Statistical Models of Risk Flux Reveal Dynamics of RBM-Managed Clinical Trials

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an empirical review of Risk Based Monitoring

- Data: 100’s of risk metrics, rolled up into 10’s of risk indicators, summarized by a total site risk score (1-4) at each monthly assessment; 30+ studies available

- Question: does the fluctuation of total risk seen across a study simply represent some random, bounded-walk, or regression to the mean (RTM)?
  - or do increases in risk lead to a concomitant increase in risk-mitigating “downward” flux in excess of that expected by the random walk/RTM models?
closed loop trial management

1. Operational metrics from CTMS, EDC and other sources are pulled into RBM database for study risk assessment

2. Central monitors review dashboards

3. RBM Lead meets study team members to discuss actions

4. Site specific targeted actions and interventions are adopted

5. Actions are recorded in the issue management system

6. CRA reviews, acknowledges and implements actions

Fulfills regulatory requirement for auditable record of mitigations
calculation of risk indicators

Ultimate decision on how to adjust the intervention level is made by the RBM Lead and takes into account additional factors, such as the volume of patients, SDV/SDR backlog, general discomfort with the site, etc. The computer recommends, the expert decides.
intervention levels and adaptive monitoring

<table>
<thead>
<tr>
<th>Intervention Level</th>
<th>Action</th>
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<tbody>
<tr>
<td>VH</td>
<td>100% SDV, 3 RMV/quarter</td>
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<tr>
<td>H</td>
<td>90% SDV, 2 RMV/quarter</td>
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<tr>
<td>S</td>
<td>80% SDV, 2 RMV/quarter</td>
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<tr>
<td>L</td>
<td>70% SDV, 1 RMV/quarter</td>
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<tr>
<td>VL</td>
<td>60% SDV, 1 RMV/quarter</td>
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</table>

- VH: Very High
- H: High
- S: Significant
- L: Low
- VL: Very Low

**Timeline:**
- **Start**
  - VH
  - H
  - S
  - L
  - VL
  - Run, Assess, Adapt

- **Month 1**
  - VH
  - H
  - L
  - VL
  - Run, Assess, Adapt

- **Month 2**
  - VH
  - S
  - L
  - VL
  - Run, Assess, Adapt

- **Finish**
  - VH
  - S
  - L
  - VL

**Notes:**
- 100% SDV: Service Delivery Volume
- RMV: Reality Monitoring Volume
- Quarter: 3 months
trial lifetime – risk level
risk changes over time; RBM reacts to mitigate
1\textsuperscript{st}-order random walk

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total risk flux parameter estimates

Unconstrained

Asymmetrically Constrained

1st - order Markov model transition matrices

Regression to the Mean

Univariate

Symmetrically Constrained
total risk flux paths appear to follow unconstrained, predominantly first-order correlations
Total risk flux paths appear to follow unconstrained, predominantly first-order correlations.
risk-mitigating flux is larger than random-walk, and not consistent with RTM
operational covariates can affect estimated risk flux significantly; all exhibit varying risk mitigation

no effect on risk flux
so is RBM effective? (in what ways?)

- this analysis is entirely observational, with no “control” studies to compare against
  - currently gathering identical risk metrics/indicators for ongoing studies that are not under RBM
  - we propose an investigational study-within-study of RBM effectiveness wherein sites are randomized to RBM to allow a direct within-study comparison of risks, economic values, timelines, etc.
- the impact/flux of individual risk metrics/indicators is yet to be analyzed
- nonetheless, we provide the first industry-wide evidence that active RBM efforts mitigate risk with a downward flux in excess of that expected by chance alone, and inconsistent with mere RTM.
does monitoring visit compliance affect risk?
over/under-visit rate varies by study…

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*actual visit rate - expected visit rate*
… but has no discernible effect on risk mitigation
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higher order interactions provide decreasing signal