Facilitating Efficient Review: A Graphics-Driven Approach to Interim Safety Reporting

Midwest Biopharmaceutical Statistics Workshop
Muncie, Indiana – May 23, 2017

Contact: Kevin Buhr <buhr@biostat.wisc.edu>
Statistical Data Analysis Center
Department of Biostatistics and Medical Informatics
University of Wisconsin – Madison
Contributors

Statistics Collaborative

– Matt Downs
– Janelle Rhorer
– Janet Wittes

University of Wisconsin

– Robin Bechhofer
– Kevin Buhr
– Tom Cook
Outline

• Introduction
• Organization of DMC reports
• Specific Analyses and Presentations
Part 1

INTRODUCTION
Structure of a clinical trial

Steering Committee → Pharmaceutical Industry Sponsor → Regulatory Agencies

Data Management Center (Sponsor or Contract Research Organization) → Clinical Centers → Participants

Central Units (Labs, etc.) → Institutional Review Boards
Structure of a clinical trial

- Steering Committee
- Independent Data Monitoring Committee
- Statistical Reporting Group
- Pharmaceutical Industry Sponsor
- Regulatory Agencies
- Data Management Center (Sponsor or Contract Research Organization)
- Central Units (Labs, etc.)
- Institutional Review Boards
- Clinical Centers
- Participants
Independent Data Monitoring Committees (IDMCs)

• Review interim data to ensure
  – Safety of participants
  – Integrity of the trial

• Meet periodically in open, closed, and exec sessions
  – Open (IDMC+SRG+Sponsor+Exec Committee Chair)
    • Operational update
    • New information on safety
    • Regulatory developments
  – Closed (IDMC+SRG)
    • Review of unblinded emerging safety (and often efficacy) data
  – Executive (IDMC)
Statistical Reporting Group (SRGs)

- Our experience is as an external group serving as an independent statistical DMC reporting center
- Receive data from Sponsor, CRO, or directly from other units (e.g., blinded laboratory data)
- Receive actual randomization codes to conduct unblinded analyses
- Prepare, distribute, and present IDMC reports at meetings
The IDMC report

- Provides analyses of trial conduct, safety, and efficacy by treatment
- Reviewed during the closed session
- Most important source of information for IDMC decision-making
And Yet....

Many reports are

• Badly organized
• Long, unclear, unfocused
• Full of errors, inconsistencies, and bad statistics
• Poorly suited to meet the DMC’s needs
Disorganized

- Report is an email with a zip file (no context):
Disorganized

• Stack of binders (no table of contents)
Disorganized

- Tabs, but not descriptive labels
Too much (but not useful) information

Protocol XXXXXX - Data cut-off date: 01DEC2015

Table 1
ECG shift table based on notable values by treatment
Safety population

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Baseline n (%)</th>
<th>&lt;=450 n (%)</th>
<th>&gt;450 - 480 n (%)</th>
<th>&gt;480 - 500 n (%)</th>
<th>&gt;500 n (%)</th>
<th>Missing n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A (N=150)</td>
<td>150 (100)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>147 (98.0)</td>
</tr>
<tr>
<td>Group B (N=82)</td>
<td>82 (100)</td>
<td>2 (2.4)</td>
<td>1 (1.2)</td>
<td>0</td>
<td>0</td>
<td>79 (96.3)</td>
</tr>
<tr>
<td>Total (N=232)</td>
<td>232 (100)</td>
<td>3 (1.3)</td>
<td>2 (0.9)</td>
<td>0</td>
<td>1 (0.4)</td>
<td>226 (97.4)</td>
</tr>
</tbody>
</table>

Slowly reached conclusion: all data are missing!

- Baseline percentage is based on N. Percentage for worst value is based on Baseline n.
Table 8 (Page 1 of 44)
Adverse events, regardless of study treatment relationship, by primary system organ class, preferred term and maximum CTC AE grade and treatment - Grade 1/2, Grade 3 and Grade 4

<table>
<thead>
<tr>
<th>Primary system organ class</th>
<th>Group A N=192</th>
<th></th>
<th></th>
<th>Group B N=98</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 1/2 n (%)</td>
<td>Grade 3 n (%)</td>
<td>Grade 4 n (%)</td>
<td>Grade 1/2 n (%)</td>
<td>Grade 3 n (%)</td>
<td></td>
</tr>
<tr>
<td>Any primary system organ class</td>
<td>87 (45.3)</td>
<td>76 (39.6)</td>
<td>20 (10.4)</td>
<td>44 (44.9)</td>
<td>41 (41.8)</td>
<td></td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaemia</td>
<td>12 (6.3)</td>
<td>4 (2.1)</td>
<td>1 (0.5)</td>
<td>3 (3.1)</td>
<td>3 (3.1)</td>
<td></td>
</tr>
<tr>
<td>Leukopenia</td>
<td>6 (3.1)</td>
<td>3 (1.6)</td>
<td>0</td>
<td>1 (1.0)</td>
<td>2 (2.0)</td>
<td></td>
</tr>
<tr>
<td>Haemolytic anaemia</td>
<td>2 (1.0)</td>
<td>0</td>
<td>0</td>
<td>1 (1.0)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Increased tendency to bruise</td>
<td>1 (0.5)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Lymph node pain</td>
<td>1 (0.5)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (1.0)</td>
<td>1 (1.0)</td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>1 (0.5)</td>
<td>1 (0.5)</td>
<td>1 (0.5)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>1 (0.5)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>0</td>
<td>1 (0.5)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Where are Grade 4 AEs?
Table 8 (Page 2 of 44)

Adverse events, regardless of study treatment relationship, by primary system organ class, preferred term and maximum CTCAE grade and treatment – Grade 1/2, Grade 3 and Grade 4

<table>
<thead>
<tr>
<th>Primary system organ class</th>
<th>Preferred term</th>
<th>Group B N=98</th>
<th>Grade 4 n (%)</th>
<th>Grade 1/2 n (%)</th>
<th>Grade 3 n (%)</th>
<th>Grade 4 n (%)</th>
<th>Total N=290</th>
</tr>
</thead>
<tbody>
<tr>
<td>-Any primary system organ class</td>
<td></td>
<td>9 (9.2)</td>
<td>131 (45.2)</td>
<td>117 (40.3)</td>
<td>29 (10.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaemia</td>
<td></td>
<td>0</td>
<td>15 (5.2)</td>
<td>7 (2.4)</td>
<td>1 (0.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukopenia</td>
<td></td>
<td>0</td>
<td>3 (1.0)</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemolytic anaemia</td>
<td></td>
<td>0</td>
<td>1 (0.3)</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased tendency to bruise</td>
<td></td>
<td>0</td>
<td>1 (0.3)</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymph node pain</td>
<td></td>
<td>0</td>
<td>1 (0.3)</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphopenia</td>
<td></td>
<td>0</td>
<td>1 (0.3)</td>
<td>1 (0.3)</td>
<td>1 (0.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td></td>
<td>0</td>
<td>1 (0.3)</td>
<td>1 (0.3)</td>
<td>1 (0.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td></td>
<td>0</td>
<td>0</td>
<td>1 (0.3)</td>
<td>1 (0.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td></td>
<td>0</td>
<td>0</td>
<td>1 (0.3)</td>
<td>0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Aha! There they are – on the next page!
Part 2

ORGANIZATION OF DMC REPORTS
Comprehensive but Comprehensible

• Comprehensive:
  – Must include all potentially relevant information
  – Report requirements: specifications & mock Tables, Listings, & Figures (TLFs) may dictate content

• Comprehensibility can suffer:
  – Risk of overwhelming with detail
  – Tendency to include useless analyses
  – Too much information makes it hard to present in an organized way
Pity the Poor DMC Member

DMC members are busy people with day jobs, and they:

• may serve on multiple DMCs for confusingly similar trials
• usually experience long intervals between reports
• always have limited time to review the report
The report must be a convenient document to work with:

- Single PDF document / hardcopy binder
- Table of contents, list of figures, captions, chapter separators, consecutive page numbers (!)
- Clear separation of “main” and supplementary material / appendices
- Hierarchical organization (chapters, sections)
# Example Table of Contents

**Contents**

1. Introduction .......................................................................................................................... 1
2. Available data ....................................................................................................................... 2
3. Accrual, demographics, and baseline characteristics ........................................................... 2
4. Treatment .............................................................................................................................. 16
5. Safety .................................................................................................................................. 18
   5.1. Deaths .............................................................................................................................. 18
   5.2. Adverse events and serious adverse events .................................................................. 21
   5.3. Laboratory Results ......................................................................................................... 57
6. Efficacy ................................................................................................................................ 62
7. Appendix A – Additional adverse event tables and listings .............................................. 71
8. Appendix B – Laboratory boxplots over time ..................................................................... 169
Bring the Reader up to Speed

The report must quickly (re)orient the reader to the trial:

• Introduction: purpose of report, data sources, general statistical and display conventions
• Protocol summary (i.e., summary of trial)
• Minutes from previous meeting
Use Efficient Presentations

The organization and presentation of analyses must allow DMC members to:
• Review the most critical analyses
• Easily locate a topic of interest
• Quickly obtain an overview for the topic
• Drill down to additional detail, as necessary

The SRG should also:
• Present analyses in a self-contained manner
• Use simple, familiar presentation elements when possible
• Leverage similarities, using similar presentations for similar analyses
Part 3

SPECIFIC ANALYSES AND PRESENTATIONS
Categories of Information

• Trial conduct
  – Accrual and subject disposition
  – Treatment adherence
  – Data availability

• Baseline data

• Safety data
  – Adverse events
  – Laboratory data

• Efficacy data
  – Clinical endpoint events
  – Tumor response
Accrual – Key Questions

- How is accrual progressing as compared to what was projected?
- Are certain sites dominating the accrual?
- What is the geographic breakdown in an international trial?
Cumulative Accrual (with projections, if possible)
Distribution of Sites by # Accrued
## Accrual by Region and Country

<table>
<thead>
<tr>
<th>Randomization by Region and Country</th>
<th>Date First Subject Randomized</th>
<th>Most Recent Subject Randomized</th>
<th>Number of Sites Randomizing Subjects</th>
<th>Number of Subjects Randomized</th>
<th>Subjects Per Site (mean)</th>
</tr>
</thead>
<tbody>
<tr>
<td>* OVERALL *</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>North America</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>United States</td>
<td>May 4, 2007</td>
<td>May 27, 2008</td>
<td>120</td>
<td>775</td>
<td>6.5</td>
</tr>
<tr>
<td>Canada</td>
<td></td>
<td></td>
<td>38</td>
<td>273</td>
<td>7.2</td>
</tr>
<tr>
<td>* REGION TOTAL *</td>
<td>May 22, 2007</td>
<td>May 27, 2008</td>
<td>53</td>
<td>369</td>
<td>7.0</td>
</tr>
<tr>
<td>Europe</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>United Kingdom</td>
<td>Jun 16, 2007</td>
<td>Apr 26, 2008</td>
<td>10</td>
<td>57</td>
<td>5.7</td>
</tr>
<tr>
<td>Spain</td>
<td>Jun 19, 2007</td>
<td>May 9, 2008</td>
<td>4</td>
<td>21</td>
<td>5.3</td>
</tr>
<tr>
<td>Germany</td>
<td>Jun 26, 2007</td>
<td>Apr 17, 2008</td>
<td>5</td>
<td>23</td>
<td>4.6</td>
</tr>
<tr>
<td>Portugal</td>
<td>Aug 30, 2007</td>
<td>Feb 12, 2008</td>
<td>3</td>
<td>16</td>
<td>5.3</td>
</tr>
<tr>
<td>Norway</td>
<td>Aug 21, 2007</td>
<td>Feb 18, 2008</td>
<td>3</td>
<td>16</td>
<td>5.3</td>
</tr>
<tr>
<td>France</td>
<td>Jul 10, 2007</td>
<td>Mar 24, 2008</td>
<td>3</td>
<td>28</td>
<td>9.3</td>
</tr>
<tr>
<td>Italy</td>
<td>Aug 10, 2007</td>
<td>Jan 31, 2008</td>
<td>3</td>
<td>12</td>
<td>4.0</td>
</tr>
<tr>
<td>Sweden</td>
<td>Aug 27, 2007</td>
<td>Apr 24, 2008</td>
<td>3</td>
<td>19</td>
<td>6.3</td>
</tr>
<tr>
<td>Finland</td>
<td>Jul 16, 2007</td>
<td>May 13, 2008</td>
<td>3</td>
<td>26</td>
<td>8.7</td>
</tr>
<tr>
<td>* REGION TOTAL *</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Subject Disposition – Key Questions

• Are subjects discontinuing from treatment early?
  – If so, what are the reasons?
  – Do they differ by treatment group?
• Are subjects who have d/c treatment continuing to be followed?
• What is the cumulative exposure/follow-up of subjects on study?
Most Recent Subject Status

![Graph showing the current status of randomized subjects. The graph divides subjects into categories: Dead, Withdrawn from study, On study, Off treatment, and On study, On treatment. The Y-axis represents the percentage of subjects, and the X-axis lists the categories. The graph includes bars for subjects A and B, indicating the distribution of subjects across these statuses.]
Reasons for W/D from Study or Treatment

- Subject died: 11.9% for A, 5.7% for B, p < 0.003
- Consent withdrawn: 6.2% for A, 2.4% for B
- Lost to follow-up: 2.9% for A, 3.1% for B
- Adverse event: 19.4% for A, 14.7% for B
- Protocol violation: 1.8% for A, 0.5% for B
- Pregnancy: 1.8% for A
- Subject request: 13.7% for A, 9.8% for B
- Other: 3.4% for A, 2.3% for B

Reason Off Study:
- Subject died: 16% for A, 8.5% for B, p < 0.002
- Consent withdrawn: 7% for B, 2.3% for A
- Lost to follow-up: 2.3% for A
- Other: 0% for A, 0.3% for B

nA = 388, nB = 387

% of Subjects
Group A
Randomized as of DATE
N=147

Follow-up data in CRF database
N=141

Known to have discontinued tx
N = 65 (42%)

Disc. b/c of progression or death
N=73 (52%)

Continued to be followed for progression after tx disc
N=6

Disease progression or death during monitoring for progression
N=2

In follow-up for survival or vital status known
N=73

Not known to have discontinued tx
N = 82 (58%)

Disc. treatment for other reasons
N=9 (6%)

No further follow-up for progression
N=3

Disease progression or death not observed
N=4

In follow-up for survival or vital status known
N=6

Follow-up for survival

3 refused further follow-up for survival

In follow-up for survival or vital status known
N=0

Post-treatment evaluation for progression

In follow-up for survival or vital status known
N=0
Time to Early Discontinuation

Event Probability over Time

pA, B = 0.041

% of Subjects Terminating Early

nEvents A - 138
nEvents B - 158

Time from Randomization (days)
Follow-up Time
Data Availability – Key Questions

• How recent are the data included in the report?

• How much data are available relative to what would be expected based on dates of study entry and data cut-off?
Data Currency

Cumulative distribution of time from last visit in database to data cut-off date

![Graph showing cumulative distribution of time from last visit to data cut-off date]
Data Availability

Figure 2. Available eCRF data during the Follow-up Phase

- Month 18: Some visit data contained in EDC database
- Month 15: Some visit data contained in EDC database
- Month 12: Some visit data contained in EDC database
- Month 9: Some visit data contained in EDC database
- Month 6: Some visit data contained in EDC database
- Month 3: Some visit data contained in EDC database
- End of treatment: Some visit data contained in EDC database

Legend:
- □: Expected, assuming real-time collection
Adverse Events – Key Questions

• Are there differences in AE rates by treatment?
• What types of AEs are being experienced?
• How about certain categories of events?
  – Serious (SAE) events?
  – Events of Grade 3 or higher?
  – Events leading to alteration or termination of treatment?
  – Pre-specified events of interest?
• Are certain events more common in one or more treatment group than in others?
• When are events occurring? Early in the treatment? Are they recurrent?
Challenges in Reporting of AEs

• Separating signal from noise
  – Important to draw attention to important issues, while not sacrificing completeness of reporting

• Identifying appropriate categories, groupings of MedDRA terms
  – Summarize by SOC, HLT
  – Use SMQs
  – Ask DMC if there are combinations of interest
Adverse Events - Presentation

• Overall summaries
  – Incidence of any AEs meeting certain criteria: serious, severe, related, causing treatment modification, death

• Comprehensive data
  – Summaries by System Organ Class (graphics)
  – Summaries by SOC and Preferred Term (tables)

• Presentation style
  – Graphics: bar charts, stacked bars, dot plots
  – Incidence tables: with or without p-values
  – Listings: for selected categories
AE Overview Graphic

Overview

- Any AE: 50.3% in A, 49.9% in B
- AE possibly related to investigational product: 19.3% in A, 21.4% in B
- Severe AE: 4.6% in A, 4.1% in B

Actions Taken with IP Due to AE

- IP withdrawn: 14.2% in A, 16.3% in B
- Dose reduced: 24.5% in A, 22.5% in B
- Dose interrupted: 10.3% in A, 8.3% in B

Subject Actions Taken Due to AE

- Withdrawn from study: 4.4% in A, 4.7% in B

nA = 388, nB = 387
Adverse Events by SOC
### Table by SOC and Preferred Term

#### AEs by SOC, High Level Term and Preferred Term

**Cardiac disorders**

<table>
<thead>
<tr>
<th>MedDRA High Level Term</th>
<th>Preferred Term</th>
<th>N Subjects (Events)</th>
<th>Percent of Subjects</th>
<th>P-Values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>A</td>
<td>B</td>
<td>ALL</td>
</tr>
<tr>
<td><strong>OVERALL</strong></td>
<td></td>
<td>98 (181)</td>
<td>75 (136)</td>
<td>173 (317)</td>
</tr>
<tr>
<td>Accelerated and malignant hypertension</td>
<td></td>
<td>0  (0)</td>
<td>1  (2)</td>
<td>1  (2)</td>
</tr>
<tr>
<td>Malignant hypertensive heart disease</td>
<td></td>
<td>0  (0)</td>
<td>1  (2)</td>
<td>1  (2)</td>
</tr>
<tr>
<td>Breathing abnormalities</td>
<td></td>
<td>1  (1)</td>
<td>1  (1)</td>
<td>2  (2)</td>
</tr>
<tr>
<td>Cardiac asthma</td>
<td></td>
<td>1  (1)</td>
<td>1  (1)</td>
<td>2  (2)</td>
</tr>
<tr>
<td>Cardiac and vascular procedural complications</td>
<td></td>
<td>1  (1)</td>
<td>2  (4)</td>
<td>3  (5)</td>
</tr>
<tr>
<td>Coronary artery perforation</td>
<td></td>
<td>0  (0)</td>
<td>1  (2)</td>
<td>1  (2)</td>
</tr>
<tr>
<td>Myocardial oedema</td>
<td></td>
<td>1  (1)</td>
<td>1  (2)</td>
<td>2  (3)</td>
</tr>
<tr>
<td>Cardiac conduction disorders</td>
<td></td>
<td>1  (1)</td>
<td>3  (4)</td>
<td>4  (5)</td>
</tr>
<tr>
<td>Bundle branch block</td>
<td></td>
<td>1  (1)</td>
<td>1  (1)</td>
<td>2  (2)</td>
</tr>
<tr>
<td>Long QT syndrome</td>
<td></td>
<td>0  (0)</td>
<td>2  (3)</td>
<td>2  (3)</td>
</tr>
<tr>
<td>Cardiac disorders NEC</td>
<td></td>
<td>1  (1)</td>
<td>3  (4)</td>
<td>4  (5)</td>
</tr>
<tr>
<td>Cardiac disorder</td>
<td></td>
<td>0  (0)</td>
<td>1  (1)</td>
<td>1  (1)</td>
</tr>
<tr>
<td>Cardiotoxicity</td>
<td></td>
<td>1  (1)</td>
<td>0  (0)</td>
<td>1  (1)</td>
</tr>
<tr>
<td>Intracardiac mass</td>
<td></td>
<td>0  (0)</td>
<td>2  (3)</td>
<td>2  (3)</td>
</tr>
<tr>
<td>Cardiac hypertensive complications</td>
<td></td>
<td>1  (2)</td>
<td>0  (0)</td>
<td>1  (2)</td>
</tr>
<tr>
<td>Hypertensive heart disease</td>
<td></td>
<td>1  (2)</td>
<td>0  (0)</td>
<td>1  (2)</td>
</tr>
<tr>
<td>Cardiac signs and symptoms NEC</td>
<td></td>
<td>1  (1)</td>
<td>1  (2)</td>
<td>2  (3)</td>
</tr>
<tr>
<td>Positive cardiac inotropic effect</td>
<td></td>
<td>1  (1)</td>
<td>1  (2)</td>
<td>2  (3)</td>
</tr>
<tr>
<td>Cardiac valve disorders NEC</td>
<td></td>
<td>2  (2)</td>
<td>3  (3)</td>
<td>4  (5)</td>
</tr>
</tbody>
</table>
Most Common by Preferred Term

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>pA,B</th>
<th>nA = 388</th>
<th>nB = 387</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic obstructive airway</td>
<td>0.000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>0.000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>0.845</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>0.088</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>0.002</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>0.157</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>0.061</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sinusitis</td>
<td>0.338</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injury</td>
<td>0.794</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection viral</td>
<td>0.871</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>0.050</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coughing</td>
<td>0.422</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>0.138</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>0.042</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rhinitis</td>
<td>0.891</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Legend:
- Mild
- Moderate
- Severe
Potential Treatment Difference

Adverse Events, by MedDRA Term
Occurring in > 0.5% of Subjects in Either Treatment Group
with a Nominally Significant (p < 0.1) Difference between Treatments

(NB: Since preferred terms are coded within high level terms, the same event may be counted under both categories.)

<table>
<thead>
<tr>
<th>Relative Frequency</th>
<th>System Organ Class</th>
<th>High Level Term (HLT) or Preferred Term (PRT)</th>
<th>Treatment Group</th>
<th></th>
<th></th>
<th>ChiSq P-val</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>A</td>
<td>B</td>
<td></td>
<td></td>
</tr>
<tr>
<td>More in A</td>
<td>Cardiac disorders</td>
<td>HLT: Myocardial disorders NEC</td>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HLT: Ventricular arrhythmias and cardiac arrest</td>
<td>14</td>
<td>3.6%</td>
<td>4</td>
<td>1.0%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PRT: Angina pectoris</td>
<td>27</td>
<td>7.0%</td>
<td>14</td>
<td>3.6%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PRT: Ventricular extrasystoles</td>
<td>6</td>
<td>1.5%</td>
<td>1</td>
<td>0.3%</td>
</tr>
<tr>
<td>More in B</td>
<td>Vascular disorders</td>
<td>HLT: Aortic aneurysms and dissections</td>
<td>0</td>
<td>0.0%</td>
<td>3</td>
<td>0.8%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HLT: Haemorrhages NEC</td>
<td>0</td>
<td>0.0%</td>
<td>3</td>
<td>0.8%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HLT: Non-site specific vascular disorders NEC</td>
<td>0</td>
<td>0.0%</td>
<td>6</td>
<td>1.6%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PRT: Aortic aneurysm</td>
<td>0</td>
<td>0.0%</td>
<td>3</td>
<td>0.8%</td>
</tr>
</tbody>
</table>
Figure 8. Volcano plot of AE risk differences by high level term (HLT)
Laboratory Data – Key Questions

• Are there any safety concerns as reflected in the laboratory data?
• Is the treatment having the anticipated effect on targeted lab parameters? (e.g. lipids)
• If there are treatment-related changes in lab parameters, do the differences persist over time?
• Is there any evidence that subjects are experiencing drug-induced liver injury?
Lab Data - Challenges

• Quantity of data
  – There may be 50+ different tests performed by the laboratory
  – Lab data may be collected/analyzed at many visits during follow-up

• How to present data without overwhelming DMC
  – Focus on a subset of tests/timepoints
  – Organize analytes into logical subsets (not alphabetically)
  – Identify potential abnormalities of interest
  – Present data in a way that makes even large quantities of information easy to review
Summary for Abnormal Hematology

Ever Below LLN

- White Blood Cells: 19.6% (A), 17.1% (B)
- Red Blood Cells: 40.7% (A), 39.8% (B)
- Hemoglobin: 34.8% (A), 43.7% (B)
- Hematocrit: 50.3% (A), 49.1% (B)
- Platelets: 14.7% (A), 15.8% (B)

Ever Above ULN

- White Blood Cells: 6.4% (A), 7.8% (B)
- Red Blood Cells: 3.1% (A), 1.6% (B)
- Hemoglobin: 1% (A), 1.3% (B)
- Hematocrit: 1.3% (A), 2.1% (B)
- Platelets: 1.5% (A), 3.9% (B)
Per-Analyte Summary Page

• Standard graphical lab page by visit
  – Box-plots
    • Presentation of data over time
    • Change from baseline by visit
  – Bar charts (simple or stacked)
    • Abnormalities (perhaps stacked), both high and low
  – Annotations
    • Number of observations, p-values
  – Visually easy to compare treatment groups and see trends over time

• Once DMC members are familiar with layout, can review a lot of data in a short period of time
Drilling Down to Specific Subjects

• Box-plots show shift in distribution but may mask subjects at extremes (if > 95th percentile)
• Extreme cases can be examined in detail with per-subject plots or listings – e.g., subjects with LFTs > 3xULN
  – Include information about treatment, dose adjustment, early discontinuation, etc.
  – Adverse events, other clinical events
  – Multiple lab measures displayed together
Liver Function Test Summary

Highest Elevation after Baseline

<table>
<thead>
<tr>
<th>Test</th>
<th>Group A</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alanine Aminotransferase</td>
<td>12%</td>
<td>10.1%</td>
</tr>
<tr>
<td>Aspartate Aminotransferase</td>
<td>7.3%</td>
<td>9.2%</td>
</tr>
<tr>
<td>Alkaline Phosphatase</td>
<td>16.2%</td>
<td>14.8%</td>
</tr>
<tr>
<td>Total Bilirubin</td>
<td>10.6%</td>
<td>9.5%</td>
</tr>
</tbody>
</table>

Elevations of Potential Clinical Concern

- ALT or AST Ever >=3xULN
- ALT or AST Ever >=3xULN and Bilirubin Ever >=2xULN

- Group A:
  - 0.3%
  - 0%

- Group B:
  - 0.6%
  - 0%
LFT Per-Patient Plot

![Graph showing LFT Per-Patient Plot with days from randomization on the x-axis and multiples of ULN on the y-axis]
How It Fits Together

• SDAC sample report
Report Length

• A common criticism
• Pogue and Sackett\(^1\)
  
  – *When we wrote to 21 colleagues from 6 countries ... [with] a single exception, they reckoned they were wasting time looking [at] reports they’d received that often exceeded a kilogram in weight, and in one case ran to 3000 pages.*

• Describe a hypothetical case of a 120-page, 88-table report that the DMC struggles to understand

• State that a good report must *surely* be less than 3000 pages and *clearly* less than 120 pages

---

Their Recommendations

- Describe a one-page summary, the “MISER”
- Suggest a report template with 25 tables/figures
- Also suggest that a figure can replace several tables (and may be “worth” a dozen of them)
Our Experience

• Most SDAC reports are 150-350 pages
• May start small (<100 pages) but grow as the program does
• Some get very large indeed
Our Experience

Very large, indeed...

Report Length over Time

- DMC Meeting Report
- Monthly Safety Report

Pages

0 6 12 18 24 30

Months
Large Reports

• May be a natural consequence of:
  – Multi-trial programs
  – Large collection of pre-specified analyses mandated by regulatory agencies or Protocol / DMC Charter
  – Analyses requested by DMC to address a particular concern that are no longer “needed”

• High page count does not, in and of itself, compromise usability
  – With respect to the 6000-page report, the DMC repeatedly remarked on their ability to efficiently review the information and refused our offers to find ways to abbreviate the analyses

• A well-organized report is useful even when very large
Take-Home Points

• DMC reports are the key decision-making tool
• Too often, organization and presentations are neglected
• Efficient review can be facilitated by:
  – Document structure
  – Top-down presentation of analyses
  – Emphasis on graphical presentations using simple, familiar graphical elements and leveraging similar presentations across multiple analyses
• Even massively comprehensive reports can be made comprehensible
Thank you!

• Questions?
Contact Information

• Kevin Buhr <buhr@biostat.wisc.edu>