

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

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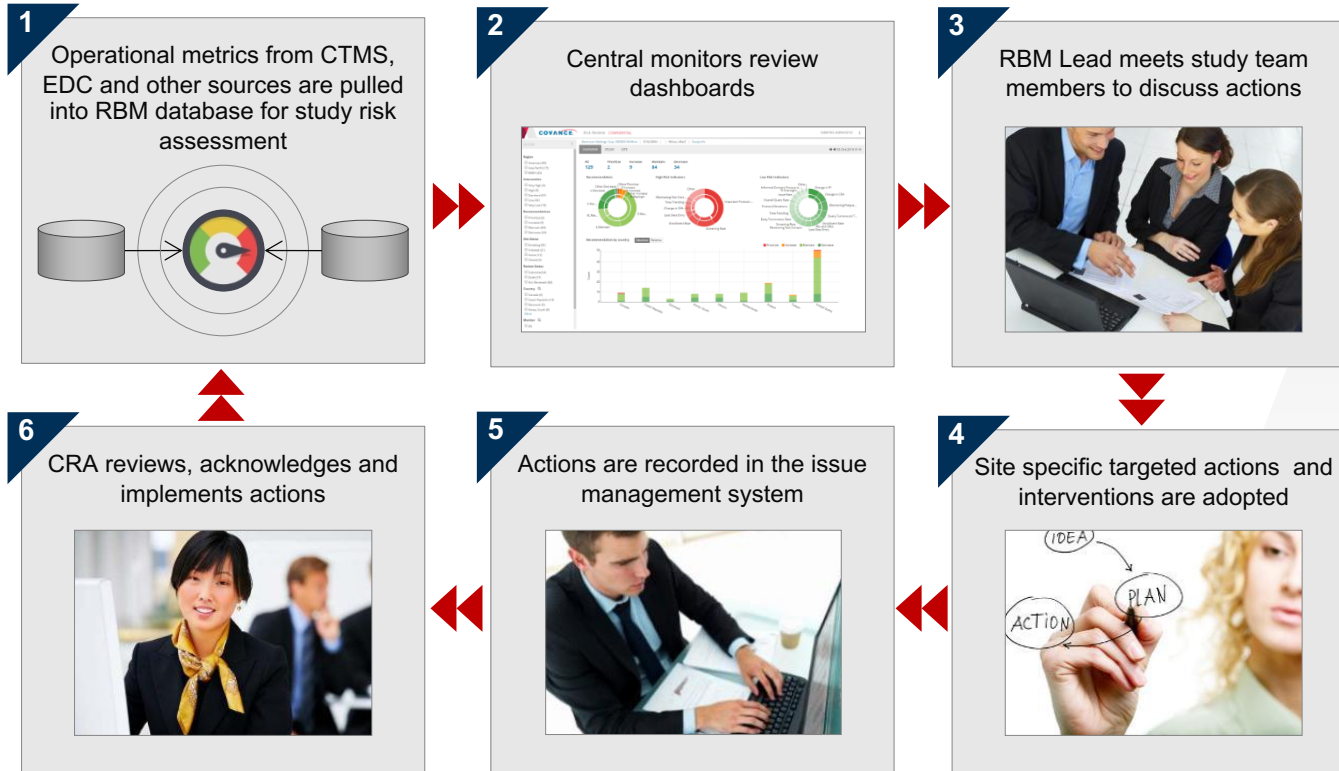
PhUSE US Connect 2019



an empirical review of Risk Based Monitoring

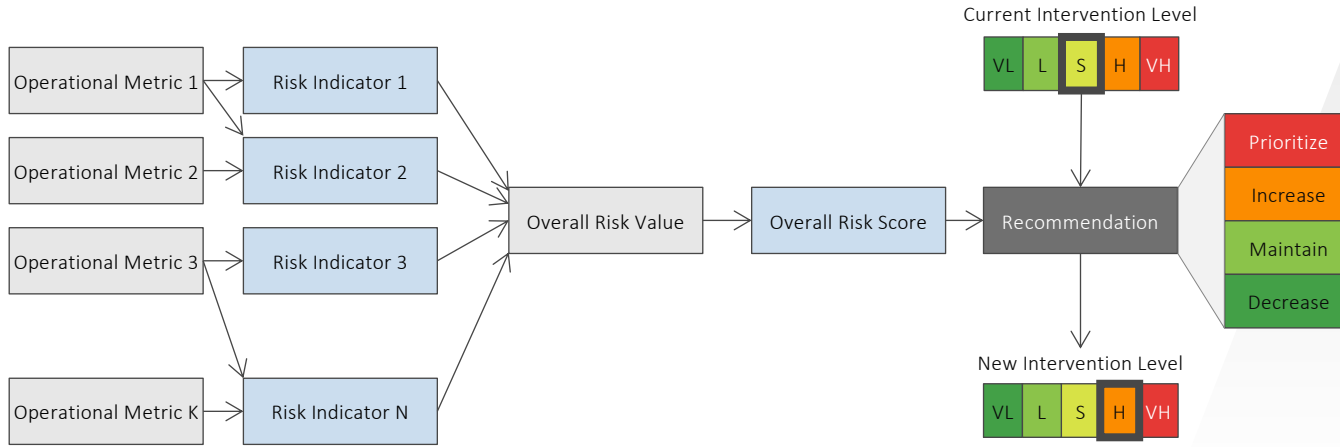
- ▶ Data: 100's of risk metrics, rolled up into 10's of risk indicators, summarized by a total site risk score (1-4) at each monthly assessment; 30+ studies available
- ▶ Question: does the fluctuation of total risk seen across a study simply represent some random, bounded-walk, or regression to the 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



Fulfills regulatory requirement for auditable record of mitigations

calculation of risk indicators

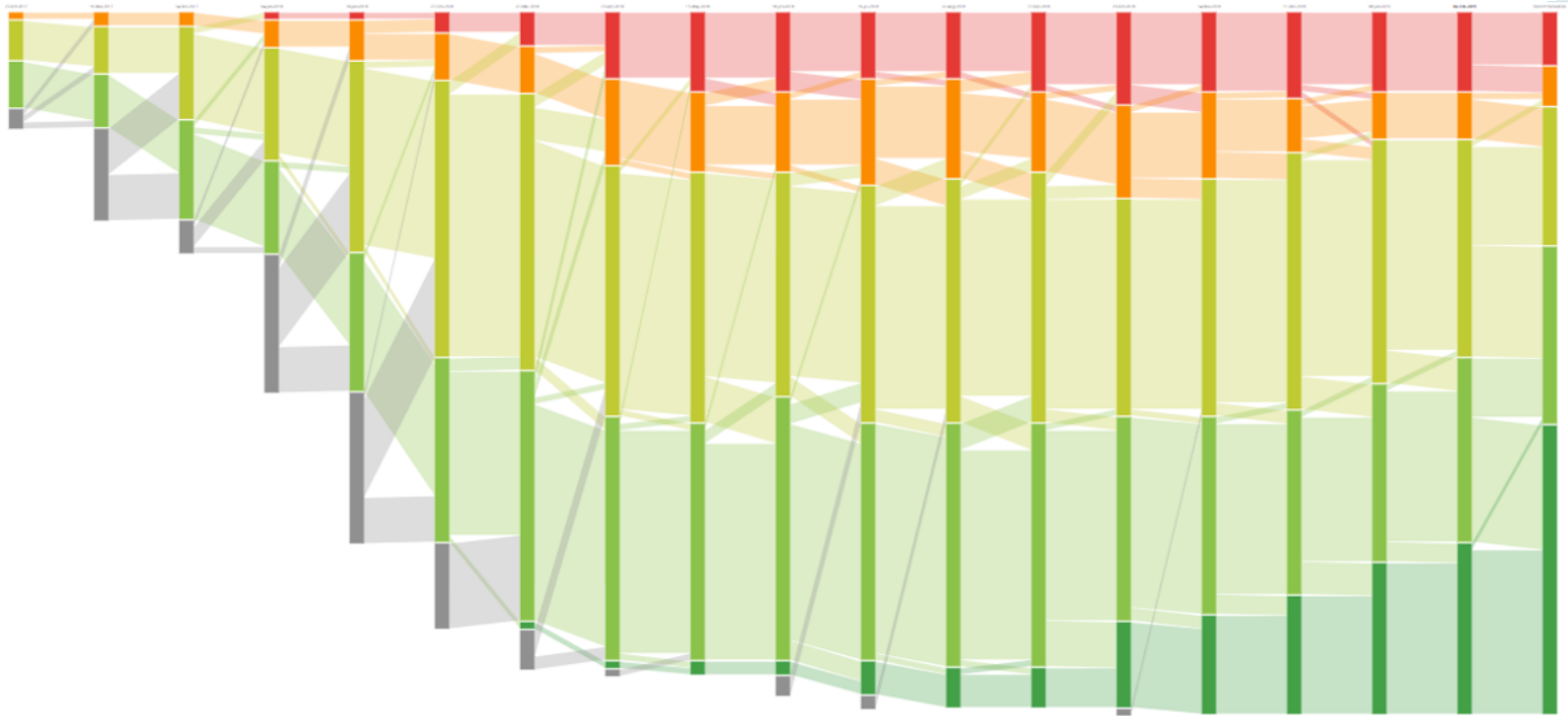


Ultimate decision on how to adjust the intervention level is made by the RBM Lead and takes into account additional factors, such as the volume of patients, SDV/SDR backlog, general discomfort with the site, etc. The computer recommends, the expert decides.

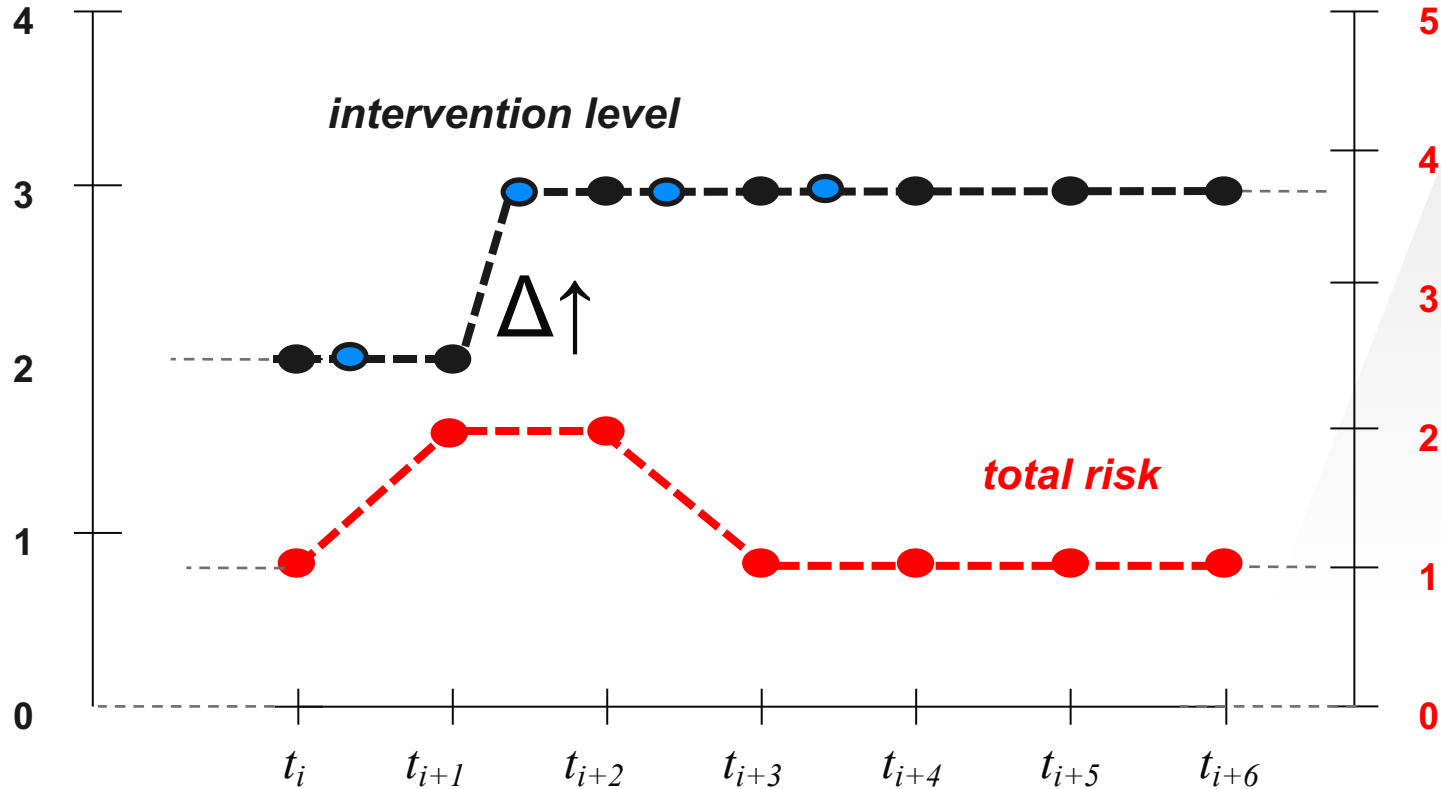
intervention levels and adaptive monitoring



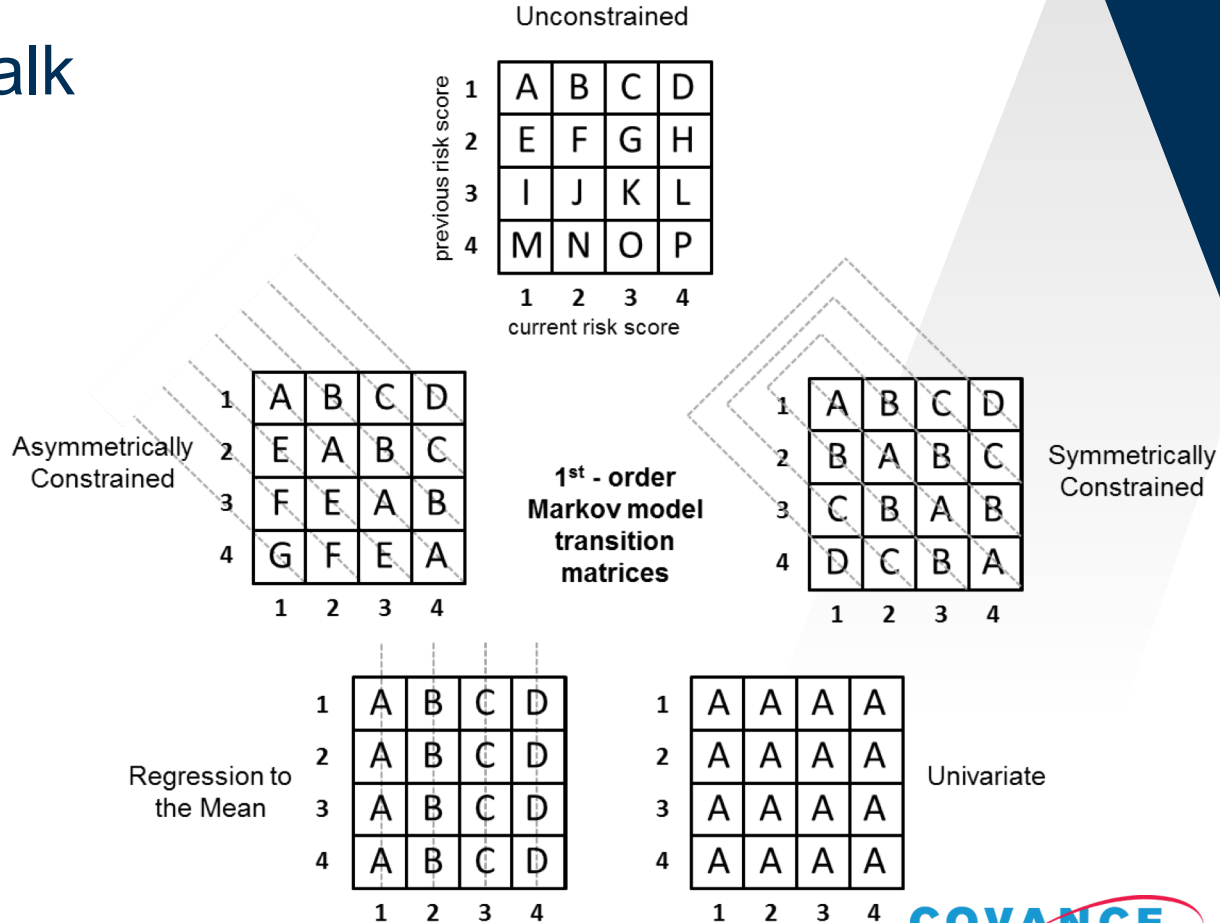
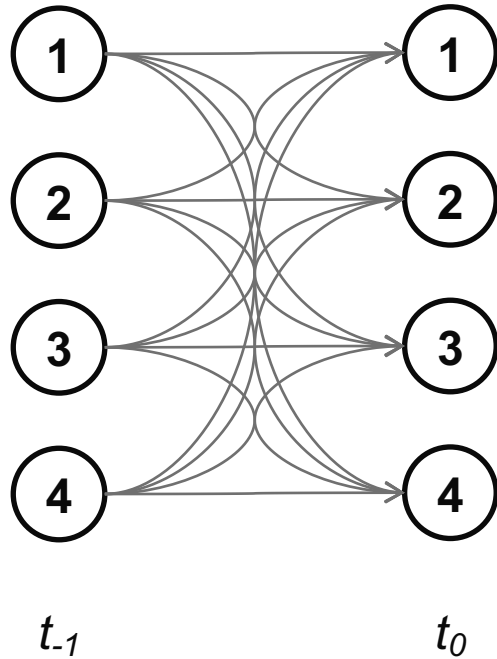
trial lifetime – risk level



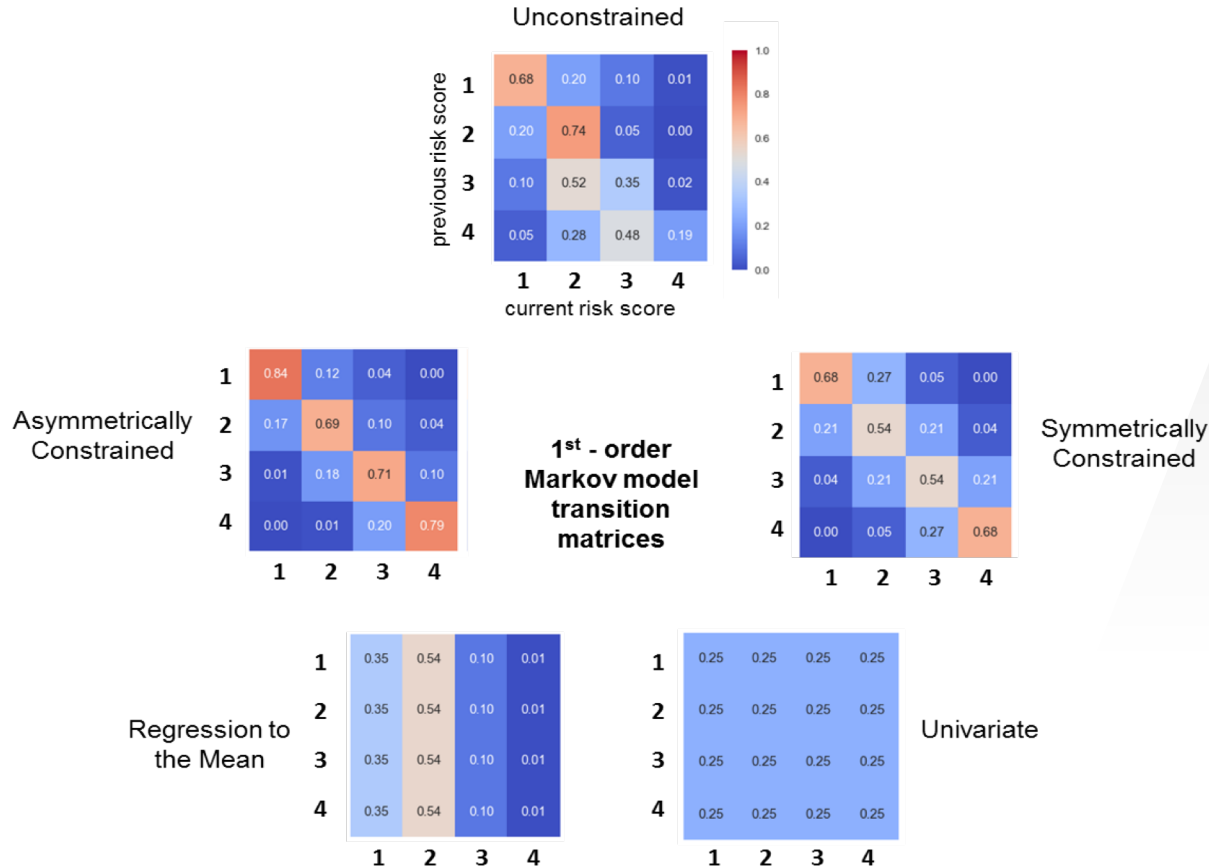
risk changes over time; RBM reacts to mitigate



1st-order random walk

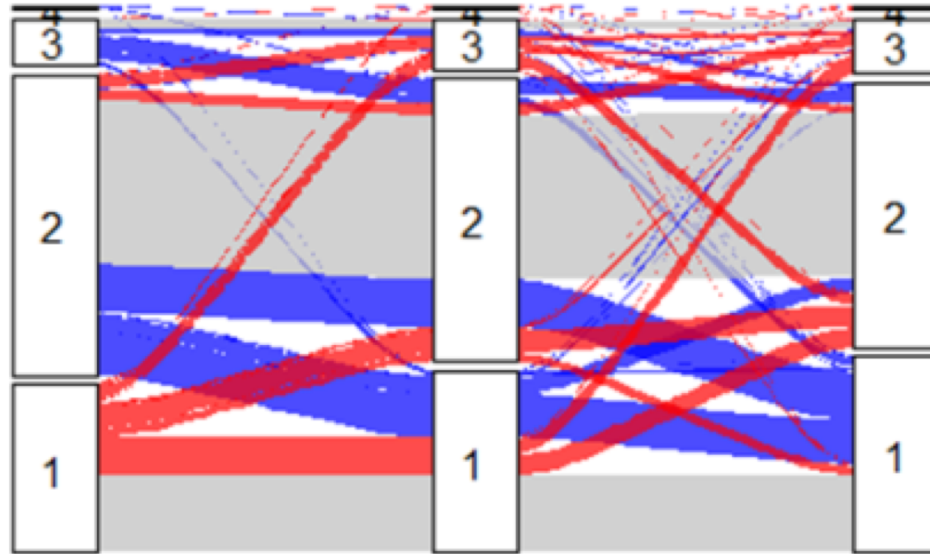


total risk flux parameter estimates

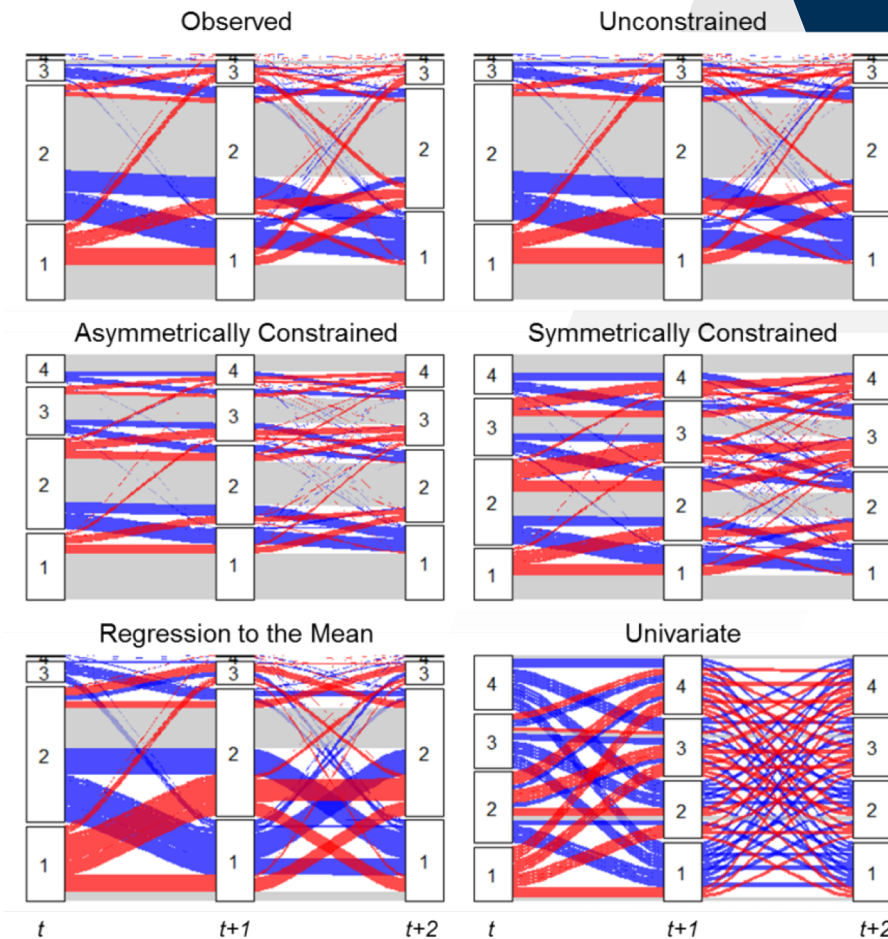
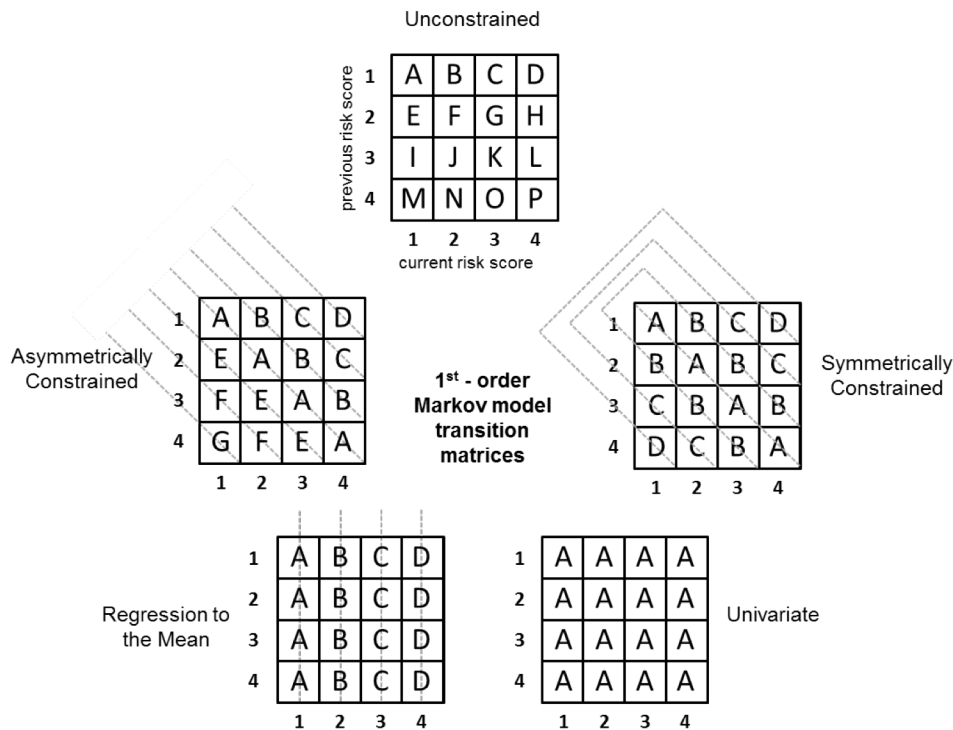


total risk flux paths appear to follow unconstrained, predominantly first-order correlations

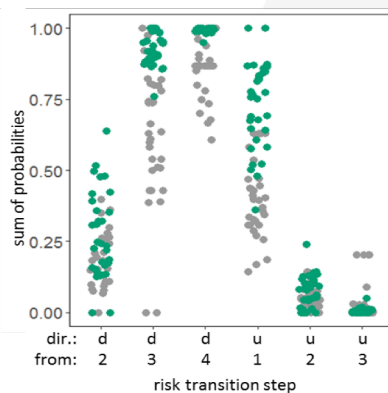
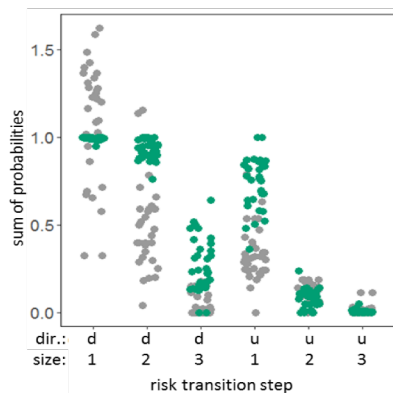
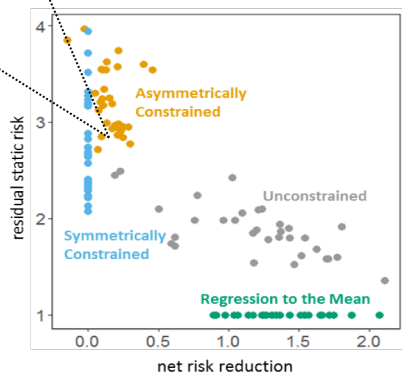
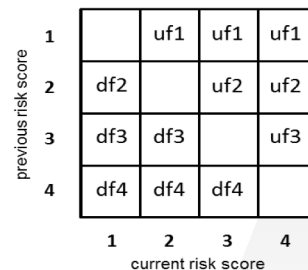
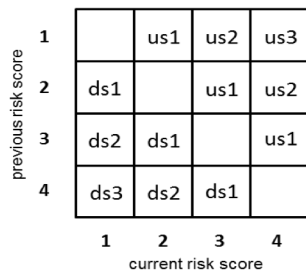
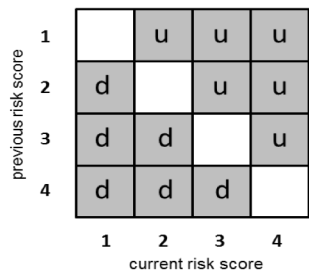
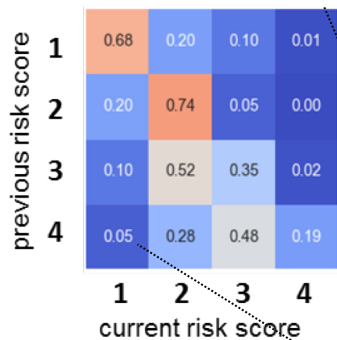
Observed



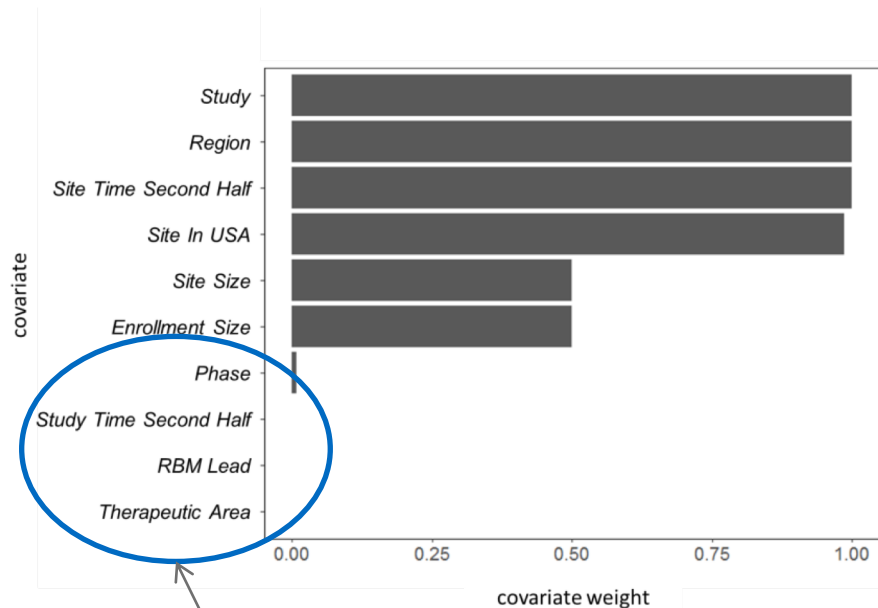
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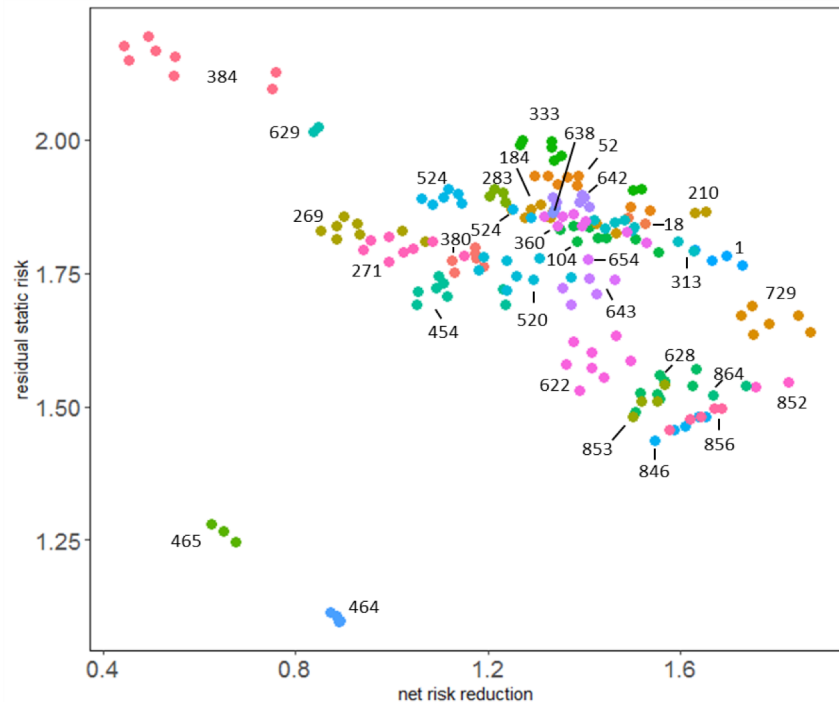
risk-mitigating flux is larger than random-walk, and not consistent with RTM



operational covariates can affect estimated risk flux significantly; all exhibit varying risk mitigation



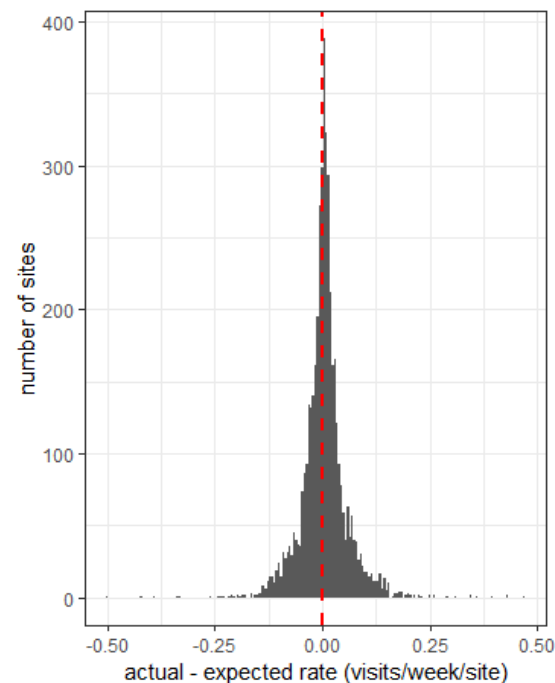
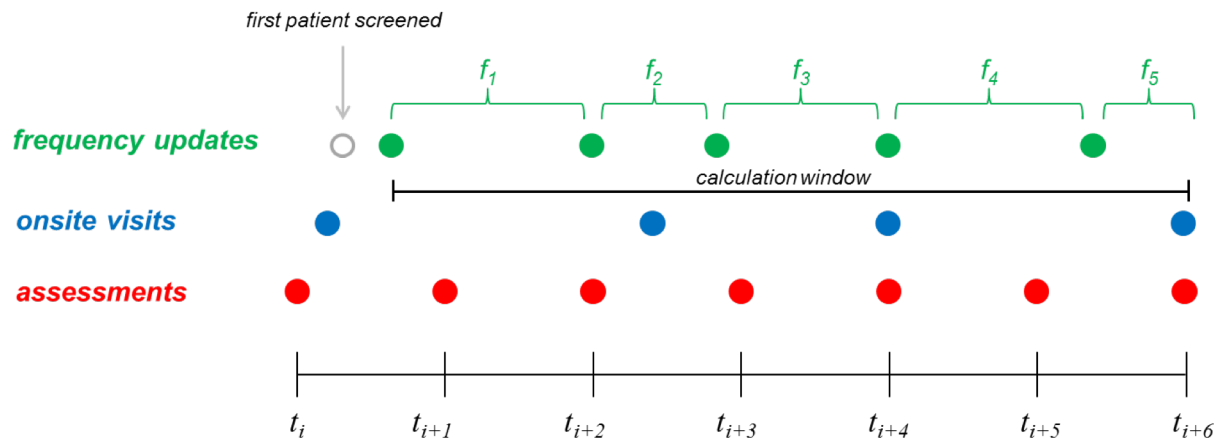
no effect on risk flux



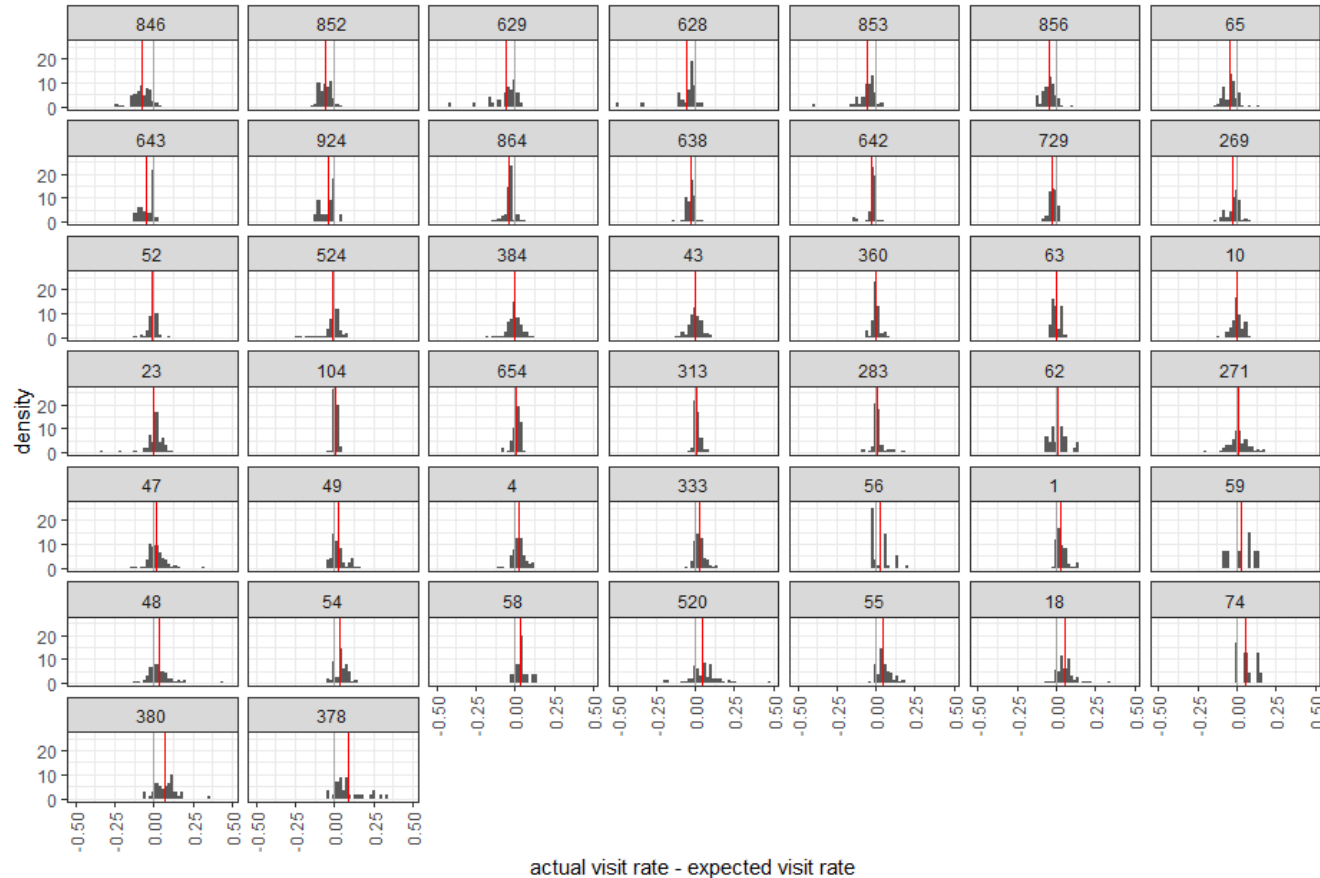
so is RBM effective? (in what ways?)

- ▶ 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.

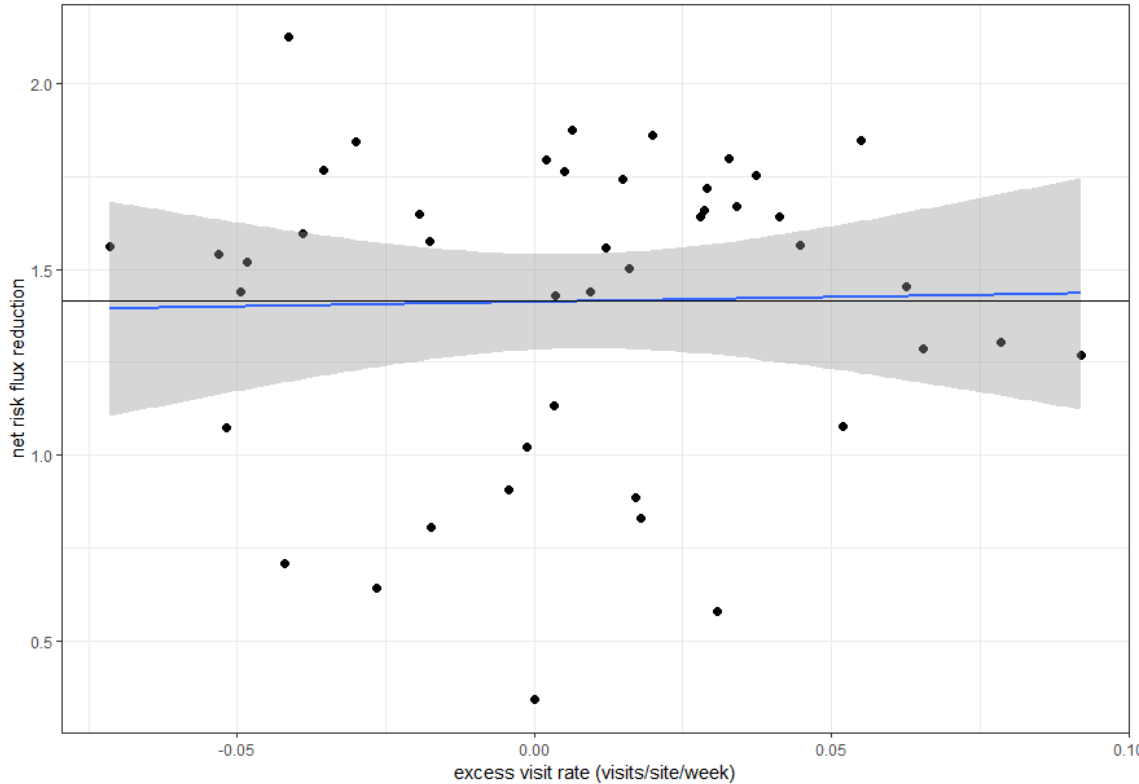
does monitoring visit compliance affect risk?



over/under-visit rate varies by study ...



... but has no discernible effect on risk mitigation





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higher order interactions provide decreasing signal

