Clinical Trials Graphical Reporting: A Rescue From Tables

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Statistical Methods in Biopharmacy
Emerging Topics for Statistical Methodology in Clinical Drug Development

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Société Française de Statistique
Paris, France

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Clinical Trial Reporting

- Miscellaneous interim analyses
- Repeated DMC and final reports
- Reviewers need help
- Make patterns and signals apparent
- Handling multiple dimensions
- Tables often require categorization of continuous variables
### What are Tables Good For?

**Inducing Sleep!**

<table>
<thead>
<tr>
<th></th>
<th>Growth</th>
<th>Mature</th>
<th>Stagnant</th>
<th>Full</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( n = 5,218 )</td>
<td>( n = 5,226 )</td>
<td>( n = 5,262 )</td>
<td>( n = 26,243 )</td>
</tr>
<tr>
<td>( R )</td>
<td>MED</td>
<td>SD</td>
<td>MED</td>
<td>SD</td>
</tr>
<tr>
<td>BM</td>
<td>0.50</td>
<td>1.37</td>
<td>0.69</td>
<td>1.47</td>
</tr>
<tr>
<td>BETA</td>
<td>0.72</td>
<td>2.02</td>
<td>1.01</td>
<td>1.06</td>
</tr>
<tr>
<td>SIZE</td>
<td>2.36</td>
<td>2.22</td>
<td>5.07</td>
<td>2.47</td>
</tr>
<tr>
<td>LEV</td>
<td>0.19</td>
<td>0.28</td>
<td>0.17</td>
<td>0.27</td>
</tr>
<tr>
<td>ΔSG</td>
<td>0.06</td>
<td>2.24</td>
<td>0.01</td>
<td>0.24</td>
</tr>
<tr>
<td>ΔCE</td>
<td>0.05</td>
<td>0.78</td>
<td>0.03</td>
<td>0.82</td>
</tr>
<tr>
<td>ΔCFO</td>
<td>0.00</td>
<td>0.37</td>
<td>0.03</td>
<td>1.09</td>
</tr>
<tr>
<td>ΔROS</td>
<td>1.21</td>
<td>30.08</td>
<td>2.20</td>
<td>50.23</td>
</tr>
<tr>
<td>ΔNI</td>
<td>0.10</td>
<td>1.06</td>
<td>0.33</td>
<td>1.38</td>
</tr>
<tr>
<td>SG</td>
<td>0.61</td>
<td>4.13</td>
<td>0.26</td>
<td>3.28</td>
</tr>
<tr>
<td>CAP</td>
<td>0.12</td>
<td>0.31</td>
<td>0.08</td>
<td>0.15</td>
</tr>
<tr>
<td>DIV</td>
<td>0.00</td>
<td>0.25</td>
<td>0.07</td>
<td>0.39</td>
</tr>
<tr>
<td>AGE</td>
<td>16</td>
<td>10.55</td>
<td>39</td>
<td>27.3</td>
</tr>
</tbody>
</table>

**Image:** AMBIEN® (zolpidem tartrate) 10 mg Tablets.
What are Tables Good For?

- Summarizing categorical variables
- Information look-up
- Pretending there is more precision in estimates than actually exists
- Providing denominators (sample sizes)
Paul Murrell’s Basic Principles for Good Graphics

1. Display data values using position or length.
2. Use horizontal lengths in preference to vertical lengths.
3. Watch your data-ink ratio.
4. Think very carefully before using color to represent data values.
5. Do *not* use areas to represent data values.
6. *Please* do not use angles or slopes to represent data values.
7. *Please, please* do not use volumes to represent data values.

Murrell [2013]
Guidelines for High Information Graphics

- Exclude unneeded dimensions and chartjunk
- Graphics don’t need to be “dumbed down” or “sexy”
- Keep continuous variables continuous
- Use graphical perception research
  - Emphasize position along a common scale
- Don’t choose a graphic requiring an arbitrary choice
  - E.g., rotation of pie chart
- Avoid bar charts
- Choose *descriptive* descriptive statistics
- *Show* differences
- Use real estate to show useful information, not Table 1

Cleveland, Tufte, Bertin, …
Classic Books

- The Elements of Graphing Data
  - William S. Cleveland

- Semiology of Graphics
  - Jacques Bertin
Showing the Difference

Glycated Hemoglobin

-0.25  0.25  0.75

Male
Female

Difference

5.0  5.5  6.0  6.5

Glycated Hemoglobin
Not This
Showing Differences: Two Kaplan-Meier Curves

sex=female − sex=male
Depicting Uncertainty

Jackson [2008]
General Examples: Dropouts

Days
Fraction Remaining in Study
0 14 28 42 56 70 84 98 112 126 140
0.0 0.2 0.4 0.6 0.8 1.0
81 77 75 73 65 61 58 55 54 50 48 A
169 165 154 149 141 137 128 120 116 109 105 B
Safety Variable Clustering

Week 8

Spearman $\rho^2$

Variables:
- bun
- creatinine
- age
- smoking
- raceCaucasian
- potassium
- chloride
- sodium
- ggt
- alat
- asat
- albumin
- protein
- rbc
- hematocrit
- hemoglobin
- bilirubin
- platelets
- pack.yrs
- glucose
- sexmale
- height
- pr
- axis
- uric.acid
- weight
- bmi
- corr.qt
- qrs
- uncorr.qt
- hr
- neutrophils
- wbc
- coad
- alk.phos
- corr.qt
- uncorr.qt
- hr
- neutrophils
- wbc
- coad
- alk.phos
Cumulative Incidence of AEs

- Headache
- Abdominal pain
- Nausea
- Dyspepsia

Week

0 4 8 12 16 20

- 0.00
- 0.01
- 0.02
- 0.03
- 0.04
- 0.05
- 0.06

Values:
- 81
- 77
- 75
- 74
- 74 A
- 169
- 155
- 153
- 152
- 151
- 150
- 149
- 147
Empirical CDFs

Serum Bilirubin (mg/dl)
Proportion <= x
0 5 10 15 20 25
0.0 0.2 0.4 0.6 0.8 1.0
D-penicillamine
placebo

Albumin (gm/dl)
Proportion <= x
2.0 2.5 3.0 3.5 4.0 4.5
0.0 0.2 0.4 0.6 0.8 1.0
D-penicillamine
placebo

Prothrombin Time (sec.)
Proportion <= x
10 12 14 16
0.0 0.2 0.4 0.6 0.8 1.0
D-penicillamine
placebo

SGOT (U/ml)
Proportion <= x
100 200 300 400
0.0 0.2 0.4 0.6 0.8 1.0
D-penicillamine
placebo
Extended Box Plots

Quantiles

Median = \( Q_2 \)

\( Q_1 \)

\( Q_3 \)

Fraction of Sample Covered

0.05 0.125 0.25 0.375 0.5 0.625 0.75 0.875 0.95
Instead of Table 1: Baseline Variables vs. Outcome

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**Clinical Trials**
- Graphical Reporting

**RCT Reporting**

**Tables**

**Guidelines**

**General Examples**

**Safety Displays:**
- Many AEs

**Mixing Tables and Graphics**

**Suggested Model**

**References**
Multi-Panel Dot Plots

Male ○ Female △

Use of medication
Attack of asthma
Waking with an attack of cough
Waking with shortness of breath
Waking with tightness in the chest
Wheezing without a cold
Wheezing and breathless
Wheezing at any time

Specificity

Sensitivity

Use of medication
Attack of asthma
Waking with an attack of cough
Waking with shortness of breath
Waking with tightness in the chest
Wheezing without a cold
Wheezing and breathless
Wheezing at any time

Mail ○ Telephone △
Dispense with Lab Parameter Change Tables

Counts

 Creatinine Day 14

Creatinine Day 3

Counts

0 2 4 6 8
0 2 4 6 8
Creatinine Day 3
Creatinine Day 14

Counts

183
156
132
111
92
75
60
48
37
28
21
15
10
7
4
2
1
Most Frequent On-Therapy Adverse Events Sorted by Risk Difference

Proportion

Risk Difference with 0.95 CI

Modification of Amit et al. [2008]
SAEs by Body System and Preferred Term

By Svetlana Eden, Vanderbilt; part of R rreport package
## Mixing Tables and Graphics

<table>
<thead>
<tr>
<th></th>
<th>D-penicillamine</th>
<th>placebo</th>
<th>Test Statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Bilirubin mg/dl</td>
<td>0.725 1.300 3.600</td>
<td>0.800 1.400 3.200</td>
<td>$F_{1,310} = 0.04$, $P = 0.842^1$</td>
</tr>
<tr>
<td>Albumin gm/dl</td>
<td>3.34 3.54 3.78</td>
<td>3.21 3.56 3.83</td>
<td>$F_{1,310} = 0$, $P = 0.951^1$</td>
</tr>
<tr>
<td>Histologic Stage Ludwig Criteria</td>
<td></td>
<td></td>
<td>$\chi^2 = 4.63$, $P = 0.201^2$</td>
</tr>
<tr>
<td>1</td>
<td>3% 1/154</td>
<td>8% 12/158</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>21% 32/154</td>
<td>22% 35/158</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>42% 64/154</td>
<td>35% 56/158</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>35% 54/154</td>
<td>35% 55/158</td>
<td></td>
</tr>
<tr>
<td>Prothrombin Time sec.</td>
<td>10.0 10.6 11.4</td>
<td>10.0 10.6 11.0</td>
<td>$F_{1,310} = 0.29$, $P = 0.589^1$</td>
</tr>
<tr>
<td>sex</td>
<td></td>
<td></td>
<td>$\chi^2 = 0.96$, $P = 0.326^2$</td>
</tr>
<tr>
<td>female</td>
<td>90% 139/154</td>
<td>87% 147/158</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>41.4 48.1 55.8</td>
<td>43.0 51.9 58.9</td>
<td>$F_{1,310} = 5.52$, $P = 0.019^1$</td>
</tr>
<tr>
<td>spiders</td>
<td>29% 45/154</td>
<td>28% 45/158</td>
<td>$\chi^2 = 0.02$, $P = 0.885^2$</td>
</tr>
</tbody>
</table>

*a b c* represent the lower quartile *a*, the median *b*, and the upper quartile *c* for continuous variables. Tests used: $^1$Wilcoxon test; $^2$Pearson test
Mixing Tables and Graphics, continued

\[ \chi^2_3 = 4.63, \quad P = 0.201^2 \]

\[ \chi^2_1 = 0.96, \quad P = 0.326^2 \]

\[ F_{1,310} = 0.29, \quad P = 0.589^1 \]
Suggested Model for Reports

- Primary presentation completely graphical
- pdf hyperlink to dense tables for value look-ups
- Alternative 1: table pop-up when hover over graphics
- Alternative 2: micrographics inside tables (limiting, difficult)
- **Better**: supplement graphics with denominators, %, etc.
- R, \texttt{LaTeX}, knitr, Markdown, RStudio
ctspedia.org/StatGraphHome

FDA/Industry/Academia Safety Graphics Working Group
References

