Understanding Clinical Trial Data Through Use of Statistical Graphics

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A picture tells a thousand words

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A picture tells a thousand words
Outline

- Introduction

- Patient Safety
  - Exposure
  - Laboratory data
  - Hy’s law
  - AE relative risk

- Efficacy data
  - Waterfall plots
  - Skyline plots
  - Forest plots
Review of safety data

- Safety data from clinical trials is usually evaluated through simple summary tables and review of individual patient data
  - Formal analysis much less developed than for efficacy
  - Scan tables and patient listings and highlight “important” results in textual summaries

- The safety of a molecule is best understood by understanding data at the individual patient level

- Ideal opportunity to use graphical methods
  - Present concise summaries
  - Communicate main messages
  - Increase efficiency of review
Exposure

- Before looking at safety we need to answer a key question:

How many for how long and at what dose?
  - What is the exposure underlying the safety profile
  - Tabular summaries are useful…. 
## Summary of Exposure

<table>
<thead>
<tr>
<th>Exposure (Days)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>225</td>
</tr>
<tr>
<td>Mean</td>
<td>198</td>
</tr>
<tr>
<td>Median</td>
<td>187</td>
</tr>
<tr>
<td>Min</td>
<td>7</td>
</tr>
<tr>
<td>Max</td>
<td>500</td>
</tr>
</tbody>
</table>
Summary of Exposure

Subjects on Trt

<table>
<thead>
<tr>
<th></th>
<th>All Subjects</th>
<th>Ongoing Subjects</th>
<th>Completed Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects</td>
<td>225</td>
<td>94</td>
<td>131</td>
</tr>
<tr>
<td>Days on Drug</td>
<td>155, 92, 31, 5</td>
<td>94, 71, 26, 4</td>
<td>61, 21, 5, 1</td>
</tr>
<tr>
<td>Number of Subjects</td>
<td>250</td>
<td>150</td>
<td>100</td>
</tr>
</tbody>
</table>
A screening tool for AEs

Figure 9.02
Most Frequent On-Therapy Adverse Events Sorted by Relative Risk

- Contusion
- Muscle spasms
- Urinary tract infection
- Sinusitis
- Stomach discomfort
- Cellulitis
- Myalgia
- Nasal congestion
- Nasopharyngitis
- Nausea

Percentage of Subjects

Relative Risk with 95% CI
Lab Data
## Routine Summary Statistics for Liver Function

<table>
<thead>
<tr>
<th></th>
<th>Any Elevation</th>
<th>Elevations &gt; 3XULN</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT (n=200)</td>
<td>40%</td>
<td>15%</td>
</tr>
<tr>
<td>AST (n=200)</td>
<td>35%</td>
<td>12%</td>
</tr>
<tr>
<td>Bilirubin (n=200)</td>
<td>25%</td>
<td>2%</td>
</tr>
</tbody>
</table>

This tabular summary does not tell the whole story.
Consider a Simple Graph

For ASAT, ALKPH, and ALAT, the Clinical Concern Level is 2 ULN;
For BILTOT, the CCL is 1.5 ULN;
where ULN is the Upper Level of Normal Range
Graphical Style

- Graphical equivalent of a “shift table”
- Reference lines at clinically important levels
- Focus on upper left quadrant of each panel
- Position legend in unused part of graph with statement of numbers of patients
- May need legend for each panel to account for varying patient numbers
- Plot control group last to more readily identify Tx effect
- Consider displaying on log scale to account for skewed distribution
Some Relevant Questions

- Do ALT and AST track together?
- Are there simultaneous elevations in ALT and Bilirubin?
- …
Another Simple Scatter Matrix
Hy’s Law

- “Hy’s Law” was developed by Hyman Zimmerman as criteria for evaluating drug induced liver injury.

- The signal for potential for severe drug-related hepatotoxicity has three components:
  - 1. Elevation of transaminases >3 ULN: ALT AST
  - 2. Concomitant elevation of Bilirubin
  - 3. Absence of other etiology

- “Hy’s Law” could be evaluated as part of the scatter matrix by generating different symbols for subjects who meet the criteria.
Another version of the Scatter Matrix – Some Hypothetical Data
Patient Profiles

Subject ID= 8, Male, 74 yrs. old

Subject ID= 13, Male, 59 yrs. old

Subject ID= 10, Female, 59 yrs. old

Subject ID= 12, Female, 67 yrs. old

Days Since First Dose

Days Since First Dose
Waterfall Plot for Evaluating Changes from Baseline
Waterfall plot showing best volumetric reduction of brain tumors

Lin et al, ASCO 2007

N=194
Graphical style of “waterfall” plot

- A method for looking at tumour shrinkage
- Can be adapted for other data
- Displays the distribution by looking at the order statistics
- Color and patterns to differentiate magnitude of changes
- Can display distributional location shifts in a comparative setting
  - Beware if randomization is not 1:1
Some examples from regulatory review
A forest plot to make a point

HR=1.0
Skyline Plot, examination of time course of hazard ratio

Figure 3: Hazard Ratio and 95% CI for IRC Time to Progression Over Time

From FDA statistical review summary of Lapatinib
Summary and Conclusions

- Lake Blanche on Sunday

- Exposure critical first step in safety analysis

- Evaluation of patient safety from clinical trials
  - summary stats alone of limited value
  - graphics must provide identification of outliers
  - careful examination of individual patient data

- Waterfall plots valuable for change data

- Skyline plots indicate the maturity of an estimate
Acknowledgements

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References


