Get SMART to Stay in CONTROL and Avoid KAOS: Signal Management for Adverse Events in Real Time

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Disclaimer

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- JMP Discussion Forum
Agenda

• Definitions

• Introduction

• Overview

• Demo

• Technical Bits

• Conclusions

• Key Learnings
Definitions
Definitions

• **Adverse Event (AE):**
  - Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related
  - Examples:
    - NAUSEA
    - VOMITING
    - HEADACHE
    - HEART ATTACK
    - MALARIA
    - ANAEMIA
Definitions

- **Positive Rechallenge:**
  - Drug administered
  - Adverse event occurs
  - Drug withheld for a time
  - Drug administered again (rechallenge)
  - Adverse event occurs again (positive rechallenge)
Definitions

- **MedDRA - Medical Dictionary for Regulatory Activities**
- Standardizes medical terminology used to classify adverse event information
- **Hierarchy:**

  - **SOC**: System Organ Class
  - **HLGT**: High Level Group Term
  - **HLT**: High Level Term
  - **PT**: Preferred Term
  - **LLT**: Low Level Term

  **SMQ**: Standard MedDRA Query
  SMQs are groupings of terms that relate to a defined medical condition or area of interest
Definitions

MedDRA Hierarchy

• **SOC**: System Organ Class (26 terms)
• **HLGT**: High Level Group Term (335 terms)
• **HLT**: High Level Term (1,700 terms)
• **PT**: Preferred Term (21,000 terms)
• **LLT**: Lowest Level Term (65,000 terms)
Partial Sample MedDRA Hierarchy for Preferred Term = HEADACHE

<table>
<thead>
<tr>
<th>Verbatim Term</th>
<th>LLT Name</th>
<th>PT Name</th>
<th>HLT Name</th>
<th>HLGT Name</th>
<th>SOC Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>SEVERE PALPITATIONS IN THE HEAD</td>
<td>HEAD THROBBING</td>
<td>HEADACHE</td>
<td>HEADACHES NEC</td>
<td>HEADACHES</td>
<td>NERVOUS SYSTEM DISORDERS</td>
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<td>FEELING OF FULLNESS IN HEAD</td>
<td>FULLNESS HEAD</td>
<td>HEADACHE</td>
<td>HEADACHES NEC</td>
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<td>NERVOUS SYSTEM DISORDERS</td>
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<td>HEADACHE</td>
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<td>CHRONIC HEADACHE WITH SUPERIMPOSED MIGRAINES</td>
<td>CHRONIC HEADACHES</td>
<td>HEADACHE</td>
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<td>ICE PICK HEADACHE</td>
<td>HEADACHE</td>
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<td>HEADACHES</td>
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<td>HEADACHE AGGRAVATED</td>
<td>HEADACHE</td>
<td>HEADACHES NEC</td>
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<td>HEADACHES NEC</td>
<td>HEADACHES</td>
<td>NERVOUS SYSTEM DISORDERS</td>
</tr>
</tbody>
</table>
Definitions

- **DME**: Designated Medical Event
- Adverse events which are
  - Rare
  - Serious
  - More likely to be associated with a high drug-attributable risk
Definitions

Alert: An automated, system-generated, notification indicating that either a pre-defined statistical threshold has been met, or a specific case characteristic has been identified.
Definitions

**Signal**: “...information that suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event(s), either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action.”

- CIOMS VIII, in EMA guideline for good pharmacovigilance practices, Module IX—Signal management
Definition of a Safety Signal

“Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously.” An additional note states: ‘Usually more than one report is required to generate a signal, depending on the seriousness of the event and the quality of the information’.

- World Health Organization (WHO)
Definitions

A signal is therefore a hypothesis together with supporting data and arguments.

A signal is not only *uncertain* but also *preliminary* in nature: the situation may change substantially over time one way or another as more information is gathered.
Definitions

**Case**: information about adverse events experienced by a person while taking a drug

- Unique ID #
- Dates (occurrence, receipt, etc.)
- Demographics (gender, age, etc.)
- Adverse Event(s)
- Drug(s)
- Narrative
Sample Narrative

Subject xxxxxx had cancer (disease needs to be specified), which was diagnosed in Jun 1998. The subject previously received treatment with vvvvvvvv, dddddd, mmmmmm, and pppppppp. The subject’s pertinent medical history included cardiac arrhythmia, myocardial infarction, deep vein thrombosis, hypercholesterolemia, acute renal failure, and hypertension.

On 30 Apr 2001 (Cycle 1, Day 33; 15 days after completing Cycle 1 therapy), the subject was admitted to the hospital for treatment of acute renal insufficiency. The subject complained of a cough one week before admission, and was treated with a dose of pppppppp for Pneumocystis carinii pneumonia and reported decreased urine output since that time. A baseline 24-hour urine collection on 14 Mar 2001 revealed 75% lambda light chain Bence-Jones protein, a total protein of 2700 mg/24 hours, and a urine M-protein of 2025 mg/24 hours; the investigator considered that the increase in monoclonal proteins was related to a dental abscess. On 27 Mar 2001, his baseline creatinine was 1.9 mg/dL. On admission, the subject’s creatinine was 4.9 mg/dL, BUN was 72 mg/dL, and potassium was 5.5 mEq/L. His cloudy yellow urine had 30 mg/dL protein and bacteria (cultured as coagulase-negative Staphylococcus). An abdominal ultrasound showed a slight increase in echogenicity and irregular renal cortices that were consistent with renal disease. A physical examination revealed right lung base crackles and a temperature of 38.1°C. On the following day, 01 May 2001, the subject’s creatinine was 4.9 mg/dL, BUN was 62 mg/dL, and potassium was 4.7 mEq/L. The subject was discharged on 4 May 2001 (Day 38) with a creatinine of 4.6 mg/dL and a BUN of 65 mg/dL, and the event was considered resolved with sequelae. The subject was given xxxxxxx at discharge. A 24-hour urine collection on 24 May 2001 revealed 5.24 g/24 hours Bence-Jones protein, total protein of 5 mg/24 hours, urine M-protein of 4 mg/24 hours, and a creatinine of 4.8 g/24 hours. The subject was discontinued from the study because of progressive multiple myeloma on 29 May 2001.

Concomitant medications included aaaaaaaa, bbbbbbbb, cccccccc, dddddddd, nnnnnnnn, gggggggg, eeeeeeee, kkkkkkkk, oooooooooo, qqqqqqqqq, pppppppp, and ssssssss.

In the opinion of the investigator, the Grade 3 acute renal insufficiency was unrelated to dexamethasone.
Safety Data Processing

1. Adverse Event Occurs → Call Center
2. Call Center → Data Entry
3. Data Entry → Case Processing
4. Case Processing → Medical Review
5. Medical Review → Signal Detection
6. Signal Detection → Regulatory Reporting
Introduction
Introduction

• **SMART**: Decision support tool for signal detection/management
• **Signal Management for Adverse Events in Real Time**
• Monitor product safety data
• Alert appropriate staff
• Analyze and assess/evaluate case data and basic trends for resultant alerts
• Document reviewer comments and signoff
• Manage workload
• Generate reports
Real-Time Surveillance – Why?

• Regulations require frequent monitoring of available safety data

• Maximize capabilities to proactively identify new safety risks

• Complete transparency from alert to final assessment

• Deliver industry-leading real-time signal detection platform
Real-Time Surveillance – Why?

• Improve timeliness of signal detection
• Improve sensitivity and specificity of methods
• Streamline processes and improve documentation
• Improve efficiency
SMART Overview
SMART System Overview

- SMART: custom application which uses multiple linked interfaces to accomplish the following objectives:
  - Create and manage AE groups for queries
  - Schedule, customize, and edit real-time surveillance queries
  - Batch job sends email to surveillance physician when alerts are found
  - Review, Triage and Analyze alerts
  - Document comments and signoff review of alerts
  - Suppress recurring alert types which, based on clinical judgment and product knowledge, do not require continued medical review
  - Manage overall surveillance strategy across all products

- Developer notes
  - JMP 11: user interface, reports, graphs
  - Oracle PL/SQL package: backend logic
  - Oracle tables: data storage
SMART System Architecture

**SMART Calendar**

**Batch Job**
Oracle PL/SQL

**SMART Database Tables**

**Notification and nag-o-grams emailed to Responsible Person**

**SCEPTRE Safety Data**

**SMART**

**Smart Medical Surveillance and Early Warning System (SMEWS)**

**Real-Time Surveillance System (RTSS)**

**Batch Job**

**Oracle PL/SQL**

**SMEWS Database Tables**

**Email Notification**

**Real-Time Surveillance System (RTSS)**

**JMP**

**Real-Time Surveillance System (RTSS)**

**SMEWS Database Tables**

**Email Notification**
Sample Notification

Dear [Name],

The Real Time Surveillance batch job found the following alerts:

<table>
<thead>
<tr>
<th>Product Name</th>
<th># Alerts</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Product A]</td>
<td>3</td>
<td>4 Weeks</td>
</tr>
<tr>
<td>[Product B]</td>
<td>6</td>
<td>4 Weeks</td>
</tr>
<tr>
<td>[Product C]</td>
<td>14</td>
<td>4 Weeks</td>
</tr>
<tr>
<td>[Product D]</td>
<td>42</td>
<td>4 Weeks</td>
</tr>
<tr>
<td>[Product E]</td>
<td>13</td>
<td>4 Weeks</td>
</tr>
<tr>
<td>[Product F]</td>
<td>24</td>
<td>4 Weeks</td>
</tr>
<tr>
<td>[Product G]</td>
<td>19</td>
<td>4 Weeks</td>
</tr>
<tr>
<td>[Product H]</td>
<td>7</td>
<td>4 Weeks</td>
</tr>
<tr>
<td>[Product I]</td>
<td>22</td>
<td>4 Weeks</td>
</tr>
<tr>
<td>[Product J]</td>
<td>18</td>
<td>4 Weeks</td>
</tr>
<tr>
<td>[Product K]</td>
<td>2</td>
<td>4 Weeks</td>
</tr>
<tr>
<td>[Product L]</td>
<td>10</td>
<td>4 Weeks</td>
</tr>
<tr>
<td>[Product M]</td>
<td>1</td>
<td>4 Weeks</td>
</tr>
</tbody>
</table>

To view these alerts in detail use the SMART menu in JMP.

smart@its.jnj.com

Connect to social networks to show profile photos and activity updates of your colleagues in Outlook. Click here to add networks.

There are no items to show in this view.
Sample Nag-o-gram

Dear [Name],

You have several alerts that are either due within 7 days or are past due:

<table>
<thead>
<tr>
<th>Product</th>
<th>Due Date</th>
<th>Alert Status</th>
<th># Alerts</th>
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<tr>
<td></td>
<td>19-May-2015</td>
<td>Open</td>
<td>3</td>
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<td></td>
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<td>Open</td>
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</tr>
<tr>
<td></td>
<td>19-May-2015</td>
<td>Open</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>19-May-2015</td>
<td>Open</td>
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<td></td>
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<td>19-May-2015</td>
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<td>7</td>
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<tr>
<td></td>
<td>19-May-2015</td>
<td>Open</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>19-May-2015</td>
<td>Open</td>
<td>6</td>
</tr>
</tbody>
</table>

To view these alerts in detail use the SMART menu in JMP.

smart@its.jnj.com

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SMART Algorithm

- SMART is designed to provide an early warning (alert) for the following reporting situations:
  - An AE or AE Group shows an increase in reporting percentage over time (Time Features Analysis)
  - A product is disproportionately reported with an adverse event (AE) or AE group ($IC025 = \text{Information Component of BCPNN} > 0^*$)
  - An AE is reported with a Fatal outcome for a product
  - An AE is reported with a positive Rechallenge for a product
  - An AE is Newly reported with a product
  - A product is reported with a Designated Medical Event (DME)
  - An AE is reported which has a 50% or greater probability of representing a safety signal (CLASP)
  - An AE is reported that is a user-defined Event of Interest (EVOI)

* Bayesian Confidence Propagation Neural Network, semi-empirical approximation
What is TFA?

- Time Features Analysis (TFA)
  - Monitor changes in reporting percentages for drug-event pairs over time
  - When “rules” are “broken”, a TFA alert is generated.
TFA Rules

• A method for identifying reporting percentage “behaviors” of a drug-event pair by a single alert.
  – Spike
  – Upward trend
  – Upward shift

• Each week of data since the last review will be evaluated against the TFA rules (e.g. a product with a biweekly review frequency will have 2 evaluation weeks)

• Historical data aggregated into time periods of:
  – 2 weeks (compared to 24 week moving average)
  – 4 weeks (compared to 48 week moving average)
  – 8 weeks (compared to 96 week moving average)
TFA Rules

- There are 3 rules applied to each of the time periods:

  - **Spike**
    - Only evaluated if there is more than 1 case for a drug-event pair in the evaluation week
    - Reporting percentage in the most recent time period (i.e. last 2, 4, 8 weeks) is greater than the average of the last 12 time periods plus 3x the standard deviation of the last 12 time periods

  - **Shift**
    - Reporting percentages of the last 5 time periods (totaling 10, 20, 40 weeks for the 2, 4, 8 week time periods, respectively) are greater than the reporting percentage over the past 12 time periods (24 week, 48 week, 96 week reporting percentage for the 2, 4, 8 week time periods, respectively)

  - **Trend**
    - Reporting percentages of the last 5 time periods are consecutively greater than the preceding time period
New TFA Rules

• TFA TREND and SHIFT rules modified

• Use 90% confidence limits to reduce the number of “spurious” TFA alerts.

• TREND rule:
  – Latest 5 time periods are each successively greater than preceding time period
  – Lower 90% confidence limit (LCL) of latest time period is greater than comparator moving moving average

• SHIFT rule:
  – Lower 90% confidence limit (LCL) from latest 5 time periods are all greater than comparator moving average
TREND Rule Example

Product: DALTSTRONG  PT: PARAESOMESIA 2/24 Wk Moving Avg

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SHIFT Rule Example

Product: DONLAB  PT: OFF LABEL USE 8/96 Wk Moving Avg

- WK8_Trend
- WK8_Shift
- WK8_Spike
- RP_8_Week_MA
- RP_96_Week_MA
- RP_Cuml_Cases
- WK8 Rule Points
- WK8 LCL

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What is CLASP?

- **Case Level Attribute Systematic Prioritization**
- CLASP model developed on case-level attributes of historical data
- Model deployed on future data to make predictions
- CLASP score
  - 0: not an alert, given past behavior
  - 1: high probability that this is an alert, given past behavior
CLASP Model Schematic

Attributes for drug-event cases

0: Not an alert
1: Alert
## Attributes used to generate CLASP alerts

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Key</th>
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</thead>
<tbody>
<tr>
<td>HAS_LAB_INFO</td>
<td>IS_SERIOUSCASE</td>
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<td>HAS_DRUG_END</td>
<td>IS_EVENT_NOT_CORELABELED</td>
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<td>HAS_DOSE_REGIMEN</td>
<td>IS_PEDIATRIC</td>
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<tr>
<td>HAS_EVENT_START</td>
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<td>HAS_PATIENTAGE</td>
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<td>IS_NEGATIVE_EQUIVEVERY</td>
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<tr>
<td>IS_PRIMREPORTER_PHARMACIST</td>
<td>IS_NARRATIVELENGTH_ABOVEOTHRESH</td>
</tr>
<tr>
<td>IS_PRIMREPORTER_PHYSICIAN</td>
<td>IS_NARRATIVELENGTH_ABOVEOTHRESH</td>
</tr>
<tr>
<td>IS_PRIMREPORTER_MEDICALPROF</td>
<td>IS_NARRATIVELENGTH_ABOVEOTHRESH</td>
</tr>
<tr>
<td>IS_DRUGOUTCOME_DOSECREASED</td>
<td>IS_NARRATIVELENGTH_ABOVEOTHESH</td>
</tr>
<tr>
<td>IS_DRUGOUTCOME_DOSEREDUCED</td>
<td>IS_NARRATIVELENGTH_ABOVEOTHESH</td>
</tr>
<tr>
<td>IS_DRUGOUTCOME_DOSESTRESSED</td>
<td>IS_NARRATIVELENGTH_ABOVEOTHESH</td>
</tr>
<tr>
<td>IS_DRUGOUTCOME_DOSESTRESSED</td>
<td>IS_NARRATIVELENGTH_ABOVEOTHESH</td>
</tr>
<tr>
<td>IS_DRUGOUTCOME_DRUGWITHDRAWN</td>
<td>IS_NARRATIVELENGTH_ABOVEOTHESH</td>
</tr>
<tr>
<td>IS_DRUGOUTCOME_NA</td>
<td>IS_NARRATIVELENGTH_ABOVEOTHESH</td>
</tr>
<tr>
<td>IS_DRUGOUTCOME_UNKNOWN</td>
<td>IS_NARRATIVELENGTH_ABOVEOTHESH</td>
</tr>
<tr>
<td>IS_FATALCASE</td>
<td>numCases_INV = 1/total # cases in series</td>
</tr>
</tbody>
</table>

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SMART Options

- **Create Alert Definition**: schedule and customize new real-time surveillance alert queries
- **Edit Alert Definition**: edit existing real-time surveillance alert queries
- **Administration submenu**: Add user/edit existing user
- **Reports submenu**: various summary reports
- **Custom MedDRA Groups**: creation and maintenance of AE Groups
- **Manage MedDRA groups**: rename groups or set group status to active/inactive
- **Alert Dashboard**: searchable, cumulative record of all alerts for each unique alert query
- **Alert Review**: supports analysis and documentation of alerts as well as suppression of recurring alerts which, based on clinical judgment and product knowledge, do not require continued medical review.
SMART Demo
Narrative Drilldown
AER (2005148071) was migrated from the Johnson & Johnson ARISg Consumer Safety Database into the Johnson & Johnson SCEPTRE Safety Database on 19-FEB-2011.

A 75-YEAR-OLD FEMALE CONSUMER HAS BEEN USING 1ML OF [REDACTED] TWICE DAILY SINCE APR2005 (DATE UNSPECIFIED) FOR BALDING. SHE STATED THAT THE PRODUCT WORKS GREAT. AS OF 29-OCT2005 PRODUCT USE WAS CONTINUED.

Additional information was received from the patient on 16-JAN-2014.
This report concerns an 85-year-old female. The patient's weight was not reported.
The patient was treated with [REDACTED] topical, batch 3323CP, unspecified formulation) "dropper full twice a day," initiated on APR-2005 for hair regrowth (wrong patient received medication).
On an unspecified date, the patient reported that she had been using the product for the past 20 years and that it has done a wonderful job (unexpected therapeutic benefit).
The dose of [REDACTED] was not changed.
The outcome for wrong patient received medication and unexpected therapeutic benefit were not reported.
This case is a duplicate of 20140110976.

2. 20131117187(2)

This spontaneous report was received from a 60 year old female patient reporting on herself from Canada: 015947717A.
The patient's weight was 129 pounds and height was not reported.
The patient's medical history was not reported.
The patient was treated with [REDACTED] 5% (foam, topical, batch L0093D38, expiry APR-2014) (foam, topical, batch 2992RD) initiated on an unspecified date for hair loss in front of head. Concomitant medications were not reported.
It was reported that it did not work for her (lack of effect). Initially, it came out as foam. Then after a week it was coming out as a liquid (product quality issue). Later completely stopped coming out. The pumps initially worked and then totally stopped dispensing (product quality issue).
Narrative Word Cloud

- Text size indicates word frequency
- Color differentiates words
Case Quality Drilldown
Case Quality Drilldown

- Case Quality score (0-5)
- Case Quality category (Low, Med-Low, Medium, Med-High, High)
- Subset of CLASP attributes indicative of case quality
- Narrative drilldown
### Case Attributes for CLASP Quality Score

<table>
<thead>
<tr>
<th>Case Attributes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary reporter is a physician, pharmacist, or other health care professional</td>
</tr>
<tr>
<td>Patient sex is reported</td>
</tr>
<tr>
<td>Patient age is reported</td>
</tr>
<tr>
<td>Patient medical history is reported</td>
</tr>
<tr>
<td>Patient social history (e.g., alcohol or tobacco use) is reported</td>
</tr>
<tr>
<td>Patient laboratory data are reported</td>
</tr>
<tr>
<td>Drug indication is reported</td>
</tr>
<tr>
<td>Drug outcome is reported</td>
</tr>
<tr>
<td>Drug start date is reported</td>
</tr>
<tr>
<td>Drug end date is reported</td>
</tr>
<tr>
<td>Drug dose and regimen are reported</td>
</tr>
<tr>
<td>Other drugs are reported</td>
</tr>
<tr>
<td>Other suspect drugs are reported</td>
</tr>
<tr>
<td>Event start date is reported</td>
</tr>
<tr>
<td>Event end date is reported</td>
</tr>
<tr>
<td>Event outcome is reported</td>
</tr>
</tbody>
</table>

**Combination:** Both drug and event outcome are reported

**Combination:** Both drug and event start dates are reported
## Case Quality Scoring

<table>
<thead>
<tr>
<th>Quality Category</th>
<th>Quality Score</th>
<th>Critical Case Information (first step in assessing score)*</th>
<th>No. Quality Attributes within Case</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>&gt; 4.0 to 5.0</td>
<td>Pos. Rechall</td>
<td>13 to 18</td>
</tr>
<tr>
<td>Med-High</td>
<td>&gt; 3.0 to 4.0</td>
<td></td>
<td>10 to 12</td>
</tr>
<tr>
<td>Medium</td>
<td>&gt; 2.0 to 3.0</td>
<td></td>
<td>7 to 9</td>
</tr>
<tr>
<td>Med-Low</td>
<td>&gt; 1.0 to 2.0</td>
<td>Neg. Latency; Multi-patient literature</td>
<td>4 to 6</td>
</tr>
<tr>
<td>Low</td>
<td>0 to 1.0</td>
<td></td>
<td>0 to 3</td>
</tr>
</tbody>
</table>

*If critical case information is available, cases are immediately categorized accordingly. Otherwise, case quality attributes are counted to derive the case score and category.
### Case Quality Output

![Case Quality Output Table](image-url)

- **Q Category**: Q Score, Report Number, Ver
- **Drug Generic Name**: ERYTHEMA
- **D-Rank**: 1
- **E-Rank**: 2
- **Core Label**: LABELLED
- **Characteristics**: Spont: S-Event
- **Fatal**: No
- **Lit.**: No
- **Primary Reporter**: Other Health Professional
- **Reported Causality**: Probable
- **Latency**: 83
- **Recovery**: 0

---

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## Case Quality Narrative Drilldown

<table>
<thead>
<tr>
<th>Q Category</th>
<th>Q Score</th>
<th>Report Number</th>
<th>Ver</th>
<th>ERank</th>
<th>Core Label</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>4.15</td>
<td>20131201196</td>
<td>0</td>
<td>1</td>
<td>LABELED</td>
<td>ERYTHEMA</td>
</tr>
<tr>
<td>High</td>
<td>4.15</td>
<td>20131202542</td>
<td>0</td>
<td>1</td>
<td>UNLABELED</td>
<td>ERYTHEMA</td>
</tr>
<tr>
<td>High</td>
<td>4.15</td>
<td>20131212877</td>
<td>0</td>
<td>2</td>
<td>LABELED</td>
<td>ERYTHEMA</td>
</tr>
<tr>
<td>Med-High</td>
<td>4.00</td>
<td>20131209409</td>
<td>0</td>
<td>2</td>
<td>LABELED</td>
<td>ERYTHEMA</td>
</tr>
<tr>
<td>Med-High</td>
<td>4.00</td>
<td>20131210171</td>
<td>0</td>
<td>2</td>
<td>LABELED</td>
<td>ERYTHEMA</td>
</tr>
<tr>
<td>Med-High</td>
<td>4.00</td>
<td>20131209529</td>
<td>0</td>
<td>2</td>
<td>LABELED</td>
<td>ERYTHEMA</td>
</tr>
<tr>
<td>Med-High</td>
<td>4.00</td>
<td>20131202540</td>
<td>0</td>
<td>2</td>
<td>LABELED</td>
<td>ERYTHEMA</td>
</tr>
<tr>
<td>Med-High</td>
<td>3.35</td>
<td>20131201192</td>
<td>0</td>
<td>3</td>
<td>LABELED</td>
<td>ERYTHEMA</td>
</tr>
<tr>
<td>Med-High</td>
<td>3.35</td>
<td>20131211921</td>
<td>0</td>
<td>3</td>
<td>LABELED</td>
<td>ERYTHEMA</td>
</tr>
<tr>
<td>Medium</td>
<td>3.00</td>
<td>20131202510</td>
<td>0</td>
<td>4</td>
<td>LABELED</td>
<td>ERYTHEMA</td>
</tr>
<tr>
<td>Medium</td>
<td>3.00</td>
<td>20131106964</td>
<td>0</td>
<td>4</td>
<td>LABELED</td>
<td>ERYTHEMA</td>
</tr>
<tr>
<td>Medium</td>
<td>2.65</td>
<td>20131206319</td>
<td>0</td>
<td>5</td>
<td>LABELED</td>
<td>ERYTHEMA</td>
</tr>
<tr>
<td>Medium</td>
<td>2.65</td>
<td>20131208285</td>
<td>1</td>
<td>5</td>
<td>LABELED</td>
<td>ERYTHEMA</td>
</tr>
<tr>
<td>Medium</td>
<td>2.65</td>
<td>20131211914</td>
<td>2</td>
<td>5</td>
<td>LABELED</td>
<td>ERYTHEMA</td>
</tr>
<tr>
<td>Medium</td>
<td>2.35</td>
<td>20131116497</td>
<td>0</td>
<td>6</td>
<td>LABELED</td>
<td>ERYTHEMA</td>
</tr>
<tr>
<td>Med-Low</td>
<td>2.00</td>
<td>20131112693</td>
<td>0</td>
<td>6</td>
<td>LABELED</td>
<td>ERYTHEMA</td>
</tr>
<tr>
<td>Med-Low</td>
<td>2.00</td>
<td>20131203193</td>
<td>1</td>
<td>6</td>
<td>LABELED</td>
<td>ERYTHEMA</td>
</tr>
<tr>
<td>Med-Low</td>
<td>1.65</td>
<td>20131208215</td>
<td>0</td>
<td>7</td>
<td>LABELED</td>
<td>ERYTHEMA</td>
</tr>
<tr>
<td>Med-Low</td>
<td>1.35</td>
<td>20131103568</td>
<td>1</td>
<td>7</td>
<td>LABELED</td>
<td>ERYTHEMA</td>
</tr>
<tr>
<td>Med-Low</td>
<td>1.35</td>
<td>20131202742</td>
<td>0</td>
<td>7</td>
<td>LABELED</td>
<td>ERYTHEMA</td>
</tr>
<tr>
<td>Low</td>
<td>1.00</td>
<td>20131203192</td>
<td>0</td>
<td>8</td>
<td>LABELED</td>
<td>ERYTHEMA</td>
</tr>
<tr>
<td>Low</td>
<td>1.00</td>
<td>20131210806</td>
<td>0</td>
<td>8</td>
<td>LABELED</td>
<td>ERYTHEMA</td>
</tr>
<tr>
<td>Low</td>
<td>1.00</td>
<td>20131206391</td>
<td>0</td>
<td>8</td>
<td>LABELED</td>
<td>ERYTHEMA</td>
</tr>
</tbody>
</table>

Drilldown to narratives for selected rows in the case quality table.
Case Quality Narrative Drilldown Output

### 1. 20131108015(0)

<table>
<thead>
<tr>
<th>DRank</th>
<th>ERank</th>
<th>Event</th>
<th>Q Category</th>
<th>Q Score</th>
<th>Batch Lot #s</th>
<th>Latest Info Recvd Date</th>
<th>Reporter qualification</th>
<th>Reaction PTs</th>
<th>Suspect Product</th>
<th>Co-suspect Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
<td>ERYTHEMA</td>
<td>Med-High</td>
<td>3.65</td>
<td></td>
<td>14-Nov-2013</td>
<td>Consumer or Other Non Health Professional</td>
<td>OFF LABEL USE</td>
<td>INFUSION RELATED REACTION</td>
<td>COUGH, HYPERHIDROSIS, ERYTHEMA</td>
</tr>
</tbody>
</table>

This spontaneous report was received from a patient’s mother and concerns her 9-year-old son from Mexico; local case ID: MEX367/2013. Initial information was processed along with the additional information received on 14-NOV-2013. The patient’s height was not reported and weight was 35 kilograms. The patient’s medical history included uveitis. The patient’s history of drug allergies was not reported. The patient was treated with lyophilized powder, intravenous (dose unspecified) initiated on 26-JUN-2013 for uveitis (off label use). Concomitant medications were not reported. On 11-NOV-2013, when the infusion began, the patient presented a forced cough, had sweating and was very red. It was stated that “he was very bad”. The treatment was suspended. Treatment with was withdrawn. The patient had recovered from cough, sweating and redness on 11-NOV-2013 and off-label use on 12-NOV-2013. This report was not serious.

### 2. 201312000192(0)

<table>
<thead>
<tr>
<th>DRank</th>
<th>ERank</th>
<th>Event</th>
<th>Q Category</th>
<th>Q Score</th>
<th>Batch Lot #s</th>
<th>Latest Info Recvd Date</th>
<th>Reporter qualification</th>
<th>Reaction PTs</th>
<th>Suspect Product</th>
<th>Co-suspect Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3</td>
<td>ERYTHEMA</td>
<td>Med-High</td>
<td>3.35</td>
<td></td>
<td>02-Dec-2013</td>
<td>Physician</td>
<td>BLOOD PRESSURE INCREASED</td>
<td>PRURITUS, ERYTHEMA</td>
<td></td>
</tr>
</tbody>
</table>

This spontaneous report was received from a physician and concerns a male patient of unspecified age from New Zealand; local case ID: ANZ0414812. The patient’s height and weight were not reported. The patient’s concurrent conditions included ankylosing spondylitis and Crohn’s disease.

The patient was treated with lyophilized powder, intravenous (10 mg once every 8 weeks, initiated on an unspecified date for ankylosing spondylitis and Crohn’s disease. Concomitant medications included hydrocortisone and loratadine. On an unspecified date (after on 3rd infusion), the patient had experienced blood pressure was raised and redness in face. Infusion stopped then restarted. On 4th infusion, dose of was reduced to 5 mg once every 4 weeks. However the patient developed an itchy as well as redness in face. Infusion was stopped. It was reported that Crohn’s symptoms had improved and gastroenterologist would like to continue with infusions. The dose of was reduced. The patient had not recovered from raised blood pressure, itchy and redness in face.

This report was not serious.

### 3. 20131201196(0)

<table>
<thead>
<tr>
<th>DRank</th>
<th>ERank</th>
<th>Event</th>
<th>Q Category</th>
<th>Q Score</th>
<th>Batch Lot #s</th>
<th>Latest Info Recvd Date</th>
<th>Reporter qualification</th>
<th>Reaction PTs</th>
<th>Suspect Product</th>
<th>Co-suspect Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>ERYTHEMA</td>
<td>High</td>
<td>4.15</td>
<td></td>
<td>02-Dec-2013</td>
<td>Other Health Professional</td>
<td>HYPERSENSITIVITY</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Technical Bits
Technical Bits

- Trend charts with tabbed interface and local data filters
- Moving averages in SQL
- DSN-less ODBC connection to Oracle
- User interface tips
Trend Charts

- Tabbed interface to easily show 12 charts
- Local data filter for all stacked bar charts
Each graph is an expression

```r
ctryrp_expr = expr(
    current_data_table(rts_strat_chart_dt);
    trend_chart_ctryrp = Graph Builder(
        Show Control Panel( 0 ),
        Variables(
            X( :Name( "CTR Year-Quarter" ) ),
            Y( :Reporting Percentage ),
            Overlay( :Country ) ),
        Elements(Bar( X, Y, Legend( 3 ), Bar Style( "Stacked" ), Summary Statistic( "Sum" ) ) ),
        SendToReport(
            Dispatch( {}, "CTR Year-Quarter", ScaleBox,
                {Min( min_date ), Max( max_date ), Interval( "Month" ), Inc( x_increment ),
                 Minor Ticks( 0 ), Show Major Grid( 1 ), Rotated Labels( "Automatic" )} ),
            Dispatch( {}, "Reporting Percentage", ScaleBox, {Show Major Grid( 1 )} ),
            Dispatch({}, "graph title",.TextEditBox, {Set Text( rts_chart_title )} ) )
    );
)

// Add data filter for country
ldf_ctryrp = trend_chart_ctryrp << Local Data Filter( Add Filter( columns( :Country ),
    Display( :Country, Size( 204, 194 ), List Display ), ) );

ldf_ctryrp << (Filter Column( :Country ) << Order by Count( 1 ));
```
Tabs Within Tabs

trend_win = new window("Trend Charts",
  .
  .
  .
trend_output = tab box(
    "Reporting Percentages",
    tab box(
      "Total RP", rp_expr,
      "Country RP", ctryrp_expr,
      "Age Group RP", agerp_expr,
      "Gender RP", sexrp_expr,
      "Serious RP", serrp_expr,
      "Indications RP", indrp_expr,
      "Approval Number RP", ndarp_expr
    ),
    "Case Counts",
    tab box(
      "Total CC", cc_expr,
      "Country CC", ctry_expr,
      "Age Group CC", age_expr,
      "Gender CC", sex_expr,
      "Serious CC", ser_expr,
      "Indications CC", ind_expr,
      "Approval Number CC", nda_expr,
    )
  )
);
Close All Data Filters Initially

trend_win[Outline Box( 2 )]  << Close( 1 );
trend_win[Outline Box( 4 )]  << Close( 1 );
trend_win[Outline Box( 6 )]  << Close( 1 );
trend_win[Outline Box( 8 )]  << Close( 1 );
trend_win[Outline Box( 10 )] << Close( 1 );
trend_win[Outline Box( 12 )] << Close( 1 );

trend_win[Outline Box( 15 )] << Close( 1 );
trend_win[Outline Box( 17 )] << Close( 1 );
trend_win[Outline Box( 19 )] << Close( 1 );
trend_win[Outline Box( 21 )] << Close( 1 );
trend_win[Outline Box( 23 )] << Close( 1 );
trend_win[Outline Box( 25 )] << Close( 1 );
Find Data Filter using Tree Structure

trend_win << show tree structure;

![Tree Structure Diagram]
Moving Averages in SQL

-- Calculate moving average for the last 30 records.

SELECT cust_no, curr_month, curr_invoice,
    AVG(curr_invoice)
    OVER (PARTITION BY cust_no ORDER BY curr_month
    ROWS 30 PRECEDING) moving_avg
FROM my_orders
Moving Averages in SQL

```
SELECT a.calendar_id, a.alert_name, a.ctr_week_dt, a.ctr_week, a.event_type, a.event_name,
    avg(a.a_cases) over (PARTITION BY a.calendar_id, a.alert_name, a.event_type, a.event_name ORDER BY a.ctr_week ROWS BETWEEN 1 preceding AND CURRENT ROW) AS a_2_week_ma,
    avg(a.ab_cases) over (PARTITION BY a.calendar_id, a.alert_name, a.event_type, a.event_name ORDER BY a.ctr_week ROWS BETWEEN 1 preceding AND CURRENT ROW) AS ab_2_week_ma,
    avg(a.a_cases) over (PARTITION BY a.calendar_id, a.alert_name, a.event_type, a.event_name ORDER BY a.ctr_week ROWS BETWEEN 3 preceding AND CURRENT ROW) AS a_4_week_ma,
    avg(a.ab_cases) over (PARTITION BY a.calendar_id, a.alert_name, a.event_type, a.event_name ORDER BY a.ctr_week ROWS BETWEEN 3 preceding AND CURRENT ROW) AS ab_4_week_ma,
    avg(a.a_cases) over (PARTITION BY a.calendar_id, a.alert_name, a.event_type, a.event_name ORDER BY a.ctr_week ROWS BETWEEN 7 preceding AND CURRENT ROW) AS a_8_week_ma,
    avg(a.ab_cases) over (PARTITION BY a.calendar_id, a.alert_name, a.event_type, a.event_name ORDER BY a.ctr_week ROWS BETWEEN 7 preceding AND CURRENT ROW) AS ab_8_week_ma,
    avg(a.a_cases) over (PARTITION BY a.calendar_id, a.alert_name, a.event_type, a.event_name ORDER BY a.ctr_week ROWS BETWEEN 12 preceding AND CURRENT ROW) AS a_13_week_ma,
    avg(a.ab_cases) over (PARTITION BY a.calendar_id, a.alert_name, a.event_type, a.event_name ORDER BY a.ctr_week ROWS BETWEEN 12 preceding AND CURRENT ROW) AS ab_13_week_ma,
    avg(a.a_cases) over (PARTITION BY a.calendar_id, a.alert_name, a.event_type, a.event_name ORDER BY a.ctr_week ROWS BETWEEN 23 preceding AND CURRENT ROW) AS a_24_week_ma,
    avg(a.ab_cases) over (PARTITION BY a.calendar_id, a.alert_name, a.event_type, a.event_name ORDER BY a.ctr_week ROWS BETWEEN 23 preceding AND CURRENT ROW) AS ab_24_week_ma,
    avg(a.a_cases) over (PARTITION BY a.calendar_id, a.alert_name, a.event_type, a.event_name ORDER BY a.ctr_week ROWS BETWEEN 47 preceding AND CURRENT ROW) AS a_48_week_ma,
    avg(a.ab_cases) over (PARTITION BY a.calendar_id, a.alert_name, a.event_type, a.event_name ORDER BY a.ctr_week ROWS BETWEEN 47 preceding AND CURRENT ROW) AS ab_48_week_ma,
    avg(a.a_cases) over (PARTITION BY a.calendar_id, a.alert_name, a.event_type, a.event_name ORDER BY a.ctr_week ROWS BETWEEN 95 preceding AND CURRENT ROW) AS a_96_week_ma,
    avg(a.ab_cases) over (PARTITION BY a.calendar_id, a.alert_name, a.event_type, a.event_name ORDER BY a.ctr_week ROWS BETWEEN 95 preceding AND CURRENT ROW) AS ab_96_week_ma
FROM
    a
WHERE
    a.calendar_id BETWEEN 95 AND 47
ORDER BY
    a.calendar_id,
    a.ctr_week
```

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Oracle ODBC DSN-Less Connection

- Control Panel > Administrative Tools > Data Sources (ODBC)
- Check **Drivers** tab for name of Oracle driver
- Use driver name in connection string

```plaintext
dsn_string = "Driver={Oracle in OraClient11g64_home1};
Dbq=database_name;UID=username;PWD=password;"
```

- **database_name** alias found in TNSNAMES.ORA
User Interface Tips

- Application Builder great for prototyping
- Keep things lined up (users can detect pixel differences!)
- Use **Panel Box** to organize things, label sections
- Use **Lineup Box** to line things up
- Use icons on buttons
### SMART: Create New Alert Definition

#### Define Alert Types

<table>
<thead>
<tr>
<th>Alert Type</th>
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#### Product Search Term

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#### Dosage Forms

(If none are selected, all will be used)

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#### Set Status

- **Active**
  - Actions: [Save], [Exit], [Help]
- **Inactive**

Saved? | 63
Conclusions

• SMART has met all of our objectives
• “Real-time” monitoring every 2, 4 or 8 weeks
• Surveillance physicians proactively identify new safety risks
• Transparency from alert to final assessment
• Industry-leading real-time signal detection platform
• Improved timeliness of signal detection
• Improved sensitivity and specificity of methods
• Streamlined processes and improve documentation
• Improved efficiency
• JMP + Oracle an excellent combination
Conclusions (why I like JMP)

- JMP Script Language (JSL)
- Application Builder: Easy interface design
- Graph Builder
- Datasets: easy to use table structure
- Oracle connection
- Tabulate
- Rich statistical platforms and functions
- Add-ins:
  - Easy menu development
  - Easy deployment
Key Learnings

• Listen to your users
• Listen some more
• Keep listening!
• Don’t say no right away
• Show prototypes
• Users don’t know what they want until they see what they don’t want
Key Learnings

• KISS

• Consistency

• Catchy name (SMART better than IRTSS)

• Give users ability to
  – Create
  – Edit
  – Configure
  – Report
Questions???

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