Graphical Analyses of Clinical Trial Safety Data

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Overview

• Current situation of clinical trial safety analyses
• Examples of statistical graphs used in safety analyses environment
• Summary
Clinical Trial Safety Analysis

• Safety assessment is crucial in drug development
• As part of risk management, safety data should be continuously monitored
• Current practice and available tools are not up to standard
• Recognize the need to develop new tools for reviewing, presenting and analyzing clinical trial safety data
Reviewing Safety Data
Safety Outputs
Building Blocks in Safety Analysis

• Standards for clinical trial data (CDISC)
  – Clinical Data Interchange Standards Consortium
• Approaches to coding of adverse events and MedDRA search strategies for use in clinical trial event counting and analysis
• Software tools for data access, exploration, analysis
• Modern statistical metrics to characterize event rates, risk and risk factors
• Some visual graphs and displays to facilitate understanding
Graphical Analyses

• A graph is worth 10000 words
• Statistical graphics are useful tools for exploring data, aiding inference and communicating results
  – Display large data coherently
  – Maximize the ability to detect unusual features
  – Facilitate communication with: regulators, investigators, collaborators, upper management, DMC, etc.
Application

• Examples of statistical graphs used to better visualize different types of clinical trial safety data and facilitate safety signal detection.

• Graphics tool-box in development

• Some questions to answer
  – Which AEs are elevated in treatment vs. placebo?
  – Any special patterns of AE onset?
  – What is the trend of treatment effects on safety outcomes over time?
  – Which patients have abrupt changes in lab tests? Is there temporal causality of drug intake?
Clinical Safety Data

• Data types:
  – Adverse Event Data
  – Lab Data
  – Other Data: demographic, exposure, vital signs, conMed, etc.

• Level of details:
  – Group level information display
  – Individual level information display
Demographic data
Drug exposure
### Table 2.1. Baseline Demographics

(Subjects Exposed to Study Drug)

<table>
<thead>
<tr>
<th></th>
<th>Study XXXX</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (N=165)</td>
<td>Drug A (N=164)</td>
<td>Total (N=329)</td>
<td></td>
</tr>
<tr>
<td><strong>Sex - n(%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>65 (39.4)</td>
<td>64 (39.0)</td>
<td>129 (39.2)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>100 (60.6)</td>
<td>100 (61.0)</td>
<td>200 (60.8)</td>
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<tr>
<td><strong>Race - n(%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>136 (82)</td>
<td>135 (82)</td>
<td>271 (82)</td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>6 (4)</td>
<td>8 (5)</td>
<td>14 (4)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>13 (8)</td>
<td>10 (6)</td>
<td>23 (7)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>6 (4)</td>
<td>7 (4)</td>
<td>13 (4)</td>
<td></td>
</tr>
<tr>
<td>Japanese</td>
<td>2 (1)</td>
<td>2 (1)</td>
<td>4 (1)</td>
<td></td>
</tr>
<tr>
<td>American Indian</td>
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<td>1 (1)</td>
<td>1 (0)</td>
<td></td>
</tr>
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<td>Native Hawaiian</td>
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<tr>
<td>Other</td>
<td>2 (1)</td>
<td>1 (1)</td>
<td>3 (1)</td>
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</table>
Baseline Demographics

<table>
<thead>
<tr>
<th>Conditioned by:</th>
<th>AGE65</th>
<th>SEX</th>
<th>RACE</th>
<th>B. WEIGHT</th>
<th>B. HEIGHT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>trtgrp: Drug A</strong></td>
<td><img src="chart1.png" alt="Chart" /></td>
<td><img src="chart2.png" alt="Chart" /></td>
<td><img src="chart3.png" alt="Chart" /></td>
<td><img src="chart4.png" alt="Chart" /></td>
<td><img src="chart5.png" alt="Chart" /></td>
</tr>
<tr>
<td>N</td>
<td>234</td>
<td>Female</td>
<td>149</td>
<td>Asian</td>
<td>Count: 349</td>
</tr>
<tr>
<td>Y</td>
<td>118</td>
<td>Male</td>
<td>203</td>
<td>Black</td>
<td>Missing: 6</td>
</tr>
<tr>
<td>Missing</td>
<td>3</td>
<td></td>
<td></td>
<td>Hispanic</td>
<td>Max: 125.91</td>
</tr>
<tr>
<td><strong>trtgrp: Drug B</strong></td>
<td><img src="chart1.png" alt="Chart" /></td>
<td><img src="chart2.png" alt="Chart" /></td>
<td><img src="chart3.png" alt="Chart" /></td>
<td><img src="chart4.png" alt="Chart" /></td>
<td><img src="chart5.png" alt="Chart" /></td>
</tr>
<tr>
<td>N</td>
<td>68</td>
<td>Female</td>
<td>50</td>
<td>Asian</td>
<td>Count: 101</td>
</tr>
<tr>
<td>Y</td>
<td>33</td>
<td>Male</td>
<td>51</td>
<td>Black</td>
<td>Missing: 0</td>
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<tr>
<td>Missing</td>
<td>0</td>
<td></td>
<td></td>
<td>Hispanic</td>
<td>Max: 161.0</td>
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<tr>
<td><strong>trtgrp: Placebo</strong></td>
<td><img src="chart1.png" alt="Chart" /></td>
<td><img src="chart2.png" alt="Chart" /></td>
<td><img src="chart3.png" alt="Chart" /></td>
<td><img src="chart4.png" alt="Chart" /></td>
<td><img src="chart5.png" alt="Chart" /></td>
</tr>
<tr>
<td>N</td>
<td>33</td>
<td>Female</td>
<td>21</td>
<td>Asian</td>
<td>Count: 47</td>
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<tr>
<td>Y</td>
<td>16</td>
<td>Male</td>
<td>28</td>
<td>Black</td>
<td>Missing: 4</td>
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<tr>
<td>Missing</td>
<td>2</td>
<td></td>
<td></td>
<td>Hispanic</td>
<td>Max: 122.0</td>
</tr>
</tbody>
</table>

- AGE65: Number of patients aged 65 or older.
- SEX: Distribution of males and females.
- RACE: Distribution of different race categories.
- B. WEIGHT: Distribution of body weight.
- B. HEIGHT: Distribution of body height.
Table 1.1 Summary of Subject-year Follow-up
(Subjects Exposed to Study Drug)
(Study XXXX)

<table>
<thead>
<tr>
<th></th>
<th>Study XXXX</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (N=184)</td>
</tr>
<tr>
<td><strong>Subjects Exposed to Study Drug (Subject-years)</strong></td>
<td></td>
</tr>
<tr>
<td><strong>N</strong></td>
<td>182</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>471.98</td>
</tr>
<tr>
<td><strong>Duration Exposed to Study Drug (Days)</strong></td>
<td></td>
</tr>
<tr>
<td><strong>n</strong></td>
<td>182</td>
</tr>
<tr>
<td><strong>Mean</strong></td>
<td>947.2</td>
</tr>
<tr>
<td><strong>SD</strong></td>
<td>302.01</td>
</tr>
<tr>
<td><strong>Median</strong></td>
<td>1094.0</td>
</tr>
<tr>
<td><strong>Q1, Q3</strong></td>
<td>1074.0, 1100.0</td>
</tr>
<tr>
<td><strong>Min, Max</strong></td>
<td>6.0, 1179.0</td>
</tr>
</tbody>
</table>
Summary of Safety Subjects Exposure by Treatment

Placebo

Drug A

Days on Study

mean

median

50% Inter-quartile

Central 95%
Summary of Safety Subjects Exposure by Treatment

Days from Randomization

Vertical bars indicate withdrawals from study due to AE.

Number of Subjects on Study

Placebo   Drug A

<table>
<thead>
<tr>
<th>Days on Study</th>
<th>Placebo</th>
<th>Drug A</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>200</td>
<td></td>
<td></td>
</tr>
<tr>
<td>400</td>
<td></td>
<td></td>
</tr>
<tr>
<td>600</td>
<td></td>
<td></td>
</tr>
<tr>
<td>800</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1200</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Placebo

- n: 182
- Min.: 6.0
- 1st Qu.: 1,074.0
- Median: 1,094.0
- Mean: 947.2
- 3rd Qu.: 1,100.0
- Max.: 1,179.0

Drug A

- n: 224
- Min.: 32.0
- 1st Qu.: 737.0
- Median: 1,094.0
- Mean: 916.3
- 3rd Qu.: 1,100.0
- Max.: 1,149.0
Adverse events data
### Table 2. Subject Incidence of All Treatment Emergent Adverse Events by Preferred Term in Descending Order of Frequency

*(Subjects Exposed to Study Drug)*

<table>
<thead>
<tr>
<th>PREFERRED TERM</th>
<th>Placebo (N = 184) n (%)</th>
<th>Drug A (N = 224) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Subjects Reporting Any Adverse Events</td>
<td>146 (79.3)</td>
<td>195 (87.0)</td>
</tr>
<tr>
<td>CONSTIPATION</td>
<td>43 (23.4)</td>
<td>59 (26.3)</td>
</tr>
<tr>
<td>ASTHENIA</td>
<td>32 (17.4)</td>
<td>39 (17.4)</td>
</tr>
<tr>
<td>BACK PAIN</td>
<td>27 (14.7)</td>
<td>37 (16.5)</td>
</tr>
<tr>
<td>BONE PAIN</td>
<td>23 (12.5)</td>
<td>34 (15.1)</td>
</tr>
<tr>
<td>FATIGUE</td>
<td>22 (12.0)</td>
<td>29 (12.9)</td>
</tr>
<tr>
<td>HYPOCALCAEMIA</td>
<td>5 (2.7)</td>
<td>16 (7.1)</td>
</tr>
<tr>
<td>INSOMNIA</td>
<td>22 (12.0)</td>
<td>10 (4.5)</td>
</tr>
<tr>
<td>DIZZINESS</td>
<td>5 (2.7)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>
AE dot plot by descending order of frequency
AE dot plot by descending order of risk difference
• P-risk plot
Serious Adverse Events Incidences (%)

Time on Study

0-6 mon  | 7-12 mon  | 13-18 mon | 19-24 mon

Drug A  | Placebo
Distribution of Days on Study to AE Onset for Subjects with AE

The image shows a bar chart illustrating the distribution of days on study to AE onset for subjects with AE. The x-axis represents the number of events, while the y-axis represents the time to AE onset in days. The chart compares placebo and Drug A, with different time intervals marked (6 mon, 12 mon, 18 mon, 24 mon). The bars indicate the number of events observed in each group at various time points.
Lab test data
Lab Shift Plots

On-Therapy Values (g/L) vs Baseline Values (g/L)

- **Albumin**
- **Hemoglobin**

- **Treatment**
- **Control**
Change of Albumin Corrected Calcium over Time by Creatinine Abnormality Grade

On study days
Creatinine increase baseline to worst on study grade shift = 1

On study days
Creatinine increase baseline to worst on study grade shift = 2
Figure 7.1. Mean (SD) Blood Pressure Subgrouped by Therapy Over Visit Weeks
Safety Analysis Set
Patient Profile

• Simultaneous display of large amount of relevant information of a subject
• Efficiently establish safety profile of a subject
• Easier to see drug effect, drug/drug interaction, connections between lab test and adverse events, etc.
Patient Profile

Basic info: demog, treatment, visit time, dosing

Lab values

AE/SAEs

serious

non-serious

Concomitant medications

ongoing

resolved
Patient Profile Legend

- Different symbols/colors to distinguish severity, seriousness
- Arrow to indicate whether AE/conMed resolved

Lab Values

- grade = 0
- grade = 1
- grade = 2
- grade = 3
- grade = 4, 5
- w/t CTCAE3.0 grade

CTDB AE/SAE Records

- Mild, Nonserious
- Moderate, Nonserious
- Severe, Nonserious
- Life-threatening, Serious
- Not-resolved
- ▲ Mild, Serious
- ▲ Moderate, Serious
- ▲ Severe, Serious
- ▲ Fatal, Serious
- Resolved
Summary

• Graphics are powerful in concisely and efficiently conveying multiple pieces of safety information
• Graphics are useful for efficacy analysis as well
• Graphs are not cure-all, should be used in combination with other statistical analyses methods and display formats
• There is a need for standardized statistical graphical language across industry and regulatory
  – SOPs on validation of graphic outputs are needed
• New tools and processes will facilitate signal detection and clinical trial safety management
• Still much to be done in this area
Reference

• Ohad Amit, Understanding Patients Safety Through Use of Statistical Graphics.
• William Blackwell, Tools for Data Mining and Signal Detection, DIA 19th Annual EuroMeeting
• Simon Day, Signal Detection from Clinical Trial Databases
• Trevor Gibbs, Pharmacovigilance and Risk Management. DIA 19th Euro meeting talk
• Michael O’Connell, Graphic analysis and reporting of safety data, 42th DIA annual meeting talk
Acknowledgement

• Rachel Flodin
• Springer Li
• Ying Tian
• Bob Treder
• Jenny Yuan
THE END
Back-up Slides
Clinical Trial Safety Analysis

• Safety data are often collected concomitantly in clinical trials - lack of proactive planning

• Safety analyses are usually descriptive in nature - lack of power

• Safety data and analysis results often reported in form of tables and listings – not easy to review and interpret
How to Lie With Statistics

• Huff’s timeless 1954 classic, How to Lie With Statistics. A beginning playbook might read as follows.

• Omit sample size, confidence, and any greeks (”The blindfolded leading the blind.”)

• Sample high, but use a flawed methodology to drive action from biased conclusions (”Measure with a micrometer, mark with a crayon, cut with an axe.”)

• Sample low, or at least sub-sample until the means tell an insightful story (”Throw it against the wall and see what sticks. Okay, throw it again.”)
Summary of Safety Subjects Exposure by Treatment

Days on Study

Placebo

Drug A

Central 95%

Mean

Median

50% Inter-quartile
Summary of Safety Subjects Exposure by Treatment

Days from Randomization

Vertical bars indicate withdrawals from study due to AE.

Number of Subjects on Study

Days on Study

Drug A
Placebo

Drug A
n :224
Min.: 32.0
1st Qu.: 737.0
Median: 1094.0
Mean: 916.3
3rd Qu.: 1100.0
Max.: 1149.0

Placebo
n :182
Min.: 6.0
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Median: 1094.0
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3rd Qu.: 1100.0
Max.: 1179.0
Baseline Lab Values

<table>
<thead>
<tr>
<th></th>
<th>Drug A</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug A</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Placebo</strong></td>
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<td><strong>Baseline Lab Values</strong></td>
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<tr>
<td><strong>Drug A</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Placebo</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Baseline Lab Values**

- **SGPT**
- **SGOT**
- **PHOS**
- **CREAT**
- **CA.CR**
- **ALP**
Glucose by Time

Glucose (ng/dL)

Moderate Hyperglycemia

Mild Hyperglycemia for Site 002

Mild Hyperglycemia for Site 001

Moderate

Severe

Life-threatening or disable

Study Day

Patient 1015 1017 1026 1050
2004 2008 2011 2023