Tools for Enhanced Pharmacovigilance and Signal Detection in Clinical Trials

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Presentation Outline

• Quantitative Signal Detection
• Signal Detection in Clinical Trials
• Regulatory Considerations
• The Importance of Data Standards
• Representative Examples
• Instream Study Review
• Implications and Conclusions
Hands-on Signal Detection

“Canada’s system of ADR reporting was set up by Dr. Ed Napke, a man who liked to see what was going on. Although the reporting system was computerized, Napke developed a system of "pigeon holes" into which reports were filed. Coloured tabs were attached to reports of severe or unusual reactions as they were filed. When clusters of coloured tabs began to emerge, Napke and his small team had a visual cue that something might be wrong.”

CBC News Online, February 17, 2004
Quantitative Signal Detection with Post-Marketing Data
Primary Sources of Safety Evidence

Clinical Trials
- **Strengths:**
  - High-quality treatment & control data
  - Randomization removes bias
  - Drugs and events clearly identified

- **Weaknesses:**
  - Small patient counts
  - Under-representation of subgroups
  - Minimal long-term exposure data
  - High costs and delays until results

Spontaneous AE Reports
- **Strengths:**
  - Clearly identifies drug-adverse event relationships
  - Timely, centralized collection and processing

- **Weaknesses:**
  - Voluntary reporting means significant underreporting
  - Biases in reporting rate
  - Lack of drug exposure data

Healthcare Records
- **Strengths:**
  - Large patient populations
  - Drug dosing information available
  - Reflects actual medical practice

- **Weaknesses:**
  - “Raw” original data does not identify adverse events *per se.*
  - Substantial coding issues: upcoding, dx codes not capturing AEs; different coding practices

Safety Data Review and Signal Detection

Signal Detection, Query, Reporting

Signal Detection, Confirmation, Evaluation

Tracking, Prioritization, Evaluation and Communication
Detecting Signals from Clinical Trial Data

• Data standards make it possible to automate statistical screening to systematically explore safety issues and generate hypotheses
• Can use techniques such as $2 \times 2$ table analyses or logistic regression after blind is broken
• Depends on effective visualizations to identify potential signals and outliers
• Bayesian models can be helpful
  – Multivariate estimation of possibly related AEs
  – Searching for syndromes (different AEs in the same patients) associated with treatment and subgroup effects
  – Borrowing strength across medically related AEs
  – But requires a priori comparator distribution.
Regulatory Considerations

- Patient safety is the paramount concern
- Ensuring *validity* of statistical inferences and minimizing bias
- Maintaining study *integrity* (preplanning endpoints and analyses and maintaining blind)
- Data Safety Review Committees to have access to blinded data is accepted practice
- No official regulatory opinion on validity of using prior distributions and surrogate placebo populations as comparators
Standards Allow Quantitative Signal Detection

- Traditional safety monitoring is slow and time-consuming
  - Sponsors review blinded CRFs and listings
  - Data Safety Review Boards are unblinded, but lack tools
- Data Standards enable standards-based tools
  - Minimizes configuration and data transfer effort
  - Facilitates data pooling and re-use of standard methods
- Standards-based tools can improve safety review processes
  - Visualize aggregate data to identify areas of interest
  - Drilldown to patient details
  - Identify and track safety issues as data accumulates
- Fundamental concepts defined by FDA Good Review Practice Guidance on Safety Review and CIOMS VI
  - Compare safety for treatment and subpopulations
  - Examine Adverse Events at all MedDRA levels and SMQs
  - Explore Laboratory data, ECG, Vitals, Discontinuations.
SDTM V3.1.2 Domain Standards

- Interventions
  - Con Meds
  - Exposure
  - Substance Use

- Events
  - Adverse Events
  - Disposition
  - Medical History
  - Clinical Events

- Findings
  - ECG
  - Incl/Excl Exceptions
  - Labs
  - Physical Exam
  - Questionnaire
  - Subject Characteristics
  - Vital Signs

- Special Purpose
  - Demographics
  - Comments

- Trial Design

Source: CDISC
Visualizations Focus Attention
Safety at a Glance Patient Profiles

- Time series graphical display of patient progression highlights potential safety issues during and after trial
- Can drill down to review specific data points
- Preserves blind – can be used during trial as well as post-lock

Liver Function Test Patient Profiles

Hematoxicity Patient Profile

- Exposure (by Dose)
- Adverse Events (by Severity)
  - Anorexia
  - Nausea
  - Abdominal pain
  - Weight decreased
- Concomitant Medications
  - SALBUTAMOL

Vital Signs

- DIA 84.95
- HT 137.975
- PUL 75.85
- SYS 134.2
- WPT 78.618

Labs (Filtered when no out of range values)

- CHLORIDE
- GLUCFAST
- GLUCRAND

- 1500 mg White F 48

Subject: CD-038861 - Age: 55 - Sex: F - Race: Caucasian
Study Arm: STUDYMED_1
Visualizations Highlight Signals

(Age_Group = '61 to 70')

White Blood Cell Count (10^9 per Litre)

Cumulative Incidence of Abdominal pain by Time of Initial Onset

Time Since Randomisation (Days)

Subjects At Risk
- PLACEBO: 74
- STDYMED_1: 79
- STDYMED_2: 92

Cumulative Proportion with Event

White Blood Cell Count
- Treatment
- Comparator
Drilldown to Evaluate Signals

- Visual presentation of clinical adverse event data for each System Organ Class (SOC)
- Tiles represent Primary Terms (PTs), High Level Term (HLTs), or High Level Group Terms (HLGTs)
- Colors and patterns provide "big picture" overview of the AE profile of the study drug vs. the controls
SDTM Simplifies Sub-population Analysis

- Results across subgroups can identify potential associations for further exploration
Advanced Statistical Signal Detection Methods

- Bayesian Logistic Regression for investigating risk factor effects on occurrence of events/issues
  - Identify events occurring with disproportionate frequency in subjects exposed to study drug
  - Events not ‘expected’ based on drug class, pre-clinical research, experience in earlier studies
  - Sufficient data is available through pooling

- Bayesian Issue Cluster Mining
  - Determines distance between each pair of issues
  - Find shortest distance between each pair
Empirical Bayes vs. Unadjusted Logistic Regression

Overall Treatment vs. Comparator Odds Ratios

Responses

Anuria (Empirical Bayes)
  Anuria (unadjusted)

Dry mouth (Empirical Bayes)
  Dry mouth (unadjusted)

Hyperkalaemia (Empirical Bayes)
  Hyperkalaemia (unadjusted)

Micturition urgency (Empirical Bayes)
  Micturition urgency (unadjusted)

Nocturia (Empirical Bayes)
  Nocturia (unadjusted)

Pollakiuria (Empirical Bayes)
  Pollakiuria (unadjusted)

Polydipsia (Empirical Bayes)
  Polydipsia (unadjusted)

Polyuria (Empirical Bayes)
  Polyuria (unadjusted)

Thirst (Empirical Bayes)
  Thirst (unadjusted)

Urine output increased (Empirical Bayes)
  Urine output increased (unadjusted)

Overall OR05-OR-OR95
Overall & Subgroup Treatment vs. Placebo Effects

Treatment vs. Comparator Odds Ratios, Overall and by Covariate Groupings (Issue = 'Dry mouth')

Predictors

<table>
<thead>
<tr>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex:F</td>
</tr>
<tr>
<td>Sex:M</td>
</tr>
<tr>
<td>Race:Black</td>
</tr>
<tr>
<td>Race:White</td>
</tr>
<tr>
<td>Race:Other</td>
</tr>
<tr>
<td>Indication:Indication 1</td>
</tr>
<tr>
<td>Indication:Indication 2</td>
</tr>
<tr>
<td>Diuretics:Y</td>
</tr>
<tr>
<td>Diuretics:N</td>
</tr>
<tr>
<td>Cardiac medications:Y</td>
</tr>
<tr>
<td>Cardiac medications:N</td>
</tr>
<tr>
<td>Urologicals:Y</td>
</tr>
<tr>
<td>Urologicals:N</td>
</tr>
<tr>
<td>Renal history:Y</td>
</tr>
<tr>
<td>Renal history:N</td>
</tr>
<tr>
<td>Age:50 and Under</td>
</tr>
<tr>
<td>Age:55 to 65</td>
</tr>
<tr>
<td>Age:65 to 75</td>
</tr>
<tr>
<td>Age:Over 75</td>
</tr>
</tbody>
</table>

OR05-OR-OR95 (Unadjusted)
Visualizing Issue Pairs in an Event Cluster

**Issues**

- SMQ: Torsade de Pointes/QT prolong [narrow]
- PT: Polyuria
- PT: Angina pectoris
- PT: Ecchymosis
- PT: Ventricular extrasystoles
- PT: Respiratory failure
- PT: Cardiogenic shock
- PT: Polydipsia

**Co-occurring Issue Pairs**

- 11
- 14
- 18
- 6
- 14
- 24
- 2
- 22
- 6
- 3
- 22
- 13
- 3
- 6
- 2
- 4
- 3
- 24
- 1
- 4
- 1
- 4
Exploring Signals in Blinded Data

- Review aggregate blinded data to identify outliers and anomalies
  - Same principles of aggregate visualization with drilldown
- Build surrogate comparator populations from appropriate past studies
  - Size should be comparable or (up to 5X larger than current study population)
  - Signals will be diluted (especially for very rare events)
  - Select data with similar treatment periods or comparable time windows exposure
  - Can use subject exposure days rather than subject counts as denominator
- Bayesian shrinkage methods reduce imbalancing effect of outliers -- provide a more trusted signal
- Use statistical screening to generate hypotheses
  - Use techniques such as logistic regression to adjust for age, sex, medical history and identify covariate effects
Implications and Conclusions

• Safety review and signal detection can be enhanced by using available technology with standardized data
  – Based on signal screening scores, aggregate visualizations and drilldowns

• Quantitative signal detection is most useful on large, pivotal late stage trials or pooled studies
  – But screening should begin early in the process

• Once safety signals or areas of interest are identified, they can be tracked over time and lead to further actions
  – Documentation can provide evidence of continuous proactive vigilance
  – Data can be compared to spontaneous reports and observational data

• Effective lifecycle safety management will require standard data, advanced tools and multiple sources of evidence.
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Thank You