility violations, and delays in reporting data), and clinical data to identify trial sites with characteristics correlated with poor performance or noncompliance

LEO standard risk indicator library

Risk Category		Risk indicator label	Description
Safety	Risk Category	Risk indicator label	Description
	Data Quality	EDC Visit-to-Entry Cycle Time	Average cycle time from patient visit to EDC Entry
		Auto-Query Rate	Rate of auto-queries generated per form submitted
	Data Quality	EDC Query Response Cycle Time	Average cycle time from EDC query issued until site response
	Enrolment & Retention	Early Termination Rate	Rate of early-terminated patients per patient day
		Screen Failure Rate	Proportion of screen-failed patients to total screened patients

Analysis of risk indicators

- RBM dashboards from EDC vendors are typically based only on operational metrics
- Some vendors tend to run black box analysis of data provided by sponsor

We developed a RI App to run the analysis that fits the collected data best by controlling self-chosen thresholds and analysis methods

Analysis of 'rates'

- Negative Binomial model is used to find 2.5%, 5%, 95% and 97.5% quantiles of residuals to highlight the most extreme sites deviating from rest.

Analysis of 'proportions'

- Logistic regression model is used to find 2.5%, 5%, 95% and 97.5% quantiles of residuals

Analysis of 'averages'

- Linear regression (with possible data transformation) model is to find 2.5%, 5%, 95% and 97.5% quantiles of residuals



Visualizing risk evolution by site and country based on multiple risk indicators



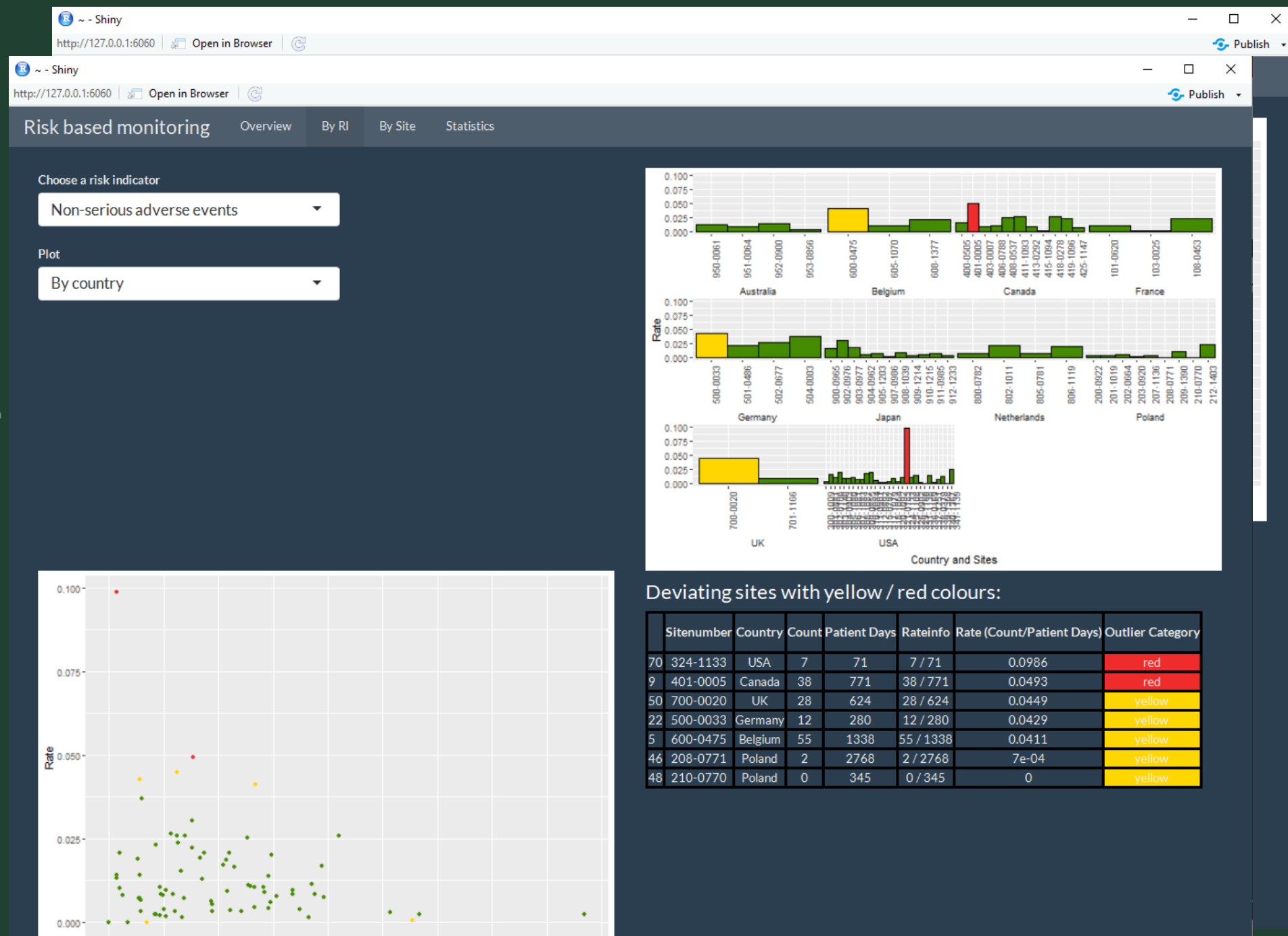
R - Shiny

http://127.0.0.1:6060 | Open in Browser

Risk based monitoring | Overview | By RI | By Site | Statistics

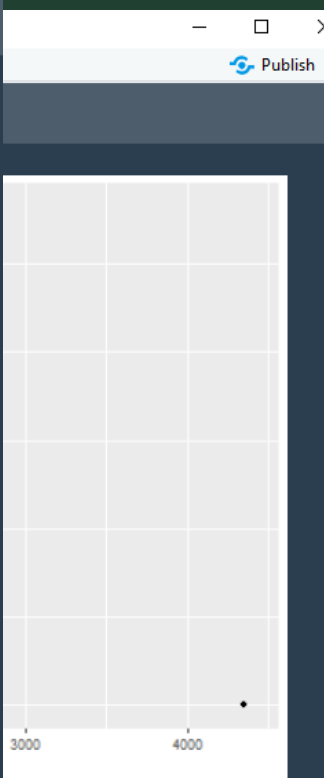
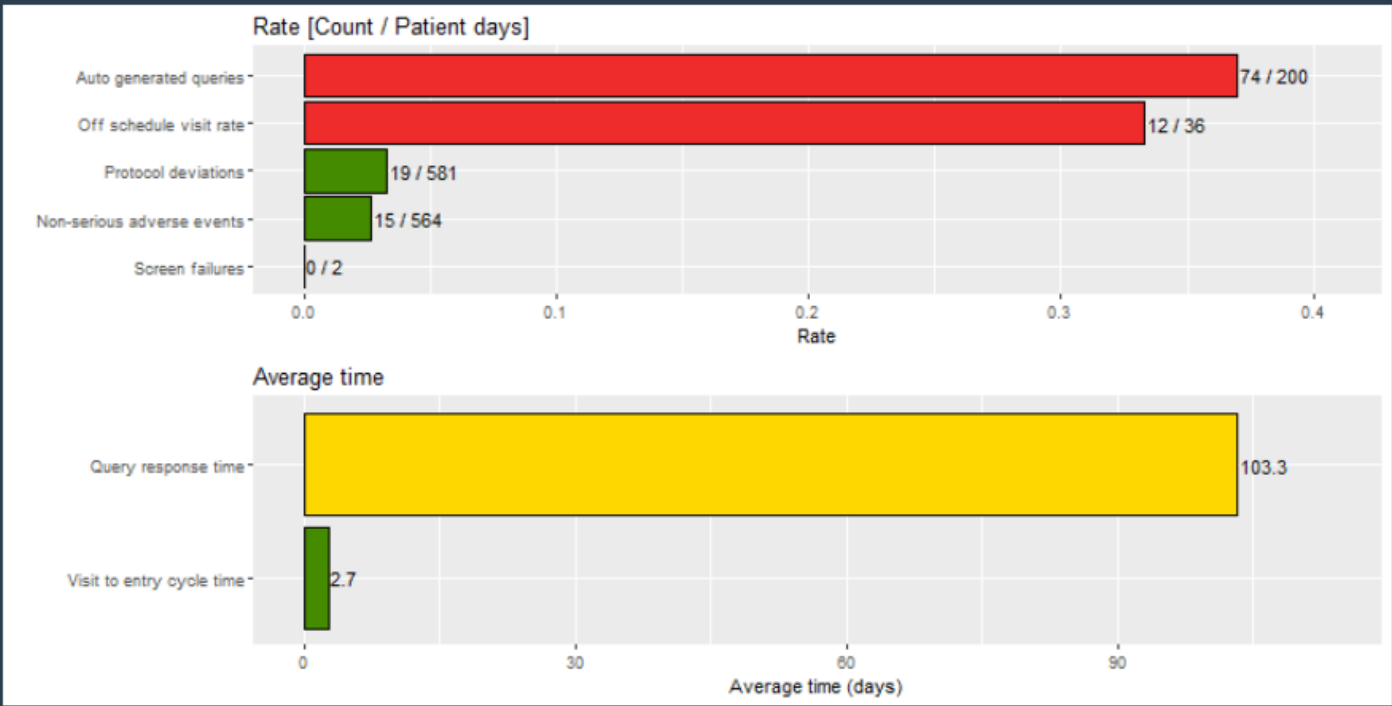
	Country	Sitenumber	Auto generated queries	Non-serious adverse events	Off schedule visit rate	Protocol deviations	Query response time	Screen failures	Visit to entry cycle time
1	Australia	950-0061	green	green	green	green	green	green	green
2	Australia	951-0064	green	green	green	green	green	green	green
3	Australia	952-0900	green	green	green	green	yellow	green	green
4	Australia	953-0856	green	green	green	green	green	green	green
5	Belgium	600-0475	green	yellow	green	green	green	green	green
6	Belgium	605-1070	green	green	green	yellow	green	green	green
7	Belgium	608-1377	green	green	green	green	NA	green	green
8	Canada	400-0505	green	green	green	green	green	green	green
9	Canada	401-0005	green	red	green	green	green	green	green
10	Canada	403-0007	green	green	green	green	green	green	green
11	Canada	406-0788	yellow	green	green	green	green	green	green
12	Canada	408-0537	green	green	green	green	green	green	green
13	Canada	411-1093	green	green	green	green	green	green	green
14	Canada	413-0292	green	green	green	green	green	green	green
15	Canada	415-1094	green	green	green	red	green	green	green
16	Canada	418-0278	green	green	green	green	green	green	green
17	Canada	419-1096	green	green	green	green	green	green	red
18	Canada	425-1147	green	green	green	green	red	green	green
19	France	101-0620	green	green	green	yellow	NA	green	green
20	France	103-0025	green	green	green	green	red	green	green
21	France	108-0453	green	green	green	green	green	green	green
22	Germany	500-0033	green	yellow	green	green	green	green	green
23	Germany	501-0486	green	green	green	green	green	green	green
24	Germany	502-0677	red	green	red	green	yellow	green	green

Displaying results statistically and descriptively by site and country



Select site

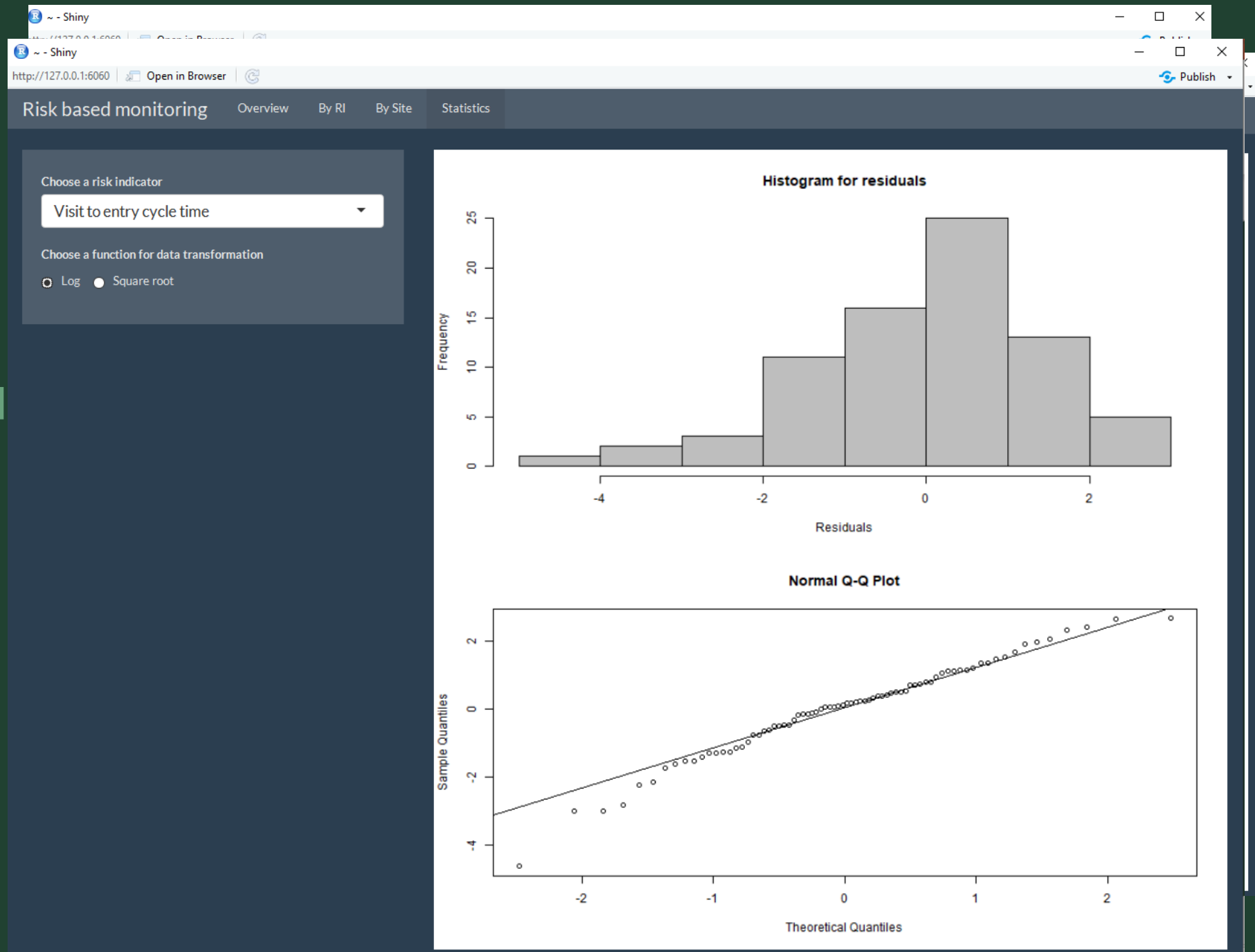
502-0677



it/Patient Days)						
						.0141
						.0071
						.0036
						.0034
						.0016
						.0015
3	952-0900	Australia	2	1458	2 / 1458	0.0014
36	911-0985	Japan	1	691	1 / 691	0.0014



Checking the assumptions behind the statistical analysis



Reporting of risk indicator evaluation with R Markdown

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Trial ID:

8 October 2019

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Overview of results

In the following, risk indicators (KRIs) are reported by sites and countries. For a given KRI it has been investigated whether a site is deviating from other sites. Outliers have been identified based on an alpha level of 5% and 10%. This has been highlighted with red and yellow colors, respectively. Sites that are not deviating from the rest of sites are highlighted with green color.

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Trial ID:

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	Country	Auto generated queries	Non-serious adverse events	Off schedule visit rate	Protocol deviations	Query response time	Screen failures	Visit to entry cycle time
101-0620	France	green	green	green	yellow		green	green
103-0025	France	green	green	green	green	red	green	green
108-0453	France	green	green	green	green	green	green	green
200-0922	Poland	green	green	green	green	green	green	yellow
201-1019	Poland	yellow	green	green	green	green	green	green
202-0664	Poland	green	green	green	green	green	green	green
203-0920	Poland	green	green	green	green	green	green	green
207-1136	Poland	green	green	green	green	green	green	green
208-0771	Poland	green	red	green	green	green	green	green
209-1390	Poland	green	green	green	green	green	green	green

