
Risk-Based Monitoring (RBM)

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JReview[®] 
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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

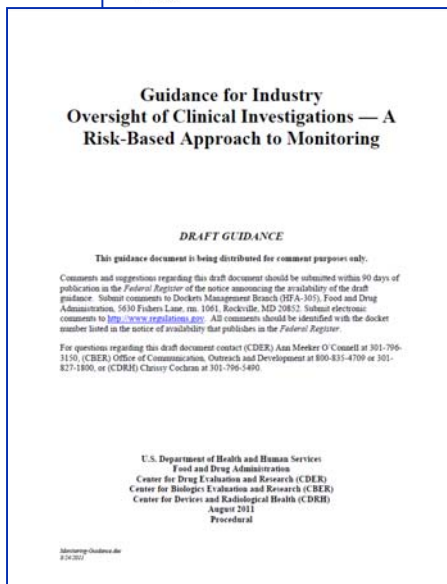
*** Focus on critical data points

Risk Based Monitoring (RBM)



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

- 4 August 2011
- EMA/TNS/ICP/194104/2011
- Compliance and Inspection
- Reflection paper on risk based quality management in clinical trials
- Draft



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

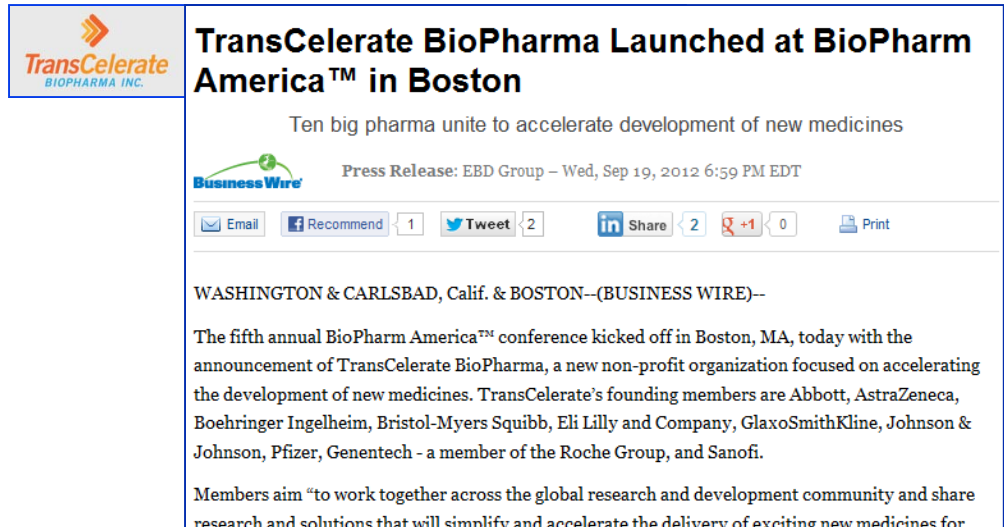
DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.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be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance.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-307), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20855. 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, (CDER) Office of Communications, Outreach and Development at 800-835-4709 or 301-827-1800, or (CDRH) Charney Cochran at 301-796-5400.

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
Precedent



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

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

*...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.*



“ 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
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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"
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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
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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 Weight	<75 6	75-99.99 25	>99.99 100
Enrolment rate	Outlier site: high enroller (ranking)	Ranges Weight	<95.01 6	95.01-98.99 25	>98.99 100
Screening failure rate	Outlier site (different from a target P value)	Ranges Weight	<1.31 2	1.31-2 4	>3 9
Discontinuation rate	Outlier site (different from a target P value)	Ranges Weight	<1.31 5	1.31-2 14	>3 60
Protocol compliance	Deviations rate (number of deviations observed at site)	Ranges Weight	<0.11 6	0.11-0.20 25	>0.20 100
Safety	% of SAE over / under reporting (compared to the mean of sites)	Ranges Weight	<90 6	90-95 25	>95 100
Data entry	Delay in Data entry (days)	Ranges Weight	<3.01 2	3.01-6 4	>6 9
Queries	Query resolution turnaround (days)	Ranges Weight	<0.01 2	0.01-5 4	>5 9

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

Risk Based Monitoring

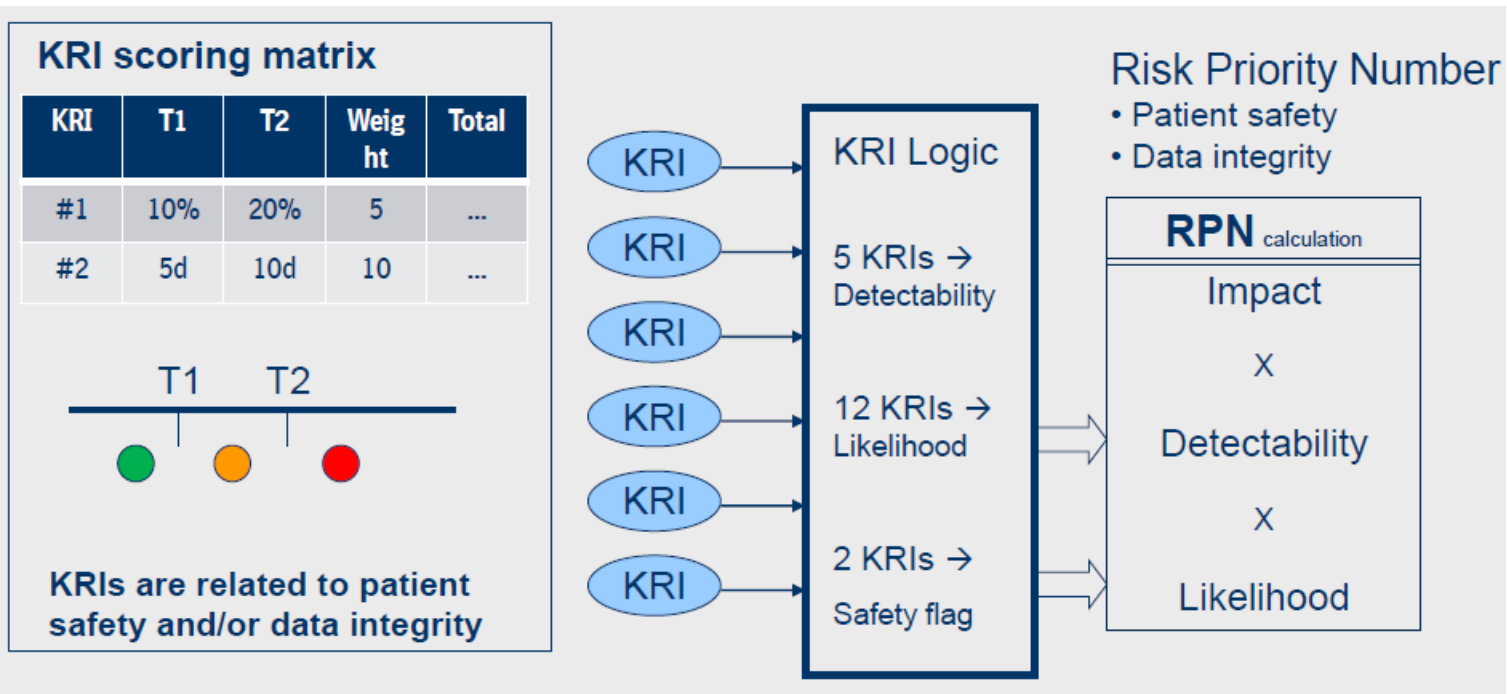
Boehringer Ingelheim's Key Risk Indicators

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

Risk Based Monitoring

Boehringer Ingelheim's Risk Priority Number



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 $> \text{ULN} * x$
 - Systolic blood pressure > 150
 - **Statistical Patterns, Distribution, etc.** – quality & fraud detection
-
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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
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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

Risk Based Monitoring Indicator Definitions [Object:1386]

Definition | Categories | Actions

List of Risk Indicators

Risk Category	Risk Indicator Description	Risk Indicator Label
Safety	Highly Probable	Highly Probable
Safety	Probable	Probable
Safety	Severe	Severe
Labs	Elevated Glucose	High Glucose
Labs	Elevated Trigs	High Trigs
Efficacy	High Total Eff	Total Eff
Study Issues	Med History Issue	Med History
Cultures	Positive Culture	Pos Culture
Cultures	Missing Cultures	Missing Cultures

Risk Indicator Category: Study Issues Weight: 1

Indicator Description: Med History Issue
 Indicator Label: Med History

Risk Indicator Definition

Patient subset Defined
 Subject Counts
 Percentage of Subjects
 Other

Indicator Thresholds Check Enable Row to Define Press ENTER or TAB to post cell changes

Enable Row?	Symbol	Label	Cut Off	Cut Off (low end)	Weight	Red Flag	Suggested Actions	Comments
<input checked="" type="checkbox"/>		Low Risk	0.0	60.0	1	<input type="checkbox"/>	<input type="button" value="Assign/Review"/> Unassigned	
<input type="checkbox"/>		Medium Low Risk	0.0	0.0	1	<input type="checkbox"/>	<input type="button" value="Assign/Review"/> Unassigned	
<input checked="" type="checkbox"/>		Medium Risk	0.0	10.0	1	<input type="checkbox"/>	<input type="button" value="Assign/Review"/> Call Medical Monitor	MH listings checked
<input type="checkbox"/>		Medium High Risk	0.0	0.0	1	<input type="checkbox"/>	<input type="button" value="Assign/Review"/> Unassigned	
<input checked="" type="checkbox"/>		High Risk	0.0	1.0	1	<input type="checkbox"/>	<input type="button" value="Assign/Review"/> Contact Investigator	

RBM Data Browser

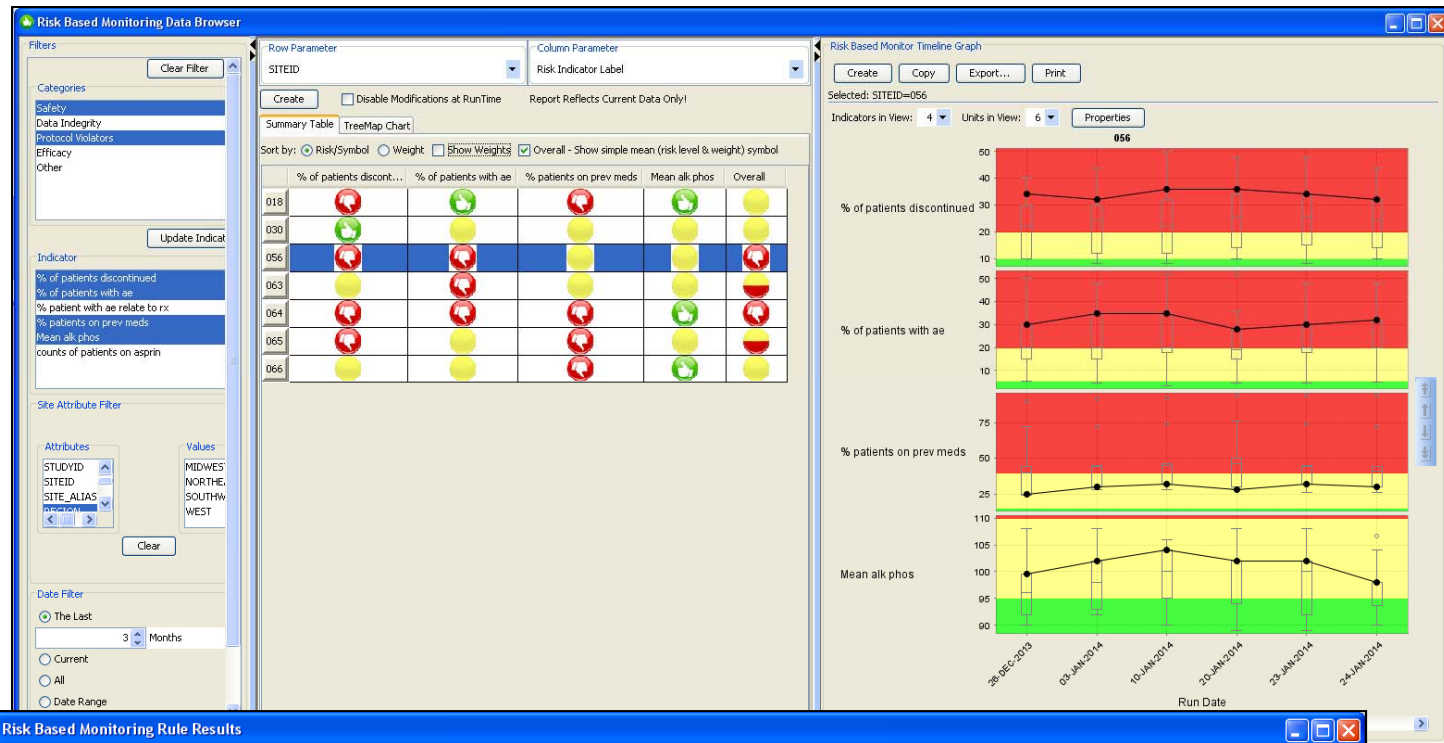
Risk Indicator Result Visualization by site, country, or region - subset by attributes - interactively sort any columns for site ranking

The screenshot displays the Risk Based Monitoring Data Browser interface. On the left, there are filter sections: 'Filters' with categories like Patient Safety, Enrollment, Population, Data Integrity, and Quality; 'Indicator' with options like Fast Enrollment, Queries - % open, etc.; 'Site Attribute Filter' with attributes like STUDYID, SITEID, and REGION; and 'Date Filter' set to 'The Last 3 Months'. The main area shows a 'Summary Table' with columns for 'Fast Enrollment', 'Queries - % open', 'Queries - No. Open/Patient', 'Slow/Delayed Enrollment', and 'Overall'. The table contains 7 rows of data for sites 018 through 066, each with colored risk indicators and numerical values. Below the table, there is a 'Site Level Information' section with tabs for 'Overview', 'Actions', and 'Edit Actions', and a 'List of Existing Actions' table.

	Fast Enrollment	Queries - % open	Queries - No. Open/Patient	Slow/Delayed Enrollment	Overall
018	1	3	1	5	10
030	1	2	1	3	7
056	1	2	1	3	7
063	1	1	1	3	6
064	1	2	1	3	7
065	1	3	1	3	8
066	1	3	1	3	8

Site Distribution Over Time

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

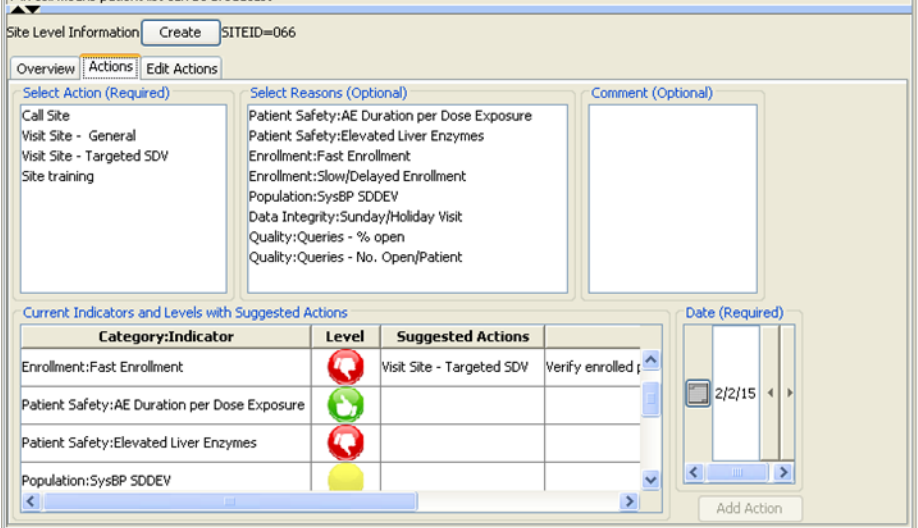


Project	Study	Site	Category	Indicator Description	Indicator Label	Threshold Weight	Red Flag	RunDate	Raw Value	High Value	Threshold Label	Symbol	Keep List of Pts.
KA	KA201	018	Safety	% of patients with ae	% of patients with ae	1		16-JAN-2014	4.55	5	Low Risk	🟢	No
KA	KA201	030	Safety	% of patients with 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.



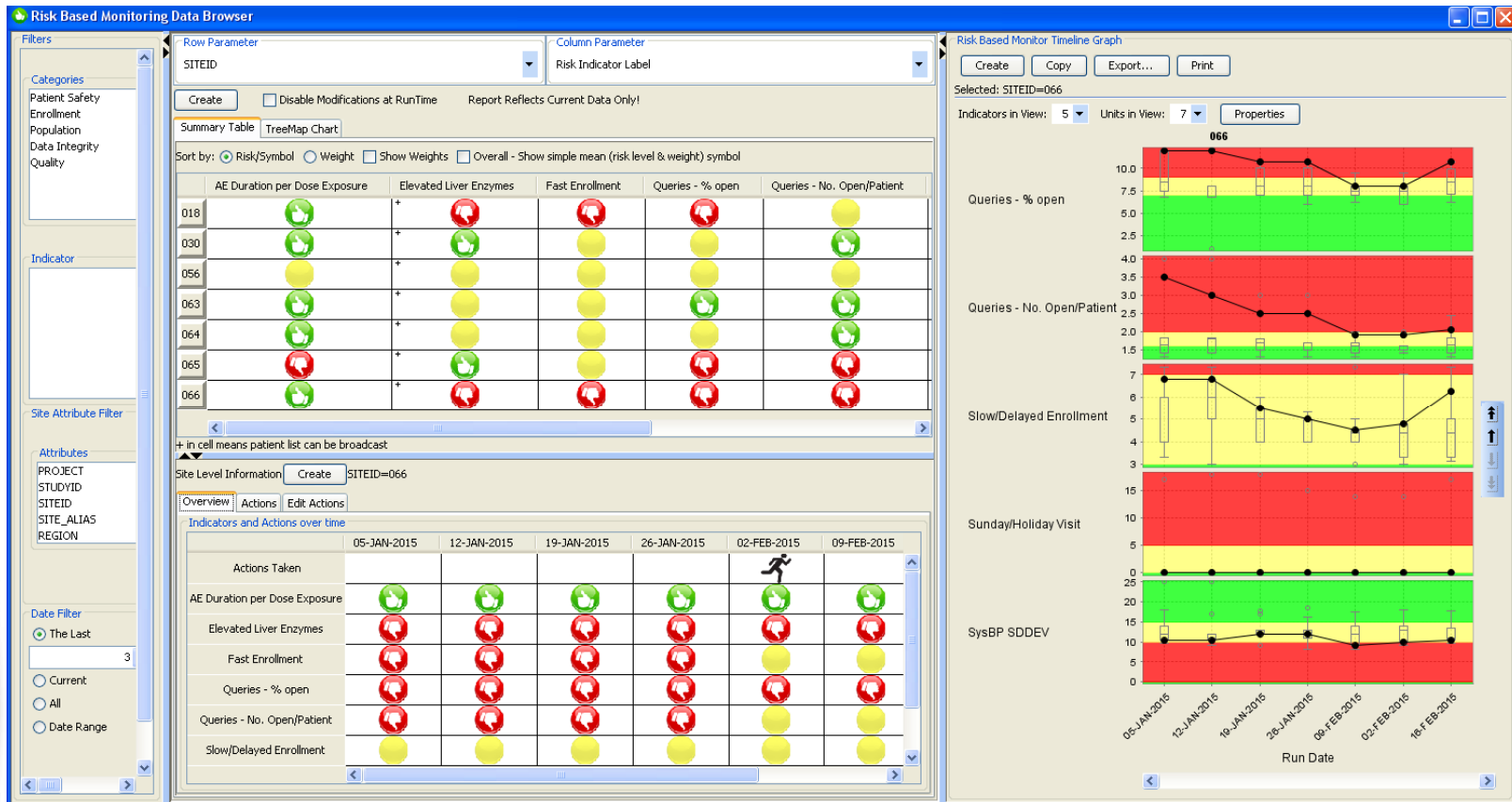
The screenshot displays the 'Site Level Information' page for SITEID=066. It features three main sections: 'Select Action (Required)', 'Select Reasons (Optional)', and 'Comment (Optional)'. Below these is a table titled 'Current Indicators and Levels with Suggested Actions' and a 'Date (Required)' field.

Category:Indicator	Level	Suggested Actions
Enrollment:Fast Enrollment	Red Stop Sign	Visit Site - Targeted SDV
Patient Safety:AE Duration per Dose Exposure	Green Checkmark	Verify enrolled
Patient Safety:Elevated Liver Enzymes	Red Stop Sign	
Population:SysBP SDDEV	Yellow Warning	

The 'Date (Required)' field is set to 2/2/15. An 'Add Action' button is located at the bottom right of the interface.

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

The screenshot displays the JReview 11.0 software interface, which is used for clinical trial data review and monitoring. The main window is titled "Risk Based Monitoring Data Browser" and shows a summary table of risk indicators across various sites. The table includes columns for "AE Duration per Dose Exposure", "Elevated Liver Enzymes", "Fast Enrollment", "Queries - % open", and "Queries - No. Open/Patient". The site ID 066 is highlighted in blue, indicating it is the selected site for further analysis.

Below the summary table, a "Liver enzymes - range checks - All Patients" window is open, displaying a table of patient data. The table includes columns for "Pat ID", "Treatment", "Visit Label", "ASAT (SGOT)", "ALAT (SGPT)", "Lactic Dehydrogenase", and "Gamma Glut Transpeptidase". The patient ID 2010661114 is highlighted in red, indicating a potential issue or alert.

On the right side of the main window, a "Risk Based Monitor Timeline Graph" is displayed, showing a line graph of "Queries - % open" over time. The graph shows a peak in queries around the middle of the timeline, with a red background indicating a high risk level. Below the graph, a "Formatted Patient Profile [066:1104]" window is open, displaying a detailed view of the patient's data, including demographics, concomitant medication, and efficacy evaluation. The patient's name is "2010661114" and the treatment is "Placebo". The efficacy evaluation table shows data for visits 1 through 6, with a "Final" row indicating the patient's status at the end of the study.

Pat ID	Treatment	Visit Label	ASAT (SGOT)	ALAT (SGPT)	Lactic Dehydrogenase	Gamma Glut Transpeptidase
1 2010661104	Active	BASELINE	22	20	118	21
2 2010661104	Active	DAY 29	30	17	166	15
3 2010661108	Active	BASELINE	26	47	124	145
4 2010661108	Active	DAY 29	42	73	150	102
5 2010661112	Placebo	BASELINE	17	17	127	18
6 2010661112	Placebo	DAY 29	31	30	137	16
7 2010661114	Active	BASELINE	19	18	116	19
8 2010661114	Active	DAY 29	27	18	138	21

Visit No	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
Visit Date	19-AUG-1991	26-AUG-1991	03-SEP-1991	09-SEP-1991	16-SEP-1991	23-OCT-1991
Visit Label	BASELINE	DAY 8	DAY 15	DAY 22	DAY 29	DAY 42
Erythema	2	1	0	0	0	0
Pruritus	0	0	0	0	0	0
Scaling	2	2	1	1	4	1
Vesiculation	0	0	0	0	0	0
Edeema	1	0	0	0	0	0
Exudation	0	0	0	0	0	0
Maceration	1	0	0	0	0	0
Papules	0	0	0	0	2	0
Burning	0	0	0	0	0	0
Pain	0	0	0	0	0	0
Fissures	2	2	1	0	0	0
Pustules	0	0	0	0	0	0
Hyperkeratosis	2	2	1	1	1	1
Final						

Risk Based Monitoring

Questions or Comments?

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