Decision Making and Safety in Clinical Trials – Graphs make a Difference!

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Signal Detection, Strengthening, and Management Based on Clinical Trial, Spontaneous, Claims, and EHR Data

Session Abstract:
• This symposium will review many aspects of signal detection. The symposium will demonstrate practical mechanisms for signal detection, and how to assess, triage, strengthen, and manage signals and safety concerns. The presentations will show how to detect and manage signals from multiple data sources including clinical trial data, spontaneous adverse event reports, claims data, and electronic health records used in Integrated Delivery Networks.
Objectives of this Talk

1. Offer convincing evidence that graphs make a difference in understanding safety results
   – What is it about the human brain?
   – ECG example

2. Given that graphs make a difference, why aren’t they used more?
   – Process, Standards, Software
Is Your Brain Frozen?

- A recent article in Newsweek confirms what we all experience.
- From brain scans - parts of the brain best at decision-making can get overloaded.
- Too much information results in poorer decisions.

Is Your Brain Frozen?

- 40-60% of the human brain is devoted to visualization
- Human visual capability is far ahead of the computer

**Data in Table Format**

<table>
<thead>
<tr>
<th>Event</th>
<th>Drug A (%)</th>
<th>Drug B (%)</th>
<th>RelRisk</th>
<th>Low95%</th>
<th>Up95%</th>
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<td>7.3</td>
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<td>Dizziness</td>
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<td>1.5</td>
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<td>3.4</td>
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<td>Headache</td>
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<td>2.3</td>
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<td>Hypertension</td>
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<td>Rash</td>
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<td>1.1</td>
<td>0.4</td>
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<td>Infection Viral</td>
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<td>2.1</td>
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<td>Upper Respir Tract Infection</td>
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<td>0.7</td>
<td>1.2</td>
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<td>1.0</td>
<td>0.4</td>
<td>2.6</td>
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<tr>
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<td>1.0</td>
<td>0.4</td>
<td>2.6</td>
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<td>Coughing</td>
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<td>8.0</td>
<td>1.0</td>
<td>0.6</td>
<td>1.9</td>
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<tr>
<td>Meninges</td>
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<td>3.2</td>
<td>0.9</td>
<td>0.3</td>
<td>2.2</td>
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<td>Rhinotis</td>
<td>2.9</td>
<td>3.1</td>
<td>0.8</td>
<td>0.4</td>
<td>1.7</td>
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<td>Bronchitis</td>
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<td>3.7</td>
<td>0.7</td>
<td>0.3</td>
<td>1.8</td>
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<tr>
<td>Chest Pain</td>
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<td>3.2</td>
<td>0.7</td>
<td>0.5</td>
<td>4.4</td>
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<td>Chronic Obstructive Airways</td>
<td>22.0</td>
<td>35.2</td>
<td>0.6</td>
<td>0.5</td>
<td>0.8</td>
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<td>Dyspnea</td>
<td>2.1</td>
<td>6.9</td>
<td>0.3</td>
<td>0.1</td>
<td>0.8</td>
</tr>
</tbody>
</table>

**Identical Data in Graph**

Most Frequent On-Therapy Adverse Events Sorted by Relative Risk

- TREATMENT A (N=216)
- TREATMENT B (N=431)

**Signals easily identified**

(where the human brain is good at pattern recognition)
Graphical Perception

“When a graph is constructed, information is *encoded*. The *visual decoding* of this encoded information is *graphical perception*. The decoding is the vital link …

No matter how ingenious the encoding … and no matter how technologically impressive the production, a graph is a failure if the visual decoding fails.”

William Cleveland, *The Elements of Graphing Data*
Table Look-Up and Pattern Perception


Concept from William Cleveland, *The Elements of Graphing Data*
Advisory Committee Example

• Context: Experimental drug had shown approx. 4 msec increase in ECG QTc for the overall phase 2/3 population
• Concern Expressed: Subjects with a high baseline would be pushed over the critical 500 msec boundary.
The mean change of 4 msec alone doesn't show the whole story, there is also a strong relationship with change from the starting value.
We All Would Agree

Study teams
Decision-makers
Prescribers
Patients

Benefit from easy ways to understand results

Obvious?
Then why aren’t there more graphs in submissions?
Let’s Take a Look at the Clinical Study Analysis Process…

#1 Barrier to Making Quality Graphs is Time!
Understanding the Problem Space, Identifying and Implementing Solutions

A. Understand the problem space:
   • Graphs take time to make and authors have many activities competing for their time
   • Primary value of graphs may be downstream from those who create them

B. Solve the problems:
   • Faster ways to make graphs
   • Better understanding of graph usage downstream

C. Solutions:
   1. Improve graphics software
   2. Standard Graphs for Common Safety Questions
How to Make Quality Graphs More Quickly?

1. Improve Statistical Graphics Software
   *Important, but not the focus of this talk*

2. Standard Graphs for Common Safety Questions
   - To address safety questions that occur time and again
   - Many become familiar with using the same figure for the same question, know how to interpret
How to Make Quality Graphs More Quickly?

Use Standard Graphs for Common Safety Questions

- FDA/Industry/Academia Safety Graphics Wiki Goals

1. Identify areas particularly applicable or useful to regulatory review in which graphics can enhance understanding of safety information.
2. Develop a palette of statistical graphics for reporting on clinical trials safety data.
3. Recommend graphics for clinical data based on good scientific principles and best practices.
4. Create a publicly-available repository of sample graphics (ensuring appropriate credits are given for contributions), including data sets and code.
5. Educate and engage stakeholders through outreach activities
How to Make Quality Graphs More Quickly?
Use Standard Graphs for Common Safety Questions

- FDA/Industry/Academia Safety Graphics Wiki
  - Has common graphs for
    - Adverse Events
    - ECG
    - Labs/Liver Events
  - And some General Principles and tips for creating effective graphics

- See slides for:
How to Make Quality Graphs More Quickly?

Use Standard Graphs for Common Safety Questions

- Industry-wide: FDA/Industry/Academia Safety Graphics Wiki

Welcome to the CTSpedia section on statistical graphics.

I WANT TO:

- Select the right graph for my question:
  - Data Visualization
  - Labs/Liver (Links to listings: Labs Liver Clinical Question Listings)
  - ECG/Vitals
  - General Adverse Events
- See all graphical entries in the library
- Search for graphics
- Contribute a graphic to the library

LIBRARY SAMPLING

Three Highest Rated Graphs

<table>
<thead>
<tr>
<th>Title of Graphic</th>
<th>Image-Click to Enlarge</th>
<th>Score-Stars</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPA Axis Suppression</td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>Survival Plot</td>
<td></td>
<td>4.11</td>
</tr>
</tbody>
</table>
You’ll Remember this Graph from Earlier in the Talk...

**Maximum Change from Baseline vs. Baseline QTc**  
(Baseline Correction)  
Phase II/III Data

![Graph showing the maximum change from baseline vs. baseline QTc](image)
Safety Graphics Wiki ECG Subteam’s Answer for a Standard Graph

• Typically Tabular summaries of Categorical QTc
  – Changes from Baseline: N’s and % changes exceeding 30 and 60 msec
  – Raw/Absolute QTc values: N’s and % exceeding 450, 470, and 500

• Problem: interpreting the changes without knowing the Baseline or absolute QTc value

• Plot shows relationship of change to the absolute
Safety Graphics Wiki ECG Subteam’s Answer for a Standard Graph

Categorical QTc plot from CTSpedia

Individual Changes from Baseline (Day 0) by Baseline (Day 0) Value Page by Hour Post Dose TQT Study

- Treatment:
  - Placebo
  - Moxi (active control)
  - Exp Drug Low Dose
  - Exp Drug High Dose

* Changes from Baseline are defined as time matched changes from the baseline day. Horizontal lines refer to 30 and 60 msec changes and diagonal lines refer to 450, 480, and 500 msec from lower left to upper right.
Interpretation of Categorical QTc plot

• Design shortcoming of this graph type: regression to the mean
  • The majority of large changes occur in subjects with low baseline
  • The majority of large absolute values started with a high baseline
• Values of real concern are large changes with large absolute values – upper right is area of concern
• This couldn’t be assessed with a table where absolute and changes are presented separately – the dependence of one on the other is lost with tabular displays
How to Make Quality Graphs More Quickly?

*Use Standard Graphs for Common Safety Questions*

- The ECG example is just one of many for ECG
  - The same is true for Adverse Events and Lab/Liver
- Each graph entry in the wiki has a description of use, sample program code & data
- The wiki is searchable, has a glossary and many other features
How to Make Quality Graphs More Quickly?

Industry-wide: FDA/Industry/Academia Safety Graphics Wiki

- ... and if you’re not sure what kind of graph you need, Safety Graphics Wiki has guidance to find the best graph type for your needs
How to Make Quality Graphs More Quickly?

Ensure Clinical Interpretation of Standard Graphs is Understood

- At my company:
  - Having standard safety graphs is not enough – must increase usage

- “Effective Graphics Design for Clinical Development” course
  - 1/3 of course devoted to clinical interpretation, with great support from colleagues in safety and therapy

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**PHARMACEUTICAL STATISTICS**

*Pharmaceut. Statist.* 2008; 7: 20–35

Published online 26 February 2007 in Wiley InterScience

(www.interscience.wiley.com) DOI: 10.1002/pst.254

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**Graphical Approaches to the Analysis of Safety Data from Clinical Trials**

Ohad Amit¹, Richard M. Heiberger²,‡ and Peter W. Lane³,⁎,†

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²Department of Statistics, Temple University, USA

³Research Statistical Unit, GlaxoSmithKline, UK
How to Make Quality Graphs More Quickly?

Ensure Clinical Interpretation of Standard Graphs is Understood

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- “Effective Graphics Design for Clinical Development” course
  - 1/3 of course devoted to clinical interpretation, with great support from clinicians in safety and therapy areas

- Improve statistical graphics software
  - Standard safety templates at launch
  - Intuitive GUI interface / Quick ramp-up
  - High quality output with little fuss
  - Easy for users to change graphs, create new ones
Conclusions

• Graphs make a difference in understanding safety results
  – Pattern recognition of human brain far superior to computer

• Thoughtful consideration of
  – Process,
  – Standards, and
  – Software

will improve graphics usage in your organization

and across our industry
Acknowledgments

• FDA/Industry/Academia Wiki Group
  – Leads: George Rochester (FDA), Mat Soukup (FDA), Ken Koury (Merck), Brenda Crowe (Lilly)
  – Rich Anziano* (Pfizer) – Head of ECG subteam
  – 30+ statisticians

• GSK Statistical Graphics Workstream
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  – Tibco Spotfire Clinical Graphics team

*special thanks to Rich & Wiki ECG subteam for the ECG example