Towards More Automated Statistical Reporting for Clinical Trials

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Purpose

- Data Monitoring Committees
- Enhance safety and risk/benefit review by DMC
- Methods useful for general RCT reports
- Provide efficient and state-of-the-art statistical reporting
- High-quality graphics (a la Bill Cleveland) and tables
- Hard copy and on-screen review

Problems to Solve

- Reproducible research: no transcription of results
- Repeated reports, main changes are updates to data
- Many response variables and repeated measurements
- Non-normality of data (especially clinical chemistry)
- Dropouts and missing data
- Graphical methods for judging differences in point estimates

Tools Needed

- Batch mode capability (scripting)
- Fine control (graphics, tables, text)
- High-level, flexible statistical language
  - graphics
  - statistical analysis
  - easy to implement new functions
  - functions are data-sensitive (unlike macros)
  - advanced tables
- Document processing (typesetting)
  - easy handling of Greek letters, subscripts, superscripts, font changes
  - no cut and paste
  - easy inclusion of chunks of text, tables, graphics
  - automatic cross-referencing and hyperlinking
  - let software worry about formatting details

Tools Selected and Developed

- R: open source statistical language (S)
- LaTeX
- Hmisc package
  - advanced table making
  - `latex` functions to convert S objects to LaTeX code
  - graphics
  - Lan-DeMets sequential monitoring stopping bands
- Design package for survival curve plotting

- New series (`rreport`) of higher-level report generation functions
  - `completenessReport`, `accrualReport`, `baselineReport`, `repVarclus`, `complianceReport`, `dropoutReport`, `aeReport`, `labReport`, `mockTable` functions
  - uses data attributes (value levels, variable labels, units)
  - generates all tables, graphs, figure and table captions
  - unified mapping of treatments to line types, with graphical legends in text captions
  - generates some sentences
  - conditional inclusion of certain graphics and sentences

Tools, *cont.*

- All non-graphical output files are LaTeX
- Generates all LaTeX `\includegraphics` calls
- Simultaneously generates open and closed meeting components
- User writes calls to modular functions, study-specific text
- `pdf` file created directly by `pdflatex`
- `hyperref` style used for automatic hyperlinking
- Easy to write script to password-encrypt `pdf` file and E-mail it to all DMC members as attachment

Concise Language for Mock Tables for SAPs

- S commands:

```
mockTable(list(
 treatments  = c('Placebo','0.01 mg/kg','0.1 mg/kg',
               '1 mg/kg'),
 Pvalues     = c('$P$\nANOVA\\tmark','$P$\nK-W'),
 CLs         = list('Bootstrap Nonparametric 95\\% Conf
                  'all'),
 byVar       = c('Age $\\leq$ 30d Group',
               'Age 1-24m Group'),
 baseListVar = c('Site','Subject','Age, $d$','Dose'),
 file        = 'mock.tex',
 keyfile     = 'defs.tex',
 datafile    = 'mock.dat',
 pos         = 'hbp!',
 defaultOrientation = 'landscape') )
```

Other commands for mock listings

- File `mock.dat`:

```
*Baseline demographics
m Demographics
p  Gestational age $<37$w
c  Age
p  Female
m  Race
p   Caucasion
p   Black
p   Asian
p   Hispanic
p   Native Am
p   Other
*Baseline hematology and clinical chemistry
m Hematology
c  RBC!$10^{12}$/L
c  WBC!$10^{9}$/L
c  Hgb!g/L
c  Hct!\%
c  Platelet count!$10^{9}$/L
m Clinical Chemistry
c  ALT!U/L
c  AST!U/L
c  ALP!U/L
c  Bilirubin!$\mu$mol/L
```

Table 1: Baseline demographics, Age $\leq$ 30d Group

	Placebo N= ##	0.01 mg/kg N= ##	0.1 mg/kg N= ##	1 mg/kg N= ##
Demographics				
Gestational age < 37w	##% (n)	##% (n)	##% (n)	##% (n)
Age	a **b** c	a **b** c	a **b** c	a **b** c
Female	##% (n)	##% (n)	##% (n)	##% (n)
Race				
Caucasion	##% (n)	##% (n)	##% (n)	##% (n)
Black	##% (n)	##% (n)	##% (n)	##% (n)
Asian	##% (n)	##% (n)	##% (n)	##% (n)
Hispanic	##% (n)	##% (n)	##% (n)	##% (n)
Native Am	##% (n)	##% (n)	##% (n)	##% (n)
Other	##% (n)	##% (n)	##% (n)	##% (n)

Table 2: Same for Age 1-24m Group

Table 3: Baseline hematology and clinical chemistry, Age $\leq$ 30d Group

		Placebo	0.01 mg/kg	0.1 mg/kg	1 mg/kg
		N = ##	N = ##	N = ##	N = ##
Hematology					
RBC	10^{12}/L	a **b** c	a **b** c	a **b** c	a **b** c
WBC	10^{9}/L	a **b** c	a **b** c	a **b** c	a **b** c
Hgb	g/L	a **b** c	a **b** c	a **b** c	a **b** c
Hct	%	a **b** c	a **b** c	a **b** c	a **b** c
Platelet count	10^{9}/L	a **b** c	a **b** c	a **b** c	a **b** c
Clinical Chemistry					
ALT	U/L	a **b** c	a **b** c	a **b** c	a **b** c
AST	U/L	a **b** c	a **b** c	a **b** c	a **b** c
ALP	U/L	a **b** c	a **b** c	a **b** c	a **b** c
Bilirubin	μmol/L	a **b** c	a **b** c	a **b** c	a **b** c

Table 4: Same for Age 1-24m Group

Graphical Method for Interpreting Differences

- Confidence limits have more information that P-values
- Graphs showing CLs for multiple treatment groups are busy
- Confidence interval for difference in two parameters not directly obtainable from individual confidence intervals
- Best to show individual estimates and include a separate panel to show difference and its CLs
- Compromise: draw half-width of CL centered at midpoint of two estimates

$$\begin{aligned} \frac{\bar{Y}_1 - \bar{Y}_2}{se} &> z \\ \bar{Y}_1 - \bar{Y}_2 &> z \times se \\ \text{Width of CL} &= 2 \times z \times se \end{aligned}$$

Example

- Data from an actual clinical trial, contributed from a pharmaceutical company
- Not included in example report:
  - efficacy analysis
  - study design
  - data monitoring plan
  - summary of previous closed reports
  - interpretation
  - protocol changes
  - screening
  - eligibility
  - waiting time until treatment commencement
- See Ellenberg, Fleming, DeMets: *Data Monitoring Committees in Clinical Trials*, 2002

Towards More Automatic Statistical Reporting for Clinical Trials

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The methods often used for generating statistical reports for clinical trials have a number of drawbacks. The most commonly used statistical software packages require users to specify somewhat tedious low-level commands, and the resulting tabular and graphical output are not optimal. Too often, statisticians still overuse tabular reports even though most consumers of the reports would rather review graphics. And in an era in which reproducible research is starting to become popular, most statisticians still engage in some level of manual intervention, such as insertion of calculated values in sentences. These issues are particularly important in reporting for data monitoring committees.

This talk will describe an approach that uses free open-source software (R and LaTeX) to produce advanced tables and graphics using a very high-level language. The component tables and graphics are automatically assembled and indexed by LaTeX, resulting in an Adobe Acrobat PDF file with hyperlinks for easy navigation. Example open- and closed-session DMC reports will be shown, which includes tables and graphics describing data completeness, subject accrual, baseline variables, compliance, dropouts, adverse events, and lab data. Some issues in statistical graphics will be discussed, such as a way to depict confidence limits for differences between treatments in graphs that show individual treatment responses.