Visual Analytics in Risk-Based Monitoring (RBM) of Clinical Trials

phuse

JReview®

Integrated Clinical Systems, Inc.

www.i-review.com

Jreview Intro

Visual Analytics tool developed specifically for reviewing clinical data

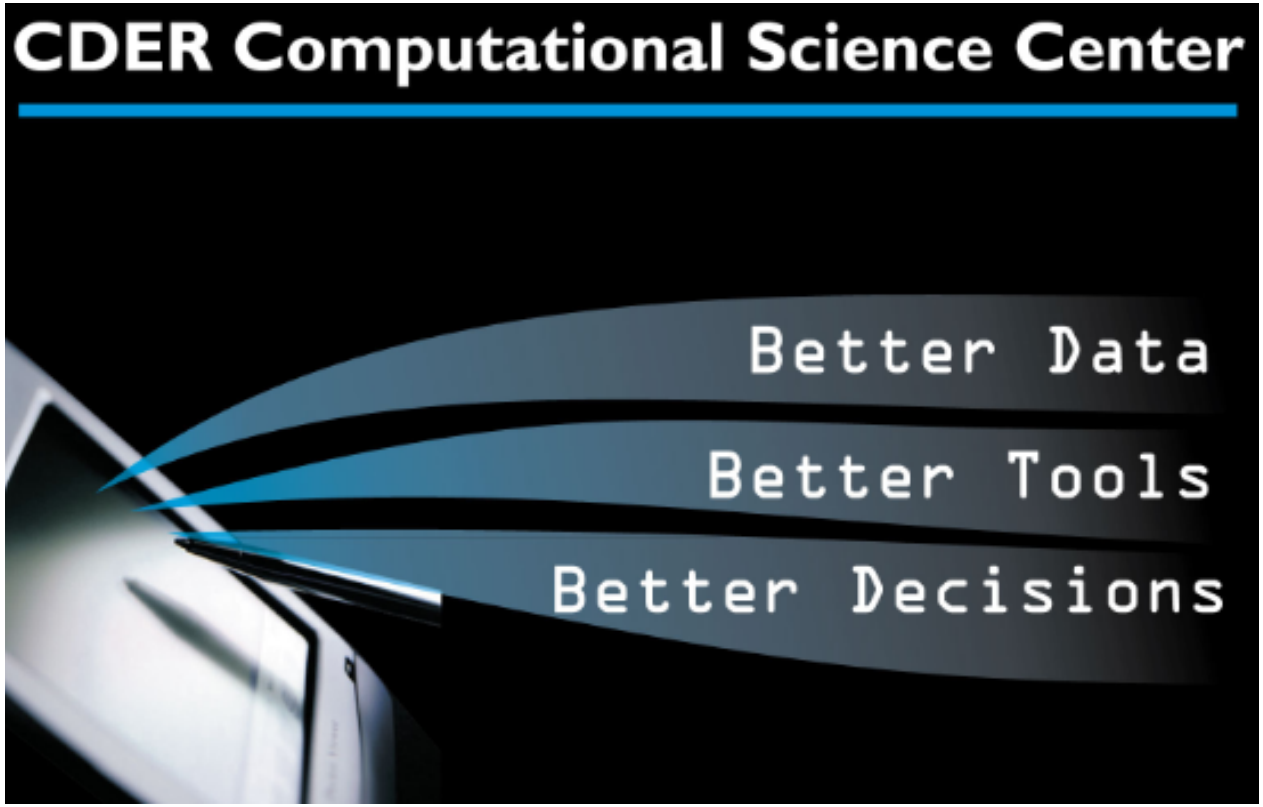
- Intuitive user interface to perform safety and efficacy review through clinically relevant reports and data visualizations
- Understands ‘patient’, ‘baseline’, ‘endpoint’, etc.
- Integrated with all industry standard clinical data sources
- Dynamic multi-study pooling
- Built-in ‘patient identification/drill down’
- Patient review tracking (with critical data review)
- Many clinical data specific graphics, tabulations, profiles, risk assessments, etc. including defining critical data

JReview

Integrated with industry standard clinical data sources – UI consistent

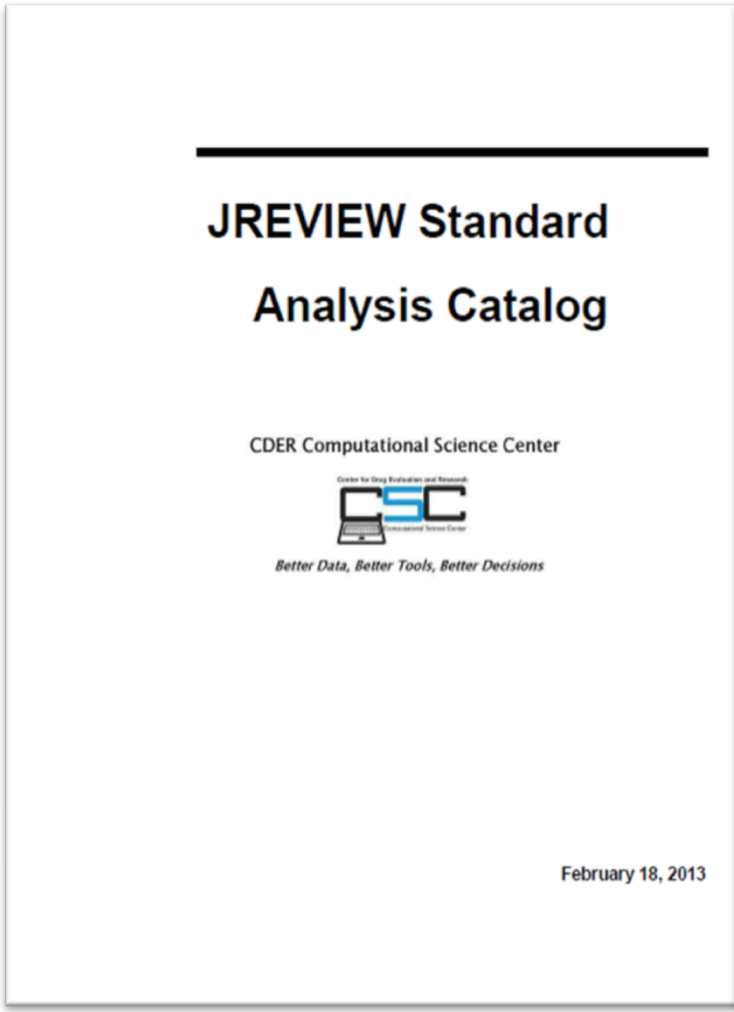
- Data Management Systems:
  - Oracle Clinical, Oracle Clintrial
- EDC Systems:
  - Medidata Rave, Oracle Inform (reporting database), DataLabs
- Drug Safety Systems:
  - Oracle ARGUS, ARISg, Oracle AERS
- Data Warehouse Environments:
  - Oracle LSH (JReview built-in LSH 'connector')
  - Oracle CDC
  - Entimo EntimICE
  - eClinical Solutions eGrex
  - SAS Drug Development
  - FDA – JANUS/CTR (new environment)
- SAS environments – 'pure SAS environment'
- Custom configured customer database environments.
- CTMS data via dblink, etc.

Facilitating Modernization of the Regulatory Review Process



Source: Lilliam Rosario, Ph.D., Director, Office of Computational Science, PhUSE CSS 2014
JumpStart the Regulatory Review: Applying the Right Tools at the Right Time to the Right Audience

JReview Standard Analysis Catalog



JREVIEW Standard

Analysis Catalog

CDER Computational Science Center

Better Data, Better Tools, Better Decisions

February 18, 2013

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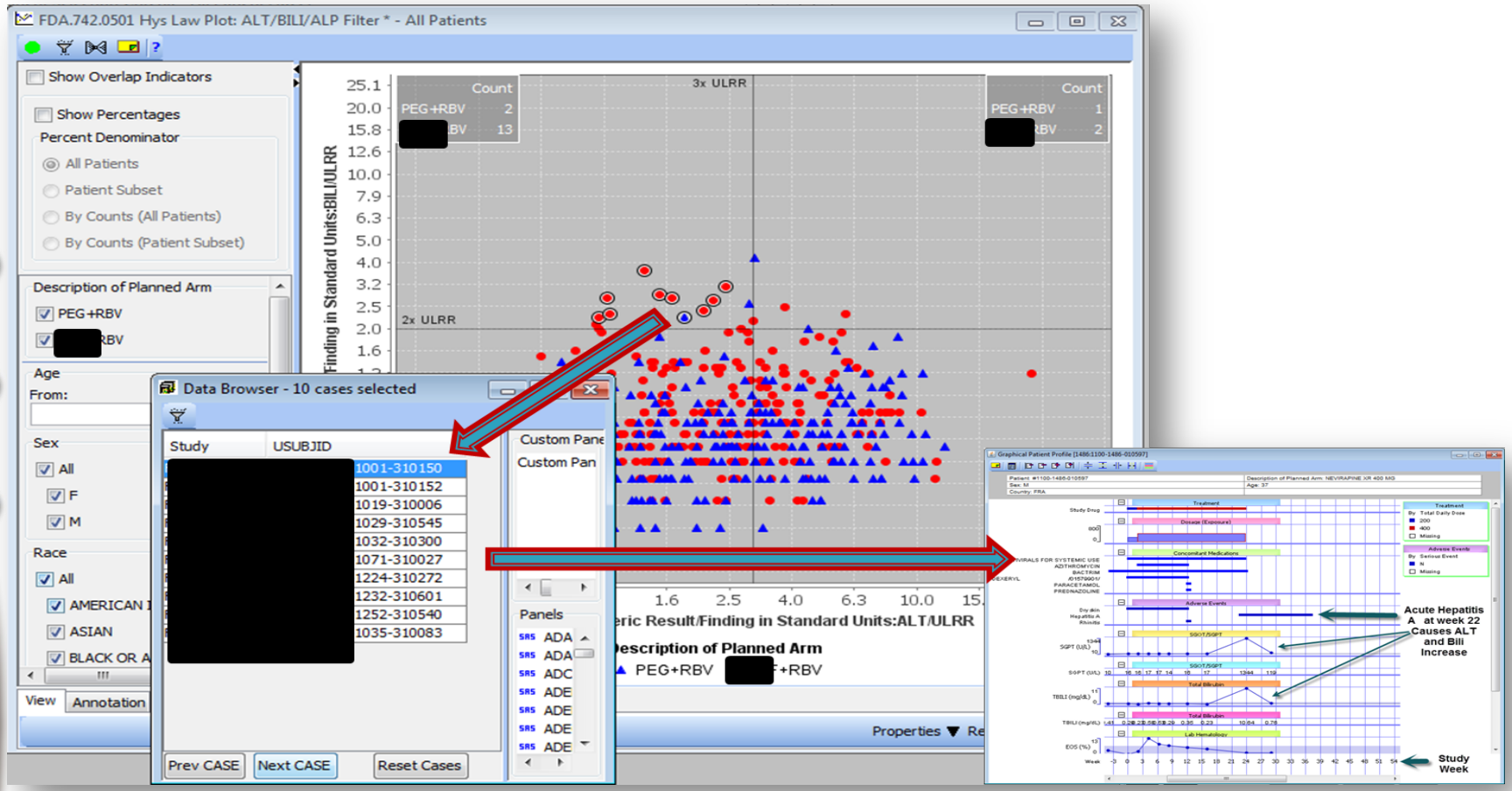
JumpStart the Regulatory Review: Applying the Right Tools at the Right Time to the Right Audience

JReview Standard Analysis – Hy's Law Plot



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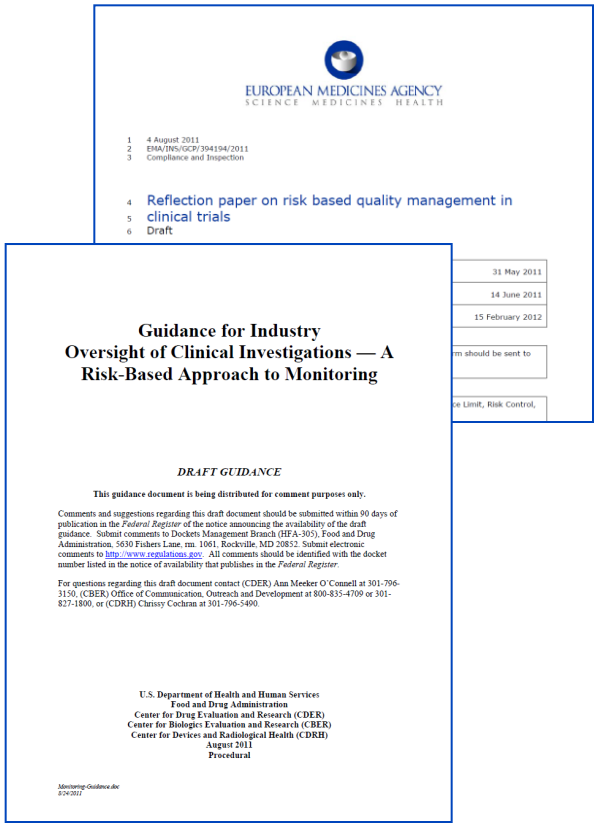
Risk Based Monitoring (RBM)



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

1 4 August 2011
2 EMA/INS/GCP/394194/2011
3 Compliance and Inspection

4 Reflection paper on risk based quality management in
5 clinical trials
6 Draft

31 May 2011
14 June 2011
15 February 2012

rm should be sent to

ce Limit, Risk Control,

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) Chrissy 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

Monitoring-Guidance.doc
8/24/2011

TransCelerate BIOPHARMA INC.

TransCelerate BioPharma Launched at BioPharm America™ in Boston

Ten big pharma unite to accelerate development of new medicines

BusinessWire **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 SCIENCE MEDICINES HEALTH | 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)

- **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
- **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

Risk Based Monitoring (RBM)

Monitoring Recommendations (FDA/EMA)

- 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:
  - Enrolment 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

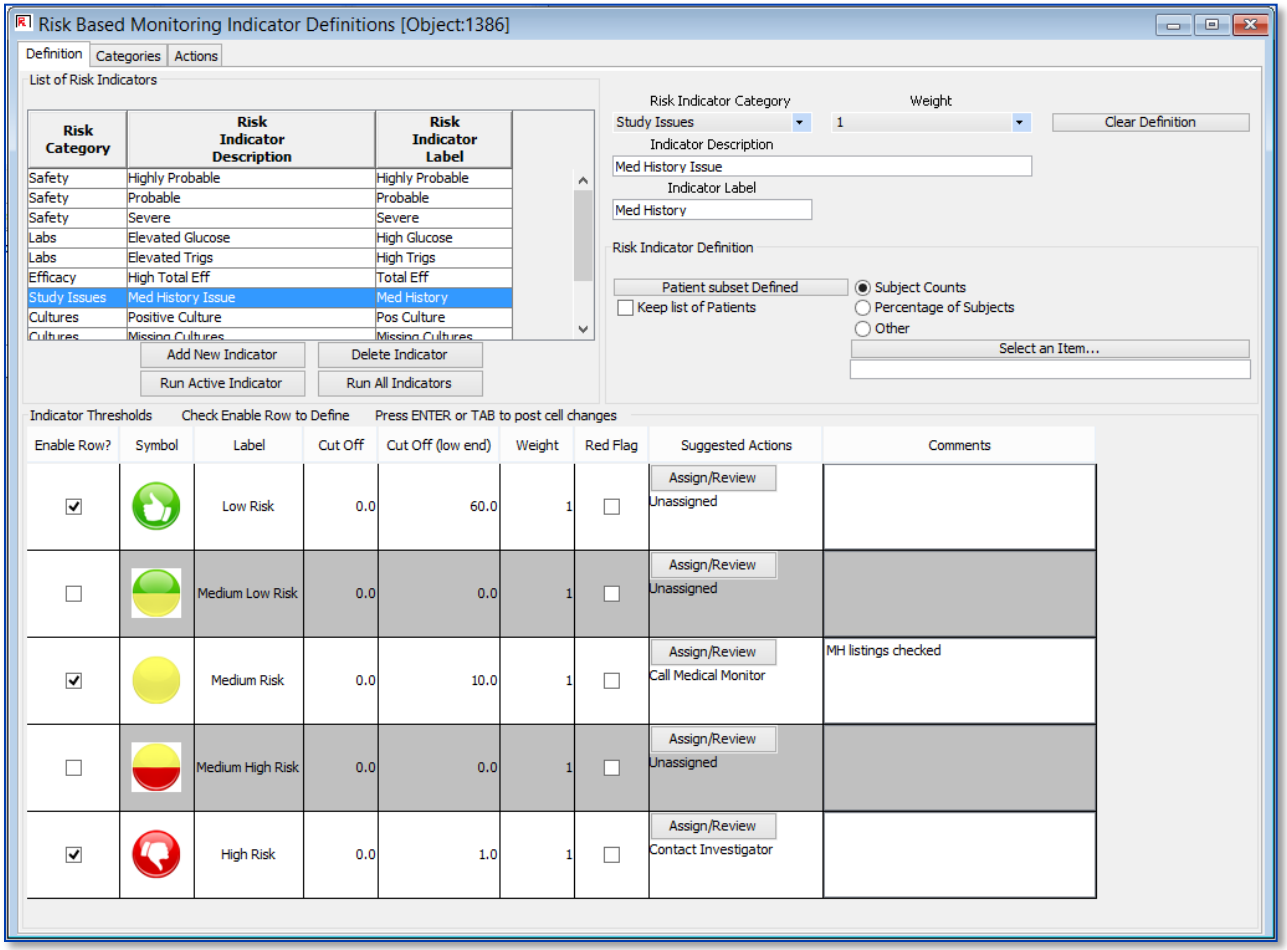
JReview – RBM Workflow

Out of the box Analytics support for Risk Based Monitoring

- Centralized monitoring teams can define key risk categories and indicators 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
- The newly developed native iPad app provides easy access to key RBM metrics and recommended actions for CRAs and monitors in the field
- Visualization of risk evolution by site/country/region based on multiple risk indicators & -categories

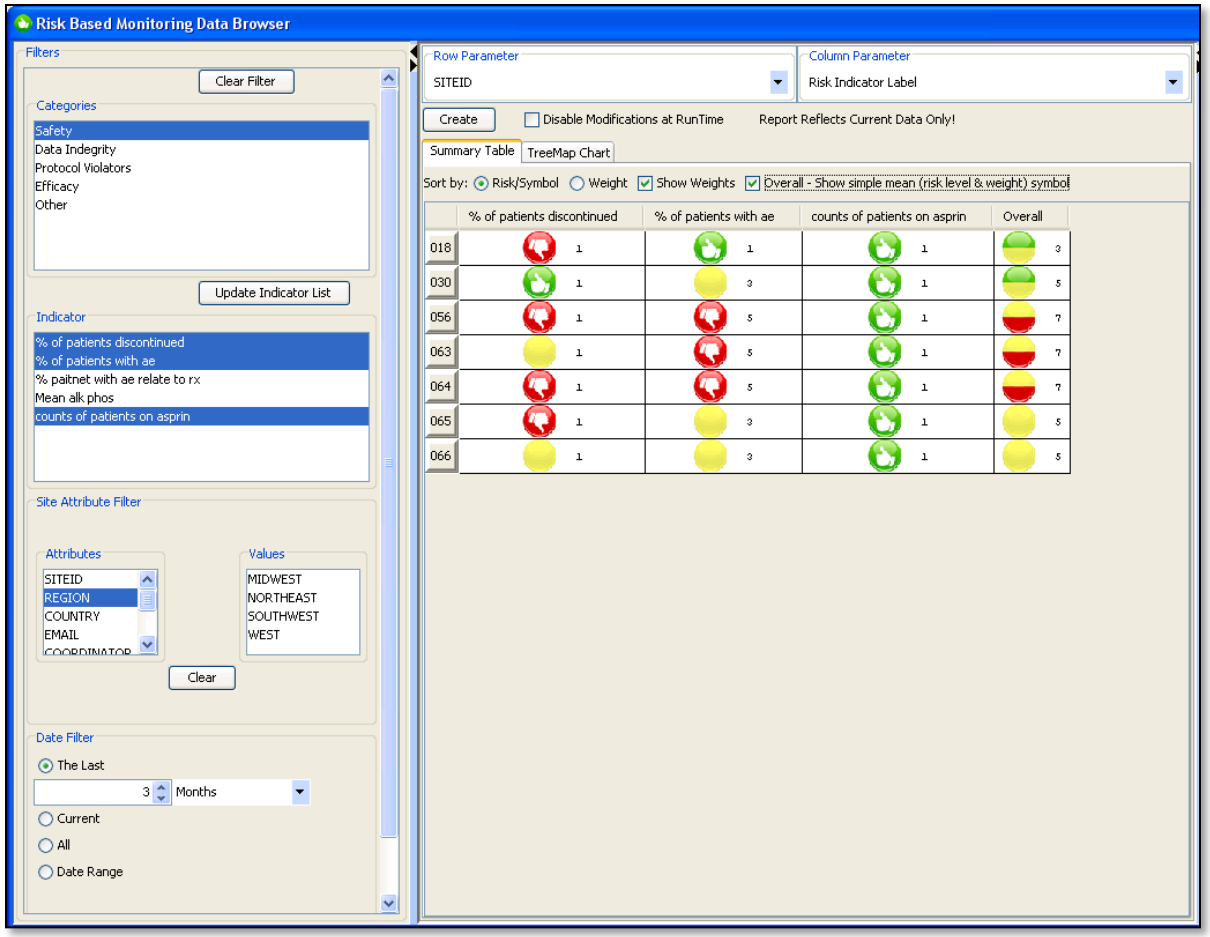
RBM Risk Indicator Definition

Key Risk Indicators, thresholds, & suggested actions Definition within JReview with test run ⇨ scheduled periodic execution



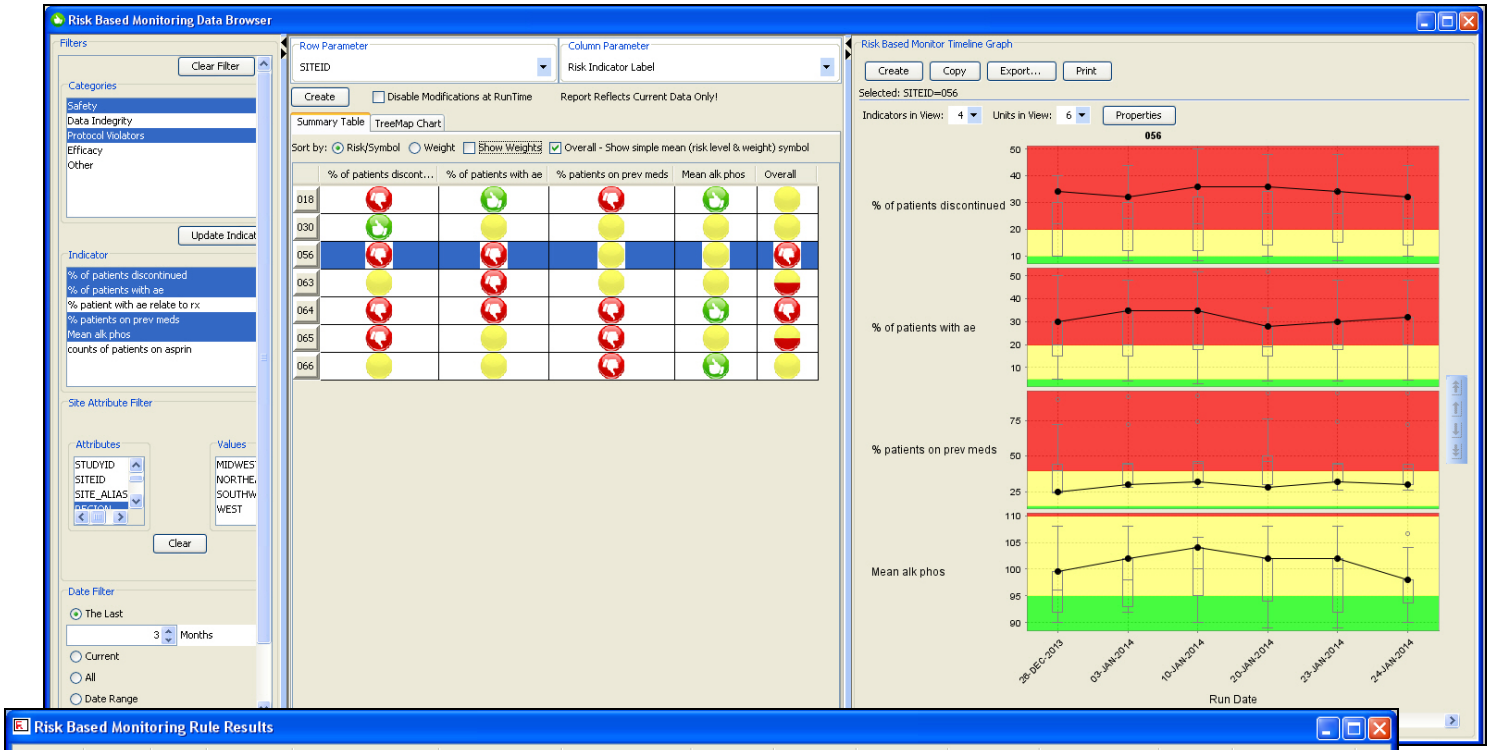
RBM Data Browser

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

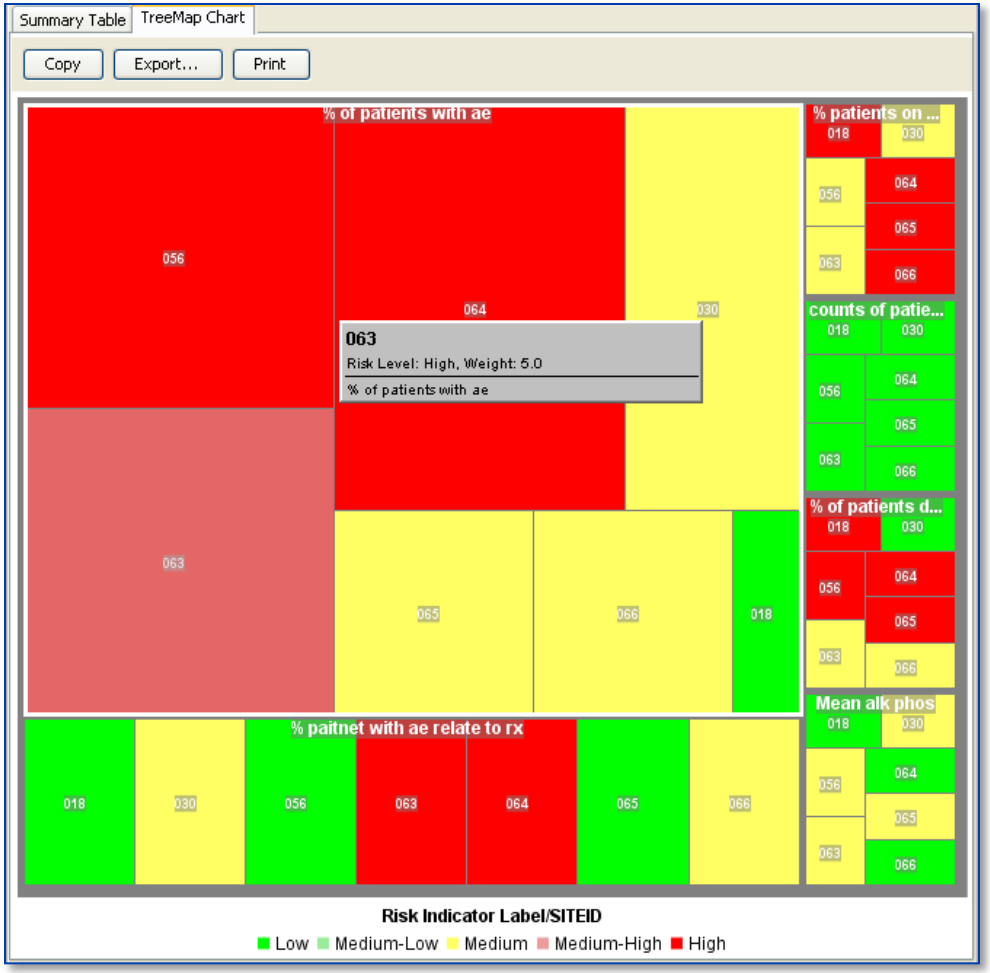


Risk Based Monitoring Rule Results

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

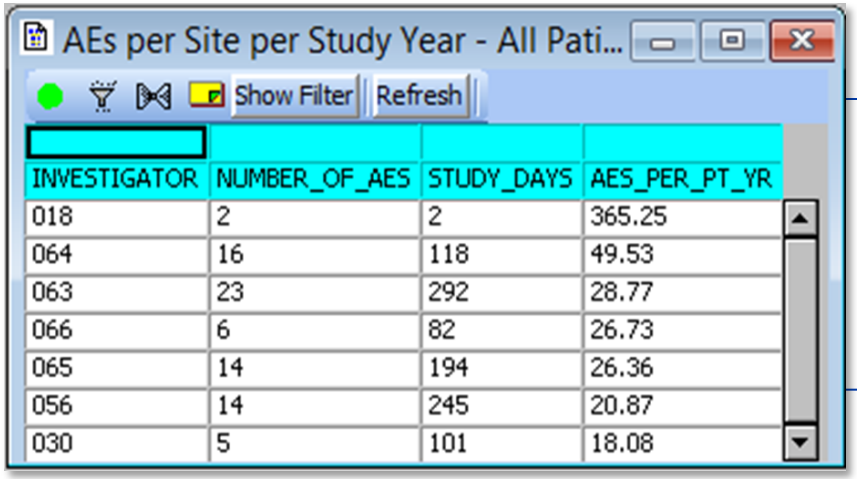
RBM Treemap

Site – Risk Indicator weight visualization – Tree Map visualization



RBM Statistics enabled via R/SAS Programs or Import SQLs

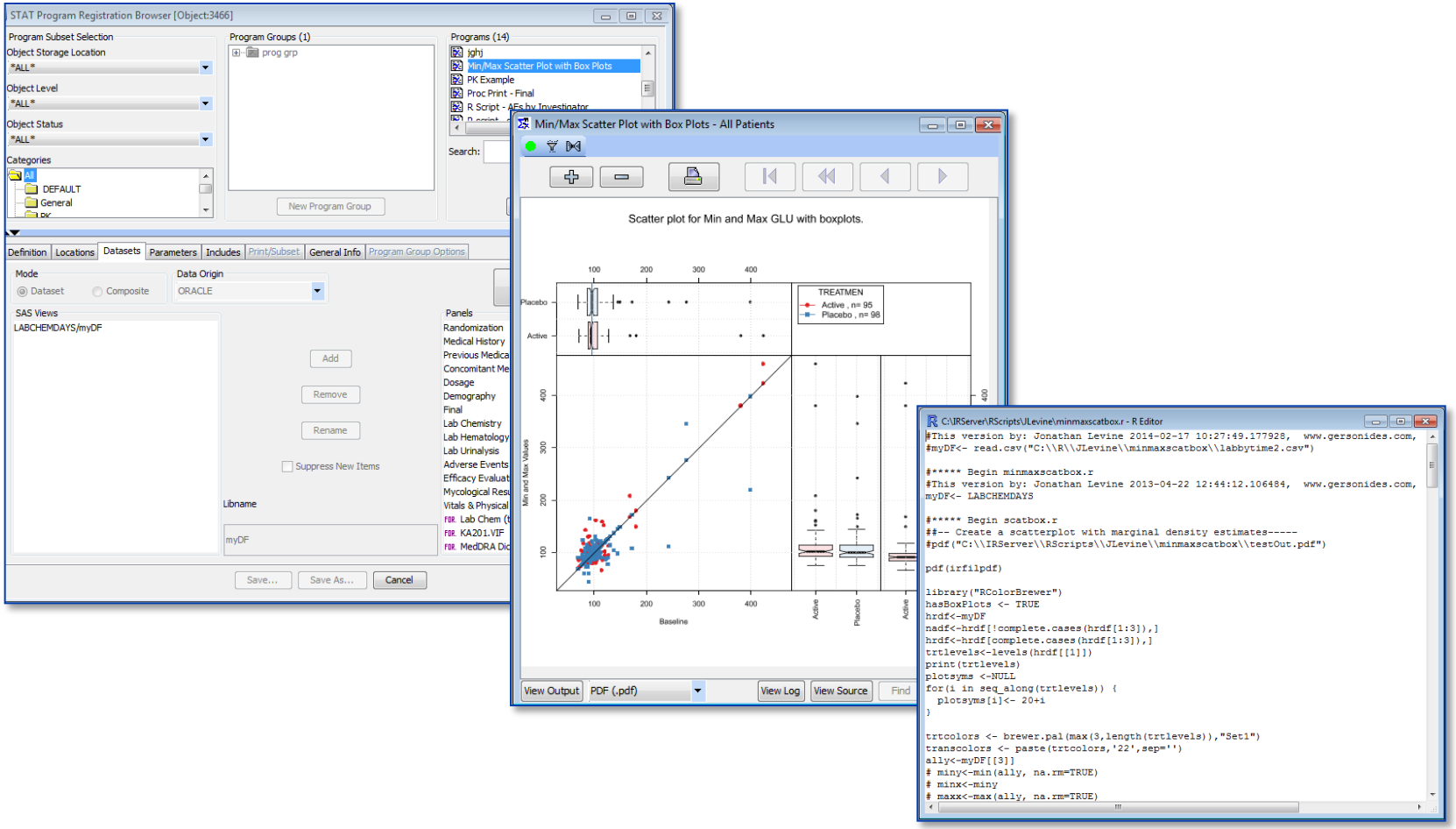
- In addition, R- and SAS programs may be executed from within JReview after definition and registration in the *JReview STAT Program Registration Browser*
- STAT programs and program groups can be executed from the Object Explorer like any other JReview objects
- Alternatively, RBM-related statistical models may be embedded in import SQLs for processing upon data import



INVESTIGATOR	NUMBER_OF_AES	STUDY_DAYS	AES_PER_PT_YR
018	2	2	365.25
064	16	118	49.53
063	23	292	28.77
066	6	82	26.73
065	14	194	26.36
056	14	245	20.87
030	5	101	18.08

Example: Listing of the exposure-adjusted adverse event rate per study site, taking into account the total treatment duration (AEs per patient year)

Statistics enabled via R & SAS programs



Source: http://gersonides.com/minmaxscatbox

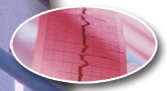
JReview RBM iPad App

New native iPad app provides easy access to key RBM metrics and recommended actions for CRAs and monitors in the field

ICS thoughts on Risk Indicators

How we do it:

- JReview 'template' for custom definition of risk indicators - providing ultimate **flexibility** in risk indicator definition
- 'Standard library' based on CDISC
- Flexibility of range definitions for 'thresholds' – 5 levels indicator results



Different types of Risk Indicator characteristics

-Indicators based on absolute values, ranges, etc. - regardless of % of population they catch (counts, %, etc.)

-Dynamic indicators, 'rolling average' – outliers from group – Z scores

-Risk indicator weighting factors

-Risk categories – not lumping into a single risk score – but by categories

-Risk Categories, Project, Study, Region, Site 'drill down' capabilities -> to site level (& patient ID)

Then what … - when a risk indicator fires -> taking action, recording action, etc.

Review over time to determine effects of actions

Open interface accessing the information available on risk indicator

Thank You!

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