Risk-Based Monitoring (RBM)

Eric S. Herbel
President
Integrated Clinical Systems, Inc.

JReview®

by Integrated Clinical Systems, Inc.

www.i-review.com

Topics

- Risk Based Monitoring – general information, approaches, etc.

- JReview – tightly integrated with
  OmniComm's TrialMaster database
  -> standard JReview capabilities
  -> but with immediate access to data when entered at site!

- JReview - Risk Based Monitoring
  and TrialMaster database
  -> access CRF and non-CRF data

Risk Based Monitoring (RBM)

- Traditional monitoring
  - 100% Source Data Verification
  - Error detection not in real time but at time of visit
  - Monitoring visits scheduled based on data volume or periodically
  - Reactive
  - Random and highly error-prone
  - Extensive resource utilization and cost

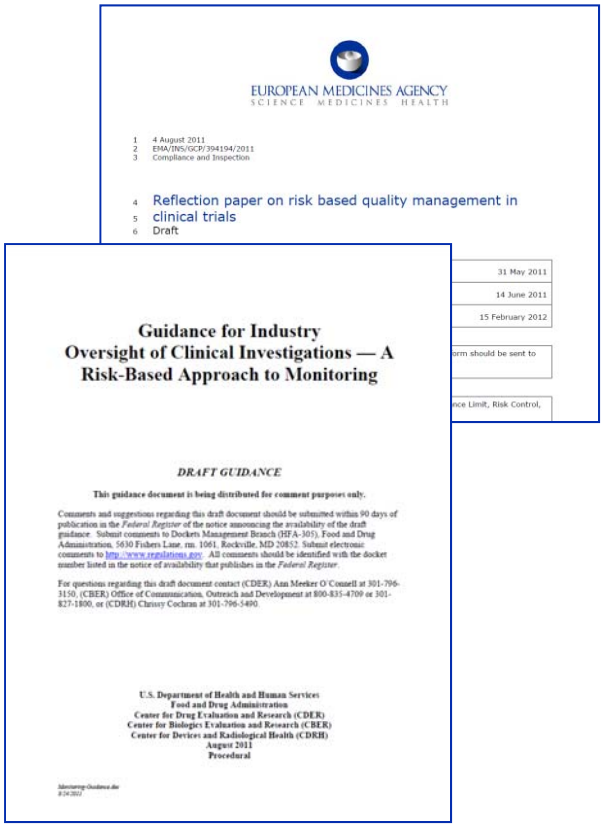
  ** 100% SDV doesn't guarantee error free results or data quality.

- Risk Based Monitoring
  - Centralized (data-driven) monitoring
  - Real-time error detection and continuous monitoring
  - Monitoring visits triggered by risk indicator thresholds
  - Proactive
  - QbD built-in via intelligent data tools and processes
  - Cost savings via targeted onsite monitoring

  *** Focus on critical data points

Evaluating Source Data Verification as a Quality Control Measure in Clinical Trials, Therapeutic Innovation & Regulatory Science (DIA) 2014, Vol 48(6) 671-680 (accepted 12-Sep-2014) - various Transcelerate authors

Risk Based Monitoring (RBM)



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

4 August 2011
EMA/INS/GCP/394194/2011
Compliance and Inspection

Reflection paper on risk based quality management in clinical trials
Draft

31 May 2011
14 June 2011
15 February 2012

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

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to http://www.regulations.gov. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Ann Meeker O'Connell at 301-796-3150, (CBER) Office of Communication, Outreach and Development at 800-835-4709 or 301-827-1800, or (CDRH) Chinny Cochran at 301-796-5490.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
August 2011
Procedural

TransCelerate BIOPHARMA INC.

TransCelerate BioPharma Launched at BioPharm America™ in Boston

Ten big pharma unite to accelerate development of new medicines

Business Wire

Press Release: EBD Group – Wed, Sep 19, 2012 6:59 PM EDT

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WASHINGTON & CARLSBAD, Calif. & BOSTON--(BUSINESS WIRE)--

The fifth annual BioPharm America™ conference kicked off in Boston, MA, today with the announcement of TransCelerate BioPharma, a new non-profit organization focused on accelerating the development of new medicines. TransCelerate's founding members are Abbott, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly and Company, GlaxoSmithKline, Johnson & Johnson, Pfizer, Genentech - a member of the Roche Group, and Sanofi.

Members aim "to work together across the global research and development community and share research and solutions that will simplify and accelerate the delivery of exciting new medicines for

rry Neil, MD, Partner at
ohnson & Johnson.

*…Members of TransCelerate have identified clinical study execution as the initiative's initial area of focus. Five projects have been selected by the group for funding and development, including: development of a shared user interface for investigator site portals, mutual recognition of study site qualification and training, **development of risk-based site monitoring approach and standards**, development of clinical data standards, and establishment of a comparator drug supply model.*

FDA | EUROPEAN MEDICINES AGENCY | Pmda

"By working together we can standardize and streamline many of the fundamental elements required for clinical trials. The efficiencies created can increase opportunities for innovation, potentially speed up the drug development process and lower the overall cost of bringing new medicines to patients."

Risk Based Monitoring (RBM)

Monitoring Recommendations (FDA/EMA/PMDA)

- Conduct a risk assessment to identify and evaluate risks to critical study data and processes
- Design a monitoring plan tailored to address important and likely risks identified during risk assessment
- Risk Metrics
- Site Performance Metrics:
  - Enrollment and randomization rates, screen fail rate/reason, dropout rate/reason, protocol violations, milestones, documentation/audit, monitoring visit attributes, …
- Site Quality Metrics:
  - Over/underreporting of lab measurements, AE rates, CTC grades, …
- Site Data Metrics:
  - eCRF entry, query rates against eCRFs, source data verification of eCRFs, missing pages, lag between visit and CRF data, lag between queries and responses
- Site Scores: Combining metrics for rapid (adaptive) assessment

Risk Based Monitoring
FDA Guidance

"There is a growing consensus that risk-based approaches to monitoring, such as focusing on the most critical data elements, are more likely to ensure subject protection and overall study quality"

- Conduct a Risk Assessment - identify critical data and processes:-
  - data that support primary and secondary endpoints
  - data critical to subject safety (SAEs, Discons)
  - processes for subject safety (medical consultation, extra visits due to clinical or lab findings)
  - processes for integrity of the science (blinding, adjudication events)

Risk Based Monitoring
Centralized versus On-Site

- Growing awareness that EDC systems as well as other technology tools (e-mail, webcasts, and online training modules) are making it possible to implement centralized monitoring methods that can enable decreased reliance on on-site monitoring.

Risk Based Monitoring
Centralized Monitoring Goals

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

Risk Based Monitoring
FDA Guidance

- As trials become larger, more complex, the use of EDC and other technology tools make centralized monitoring more effective in ensuring the quality and integrity of data.

- Even though the FDA is placing greater emphasis on centralized monitoring, their guidance is still consistent with ICH E6 in recognizing some amount of on-site monitoring will remain critically important in most cases (especially in the early stages of a study). SDV -> SDR

- Guidance suggests using centralized tools to augment and target onsite monitoring.

Risk Based Monitoring
Informal Survey of JReview Customers

- A number of pharma companies and CROs were starting in-house development of RBM applications
- Informal survey conducted with a number of JReview customers on their plans and thoughts of RBM – many of whom are also TransCelerate members
- A number of JReview customers thought that Risk Indicators should be a mixture of clinical study data based indicators (about 75%) and operational metrics based indicators (about 25%)
- Discussions and presentation of approach with TransCelerate team

Risk Based Monitoring
Sanofi's Quality Risk Indicators

QRIs	Description	Ranges / Weight	Low risk	Medium risk	High risk
Start of enrolment activity *	Delay in enrolment start (days)	Ranges	<30	30-59.99	>59.99
Enrolment cap	Site enrolment control (% of max enrolment)	Ranges	<75	75-99.99	>99.99
		Weight	6	25	100
Enrolment rate	Outlier site: high enroller (ranking)	Ranges	<95.01	95.01-98.99	>98.99
		Weight	6	25	100
Screening failure rate	Outlier site (different from a target P value)	Ranges	<1.31	1.31-2	>3
		Weight	2	4	9
Discontinuation rate	Outlier site (different from a target P value)	Ranges	<1.31	1.31-2	>3
		Weight	5	14	60
Protocol compliance	Deviations rate (number of deviations observed at site)	Ranges	<0.11	0.11-0.20	>0.20
		Weight	6	25	100
Safety	% of SAE over / under reporting (compared to the mean of sites)	Ranges	<90	90-95	>95
		Weight	6	25	100
Data entry	Delay in Data entry (days)	Ranges	<3.01	3.01-6	>6
		Weight	2	4	9
Queries	Query resolution turnaround (days)	Ranges	<0.01	0.01-5	>5
		Weight	2	4	9

** The QRI Start of enrolment activity is calculated up to "First Patient First Visit" date*

* Presentation at DMB Annual Meeting, Paris, Nov 2012

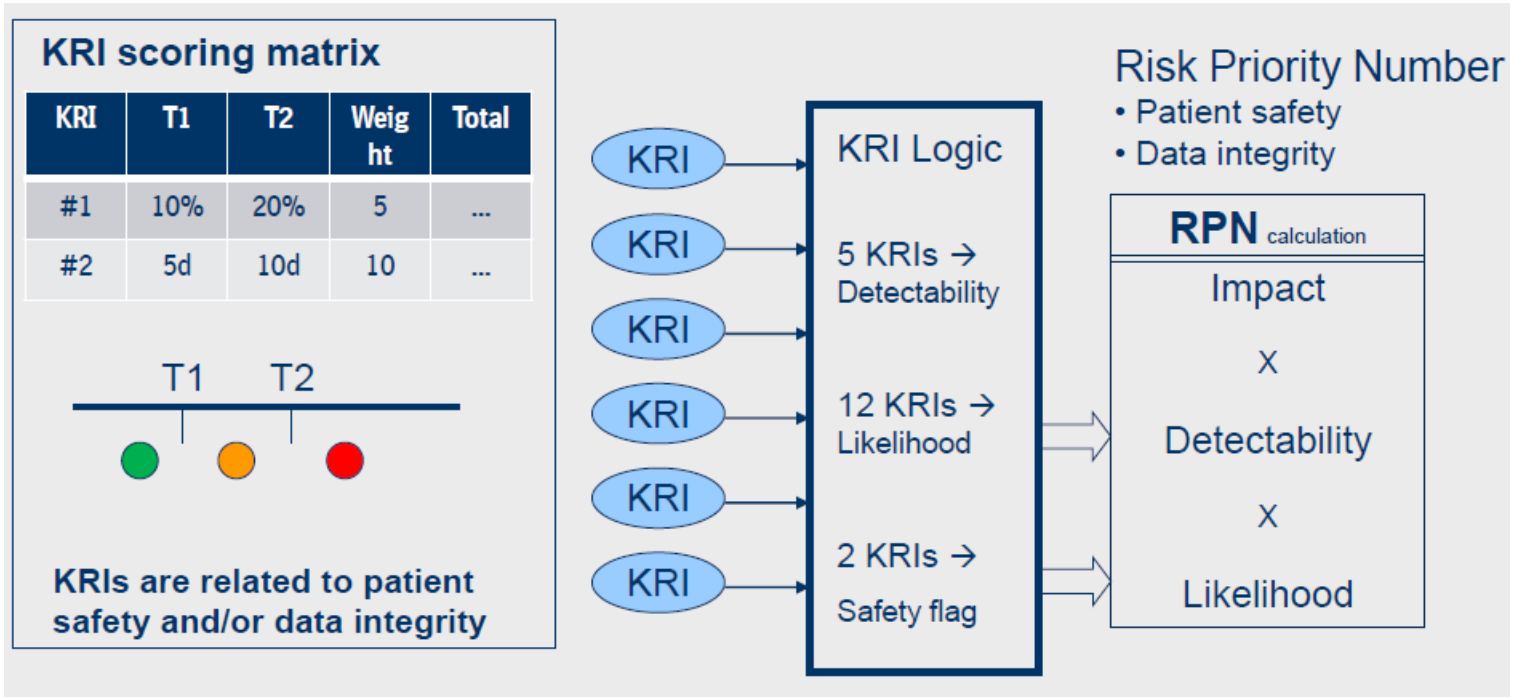
Risk Based Monitoring
Boehringer Ingelheim's Key Risk Indicators

KRI Description	**Actual visit date from IXRS compared with data entry in O*C (Planned visit date from O*C compared with data entry in O*C)**
Possible Root Cause	Site management
Risk Element	DETECTABILITY
KRI Scope	Per Site, Per Patient
Affected Trial Phase	Recruitment, Treatment

Risk Area (weight)	**Thresholds**			**Safety Flag**
				
Data Integrity Patient Safety (L)	maxOcDataEntryDelay (>= 0 .. < X days)	maxOcDataEntryDelay (>= X .. < Y days)	maxOcDataEntryDelay (>= Y days)	No

* Presentation at DMB Annual Meeting, Paris, Nov 2012

Risk Based Monitoring
Boehringer Ingelheim's Risk Priority Number



* Presentation at DMB Annual Meeting, Paris, Nov 2012

Risk Based Monitoring
Risk Types

- Focus on **Relative** – how sites are performing relative to all other sites – as Z Scores examples:-
  - Average number of AE's (over time, per subject) – 10% 'worst'?
  - Percentage of Screen Failures – 10% 'worst'?

- **Absolute**
  - Deaths
  - Drug Induced Liver Injury (DILI)
  - SAEs

- **Numeric Outliers**
  - Lab values > ULN * x
  - Systolic blood pressure > 150

- **Statistical Patterns, Distribution**, etc. – quality & fraud detection

Risk Based Monitoring
High Level Survey of Approaches

- RBM 'dashboards' from EDC vendors –
  typically based only on operational metrics

- Hosted RBM solutions – 'give us your data'
  black box analysis of data you provide
  -> report

- Hosted solutions – setup to receive or 'pull' selected data

- JReview – built into JReview (standard part of product)
  regular RBM analysis – against your data where it lives
  plus other sources (operational metrics, IVRS, etc.) – integrated data

  typically 75% of risk indicators from clinical data

JReview RBM

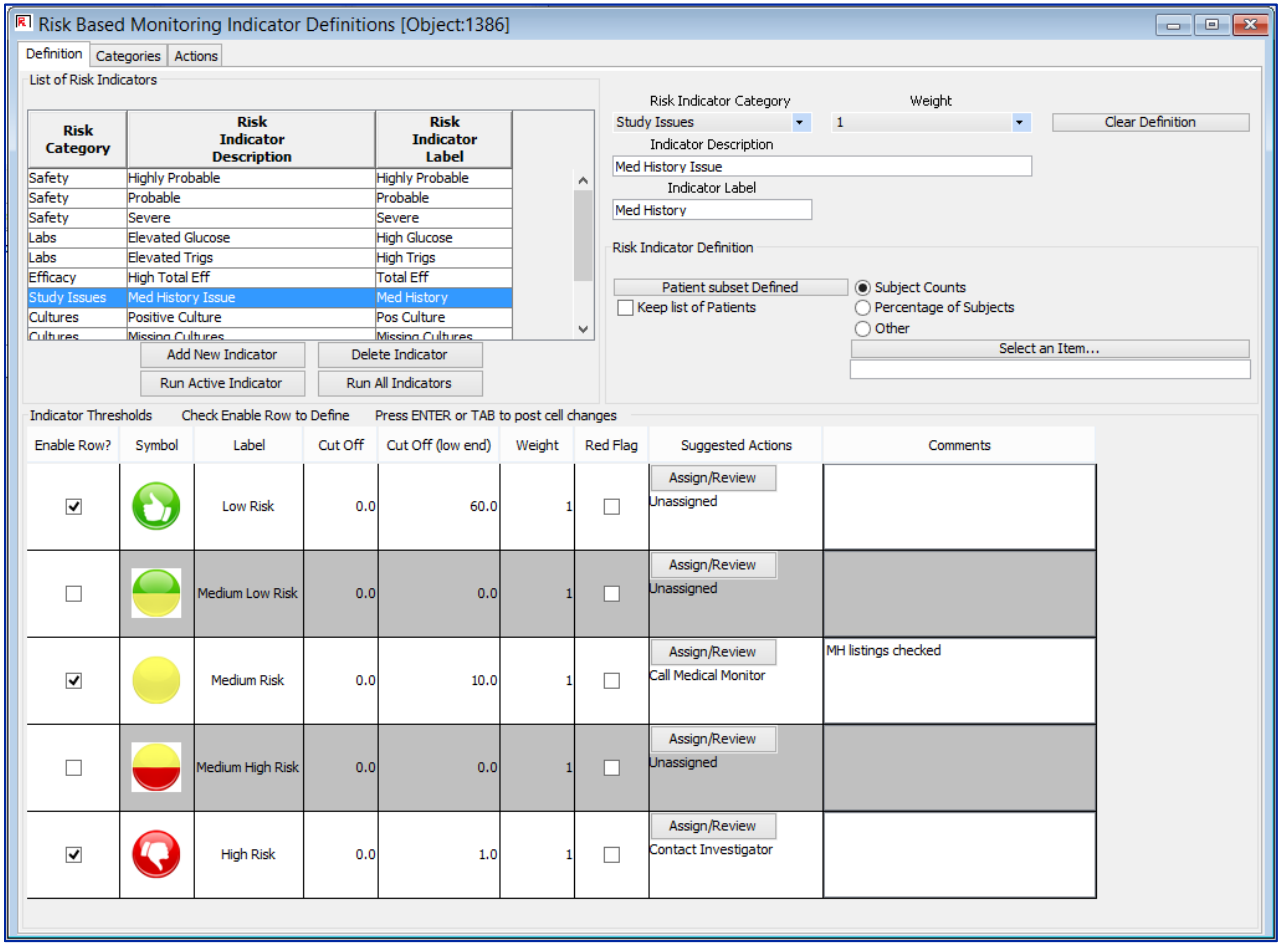
JReview - out of the box Analytics support for RBM

- Centralized monitoring teams can define key **risk categories,** risk indicators, **weighting factors** from all clinical & operational source data available, set thresholds, and specify suggested actions
- The JReview RBM Data Browser allows for the design of aggregated risk-based monitoring reports which can be scheduled in regular intervals to push monitoring activity plans out to site monitors/CRAs
- Periodic 'risk factor' batch execution
- A native iPad app provides easy access to key RBM metrics and suggested actions for CRAs and monitors in the field, followed by entry of Actions Taken
- Visualization of risk evolution by site/country/region based on multiple risk indicators & -categories

RBM Risk Indicator Definition

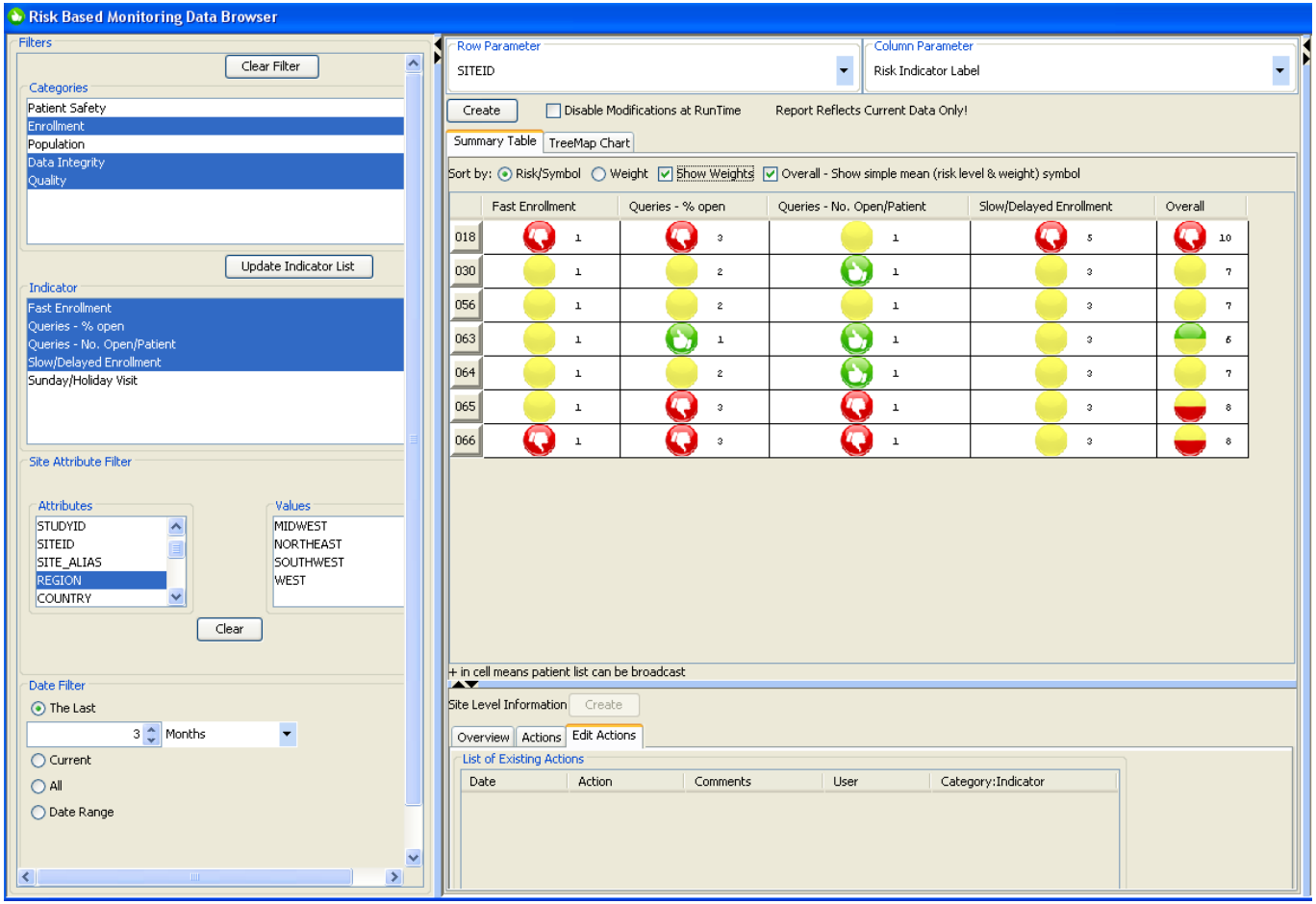
Key Risk Indicators, thresholds, & suggested actions

Definition within JReview with test run ⇨ scheduled periodic execution



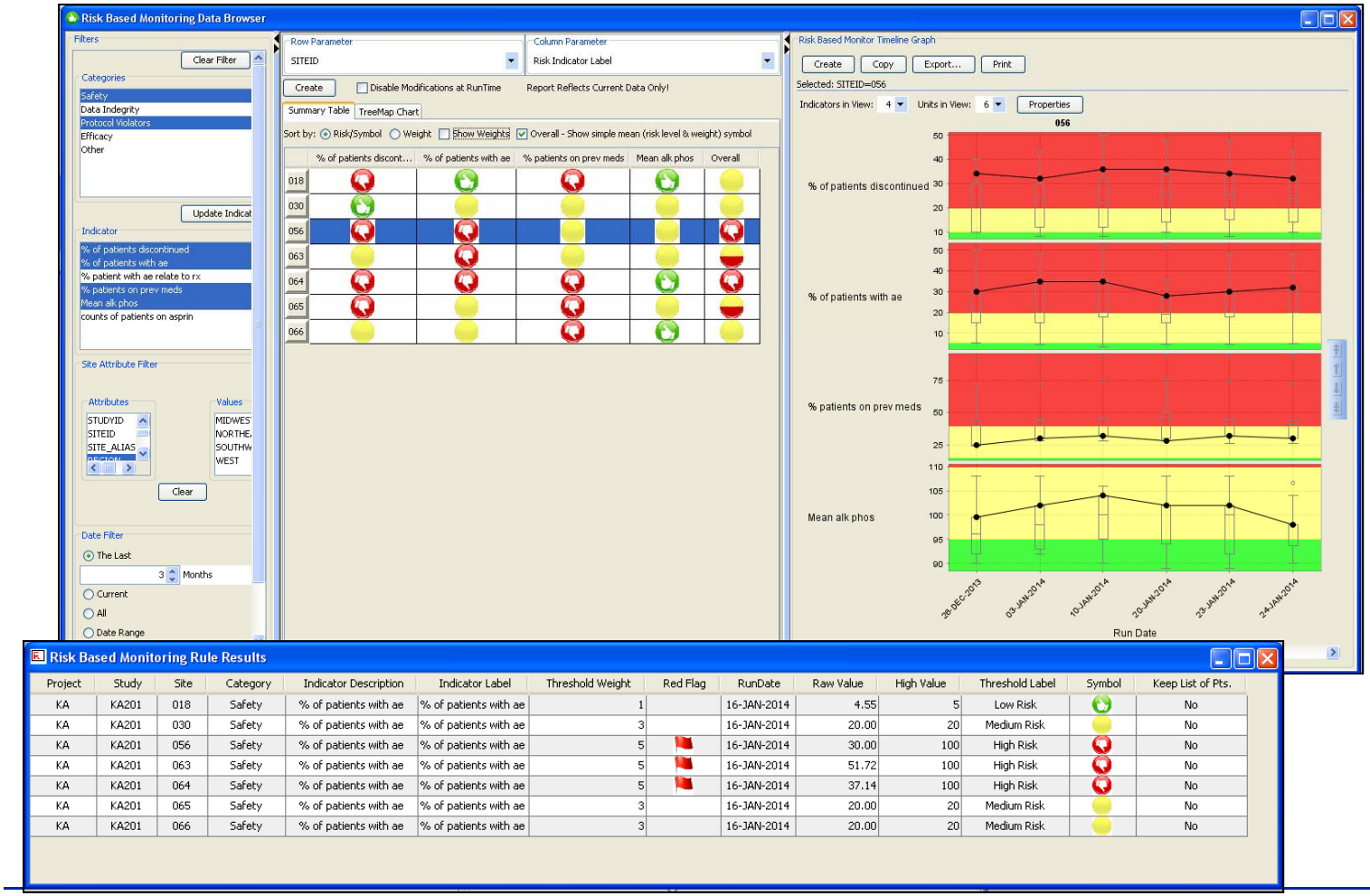
RBM Data Browser

Risk Indicator Result Visualization by site, country, or region - subset by attributes - interactively sort any columns for site ranking



Site Distribution Over Time

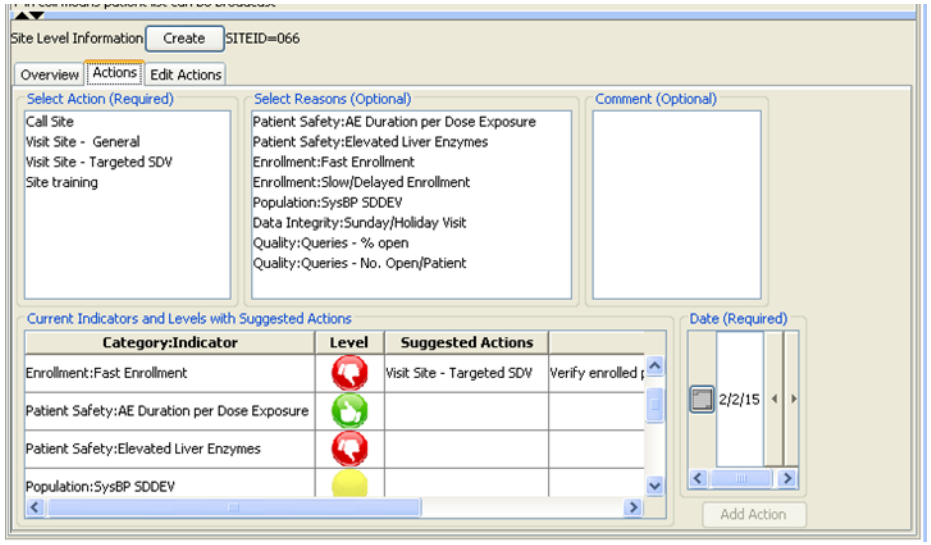
Site Distribution (Box Whiskers) over time – for selected site & RBM rule results table



Project	Study	Site	Category	Indicator Description	Indicator Label	Threshold Weight	Red Flag	RunDate	Raw Value	High Value	Threshold Label	Symbol	Keep List of Pts.
KA	KA201	018	Safety	% of patients with ae	% of patients with ae	1		16-JAN-2014	4.55	5	Low Risk		No
KA	KA201	030	Safety	% of patients with ae	% of patients with ae	3		16-JAN-2014	20.00	20	Medium Risk		No
KA	KA201	056	Safety	% of patients with ae	% of patients with ae	5		16-JAN-2014	30.00	100	High Risk		No
KA	KA201	063	Safety	% of patients with ae	% of patients with ae	5		16-JAN-2014	51.72	100	High Risk		No
KA	KA201	064	Safety	% of patients with ae	% of patients with ae	5		16-JAN-2014	37.14	100	High Risk		No
KA	KA201	065	Safety	% of patients with ae	% of patients with ae	3		16-JAN-2014	20.00	20	Medium Risk		No
KA	KA201	066	Safety	% of patients with ae	% of patients with ae	3		16-JAN-2014	20.00	20	Medium Risk		No

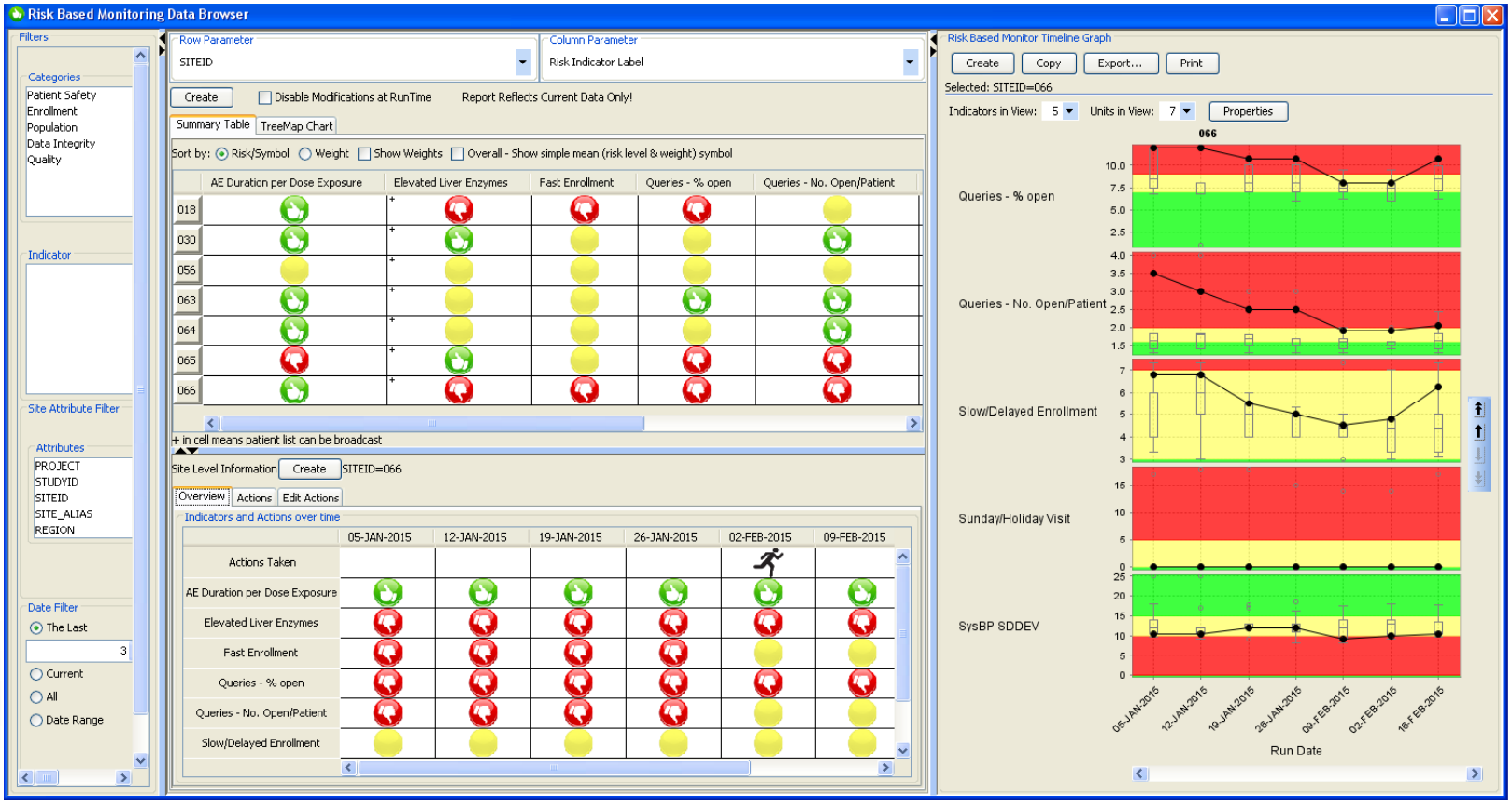
JReview RBM
Suggested Actions -> Actions Taken

- Consensus of customers during JReview 2013 user group meeting discussions:
- JReview RBM analytics – not only provide interactive review of RBM results, but also become a 'communication mechanism'
- Define Suggested Actions to be taken when risk indicator at specified level fires.
- CRAs or other field personnel review suggested actions then enter 'Actions Taken' in response to the Suggested Actions.



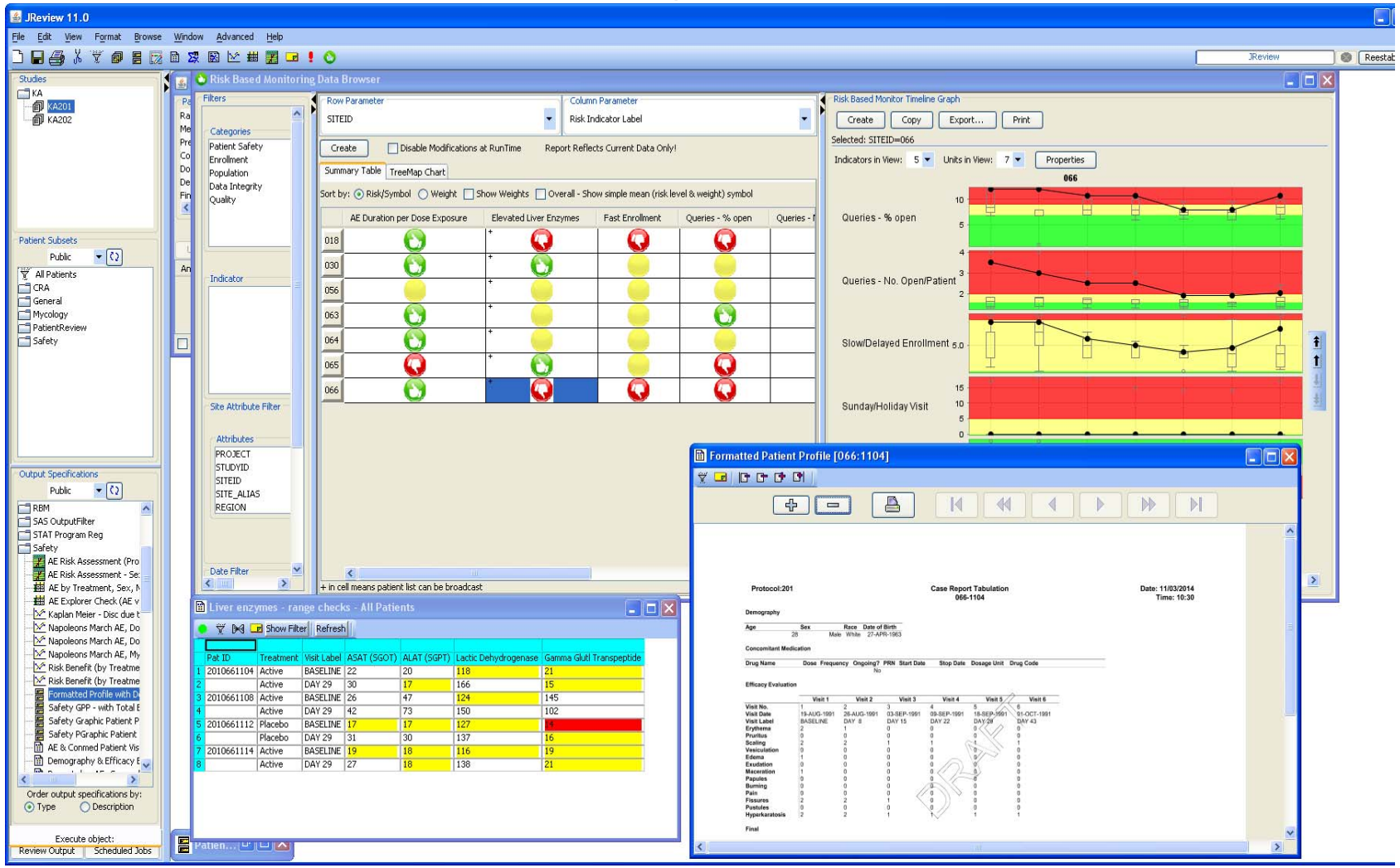
Suggested Actions -> Actions Taken

Site – Timeline Trend, Suggested Actions -> Actions Taken



Review Sites->Patients-> Targeted SDV?

When rules fire, patients are noted, supporting patient drill down from sites/risk indicators of interest -> targeted SDV via Tabular Profiles



Risk Based Monitoring

Questions or Comments?

Contact: Eric S Herbel
Integrated Clinical Systems, Inc.
email: eherbel@i-review.com
phone: +1 908 996 3312