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Comparing Methods of Identifying High-Risk Sites

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Introduction

ICH E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1), published in March 2018, states:

> The sponsor should develop a systematic, prioritized, risk-based approach to monitoring clinical trials.

For years, our company, MSD, has used a home-grown "risk-based auditing" (RBA) tool to evaluate study site risk. The emergence of new, commercially available risk-based monitoring (RBM) tools led us to investigate whether one of those tools could improve study quality.

Two Risk Assessment Tools Compared

There is no conceptual distinction between our RBA tool and the commercial RBM tool we chose to evaluate. Both tools:

- Use site and subject trial data.
- Rank sites for risk based on statistical analysis of patterns and outliers in key risk indicators (KRIs).
- Identify the KRIs of concern and provide the supporting data.
- Employ graphical visualization.

There are, however, some differences between the tools:

- The RBA tool uses the same KRIs across studies (enabling comparisons across regions, studies and even therapeutic areas). While the RBM tool can be configured to use different KRIs for each study and even each site.
- The RBA tool uses deviation from mean to assess risk, while the RBM tool uses KRI threshold values.
- The RBA tool analyzes cumulative study-to-date data, while the RBM tool analyzes data by time period, e.g., month.
- The RBA tool gives the riskiest sites low scores, while the RBM tool gives the riskiest sites high scores.
- The KRIs are different in the two tools (see Figures 1 and 2).

Figure 1. RBA KRIs

Adverse Events per Subject
CRA Turnover Rate
Data Queries per Subject
Deviations per Subject
Enrollment Rate
Mean Time to Enter AE data
Number of Early Terminated Subjects
Number of Ongoing Subjects
Number of Randomized/Treated Subjects
Screen Failure Rate
Site Personnel Turnover Rate

The Pilot Study

In this pilot study of the two tools, we focused on the 10 riskiest sites each tool identified during the same vaccine study. We compared results from the tools each month over a six-month period.

Each month, the two tools agreed on two to four (20-40%) of the 10 highest risk sites but disagreed on the others. Of those sites that were identified as high risk by both tools, the KRIs driving the high risk score usually related to the same risk area, e.g., Protocol Deviation Ratio, Adverse Events per Subject, or Enrollment Count.

With both systems, the top-10 lists changed 10%-30% from month to month. RBM risk scores were more volatile than RBA scores, at least in part because RBM scores were calculated monthly, while RBA scores were calculated cumulatively. Monthly calculations are more likely to generate false positives, while cumulative RBA scores are more likely to miss recent trends.

The study team was already aware that some of these sites were high risk. For others, the two tools gave the first sign of potential issues.

In some cases, a small sample size might have contributed to a false-positive high-risk signal. In other cases, review by a clinical research associate (CRA) concluded that a high-risk signal was false. For example, eCRF data entry was slow at one site because a quality-control (QC) person reviewed all source data prior to eCRF entry. In other words, positive signals from an RBA/RBM tool should not be considered definitive. Nevertheless, high risk scores can indicate that further investigation is merited.

Figure 2. RBM KRIs in Pilot Study

Adverse Event Rate

Serious Adverse Event Rate

Enrollment Rate

Open Packages (RBM alert)

Open Workflows (RBM alert actions)

Adverse Event Count: By Subject by Site by Month

Adverse Event Count by Month

Adverse Event Ratio: Total

Average Days to Case Report Form Completion: Overall

Average Days to Case Report Form Completion by Month

Early Termination Date

Enrollment Count

Enrollment Start Date

Protocol Deviation Count by Month

Total Important Protocol Deviation Ratio

Protocol Deviation Ratio: Total Overall

Serious Adverse Event Count: By Month

Query Count: Open More Than 15 Days

Important Protocol Deviation Ratio: Informed Consent

Important Protocol Deviation Ratio: Prohibited Meds

Deviation Supplies Ratio: Site Study Month

Important Protocol Deviation Ratio: Trial Procedures

Important Protocol Deviation Ratio: Safety Reporting

Missed Samples by Month

Missed Sample Ratio

Important Protocol Deviation Ratio: Inclusion/Exclusion Criteria

Enrollment Rate Site Study Month

Because we implemented the RBM pilot after the vaccine study had already started, we were able to hypothesize what might have been driving monitoring behavior/visit frequency outside the monitoring plan. For example, we saw that the site with the most on-site visits had been inspected by FDA for another sponsor's trial and had received an FDA warning letter (FDA Form 483). This site was not exhibiting atypical risk in either the RBA or RBM system. Aside from the prescribed visits per the study monitoring plan, there were sites that had fewer or more than the expected number of monitoring visits. For these sites, we saw that CRAs had increased visit

frequency because of perceived risks that could have a higher likelihood of being chosen by health authorities for inspection. Our concern was with sites that had higher risk scores in one or both tools and had fewer visits than the prescribed by the monitoring plan. One of the pilot study's Clinical Quality Control managers held update meetings with the study CRAs to review risk scores for the higher risk score sites to learn why certain sites were monitored more or less frequently than expected. As noted previously, a high risk score does not necessarily mean there is an issue at a study site, but the reasons for the high risk score should be investigated.

Another Analysis

With certain types of studies, there might be useful measures that would not be found in an RBM library of KRIs. In our pilot study, we investigated the possibility of identifying site risks by looking at subject temperature measurement data. The study's protocol required that, if a subject's temperature was higher than a certain level — suggesting an immune response to a pre-existing infection — vaccination should be postponed. We asked two questions:

> Is the average recorded subject temperature at a site significantly lower or higher than at other sites? A positive answer would suggest a problem with the thermometer or its use.
>
> Compared to other sites, does a site have too many records just under the threshold temperature? A positive answer could indicate that a site was falsifying data so it could proceed with the vaccinations.

Average temperatures that are too high or low could indicate mis-calibration or misuse of thermometers. We did not find systemic temperature measurement problems at any sites. Figure 4 on the next page shows the temperature charts of the four sites with the biggest deviations in average temperature. Significance by t-test p-value, assuming normal distribution, flagged anomalous measurements (marked in red) at each of the four sites. These measurements appear to be aberrations affecting only a few subjects.

Figure 2 on the next page shows that subject temperatures in the study follow a normal distribution with minimal skew. There does not appear to be fitting at the limit.

Figure 3. Acronyms

CRA	Clinical Research Associate
QC	Quality Control
KRI	Key Risk Indicator
RBA	Risk-Based Auditing
RBM	Risk-Based Monitoring

Figure 4. Temperature Charts of The Four Sites with The Biggest Deviations in Average Temperature

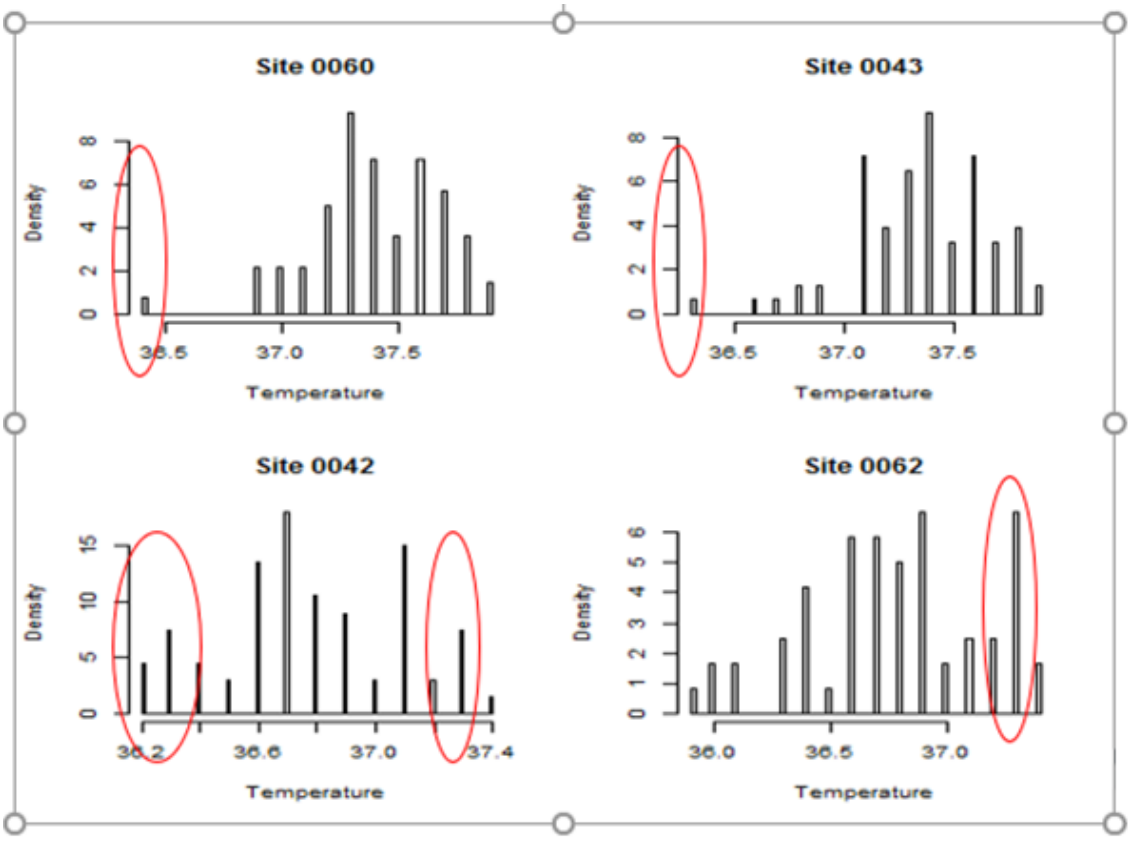
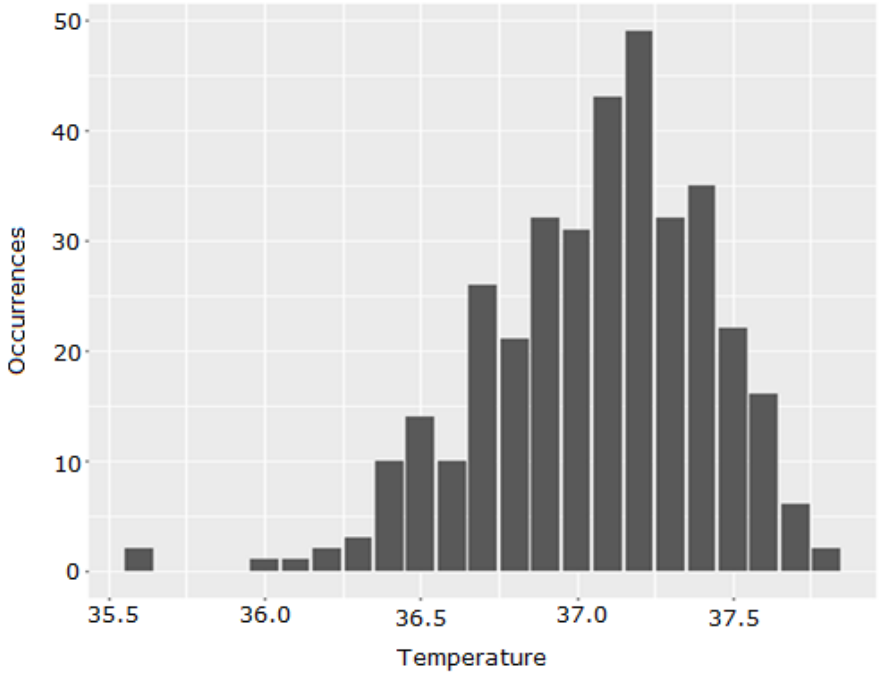


Figure 2. Distribution of Temperature Results by Sites



Conclusion

Based on our pilot study of the RBA and RBM tools, along with the analysis of subject temperatures, we reached the following conclusions:

- Both tools provided useful but not definitive risk information.
- The two tools identified different sites as high risk.
- If both tools identified the same site as high risk, the probability that that site was, in fact, high risk increased.
- Monthly analysis is more sensitive than cumulative analysis, but more prone to false positives due to small sample sizes.
- Neither tool obviated the need for risk assessment by the study team (CRA, clinical research manager, clinical quality manager, study manager, clinical data manager, and others), based on their experience and knowledge of the sites.

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