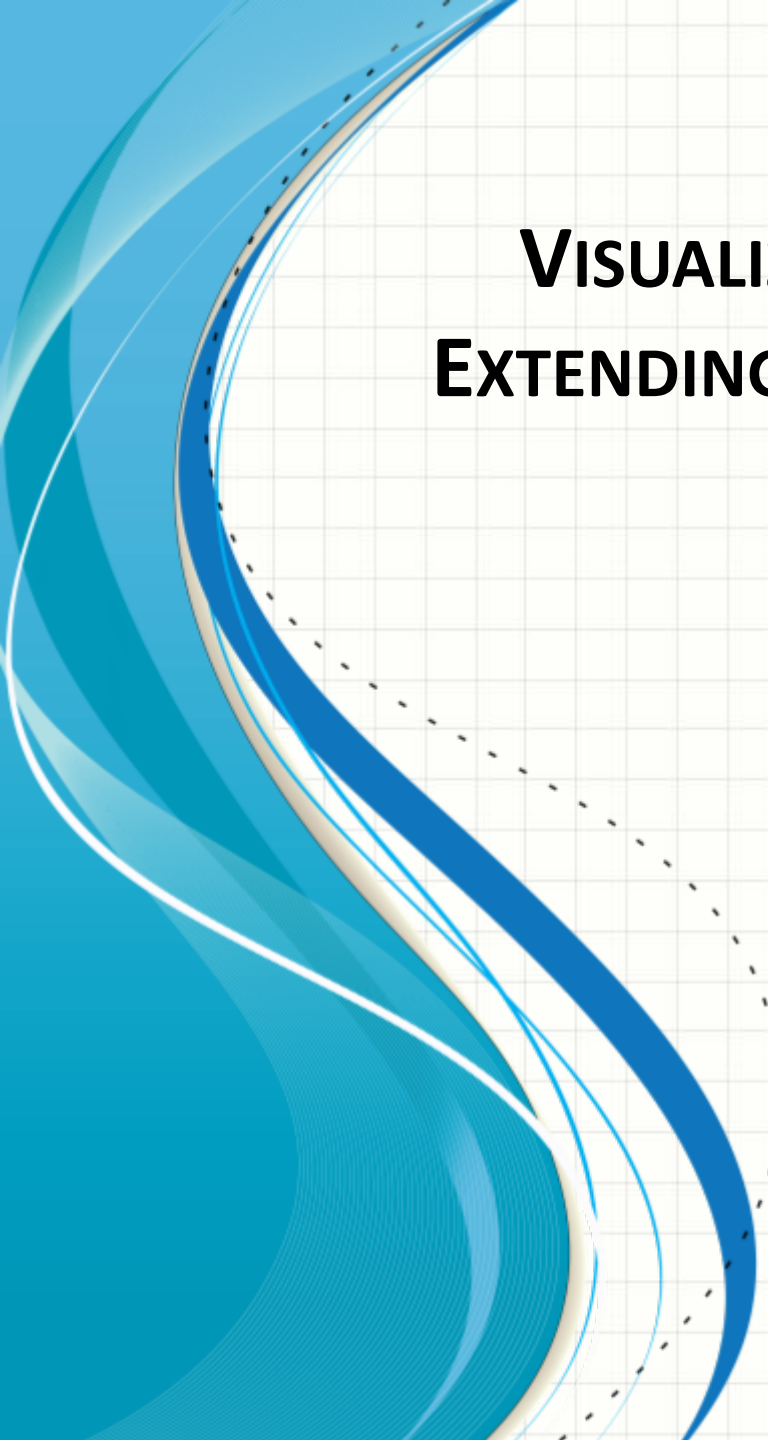


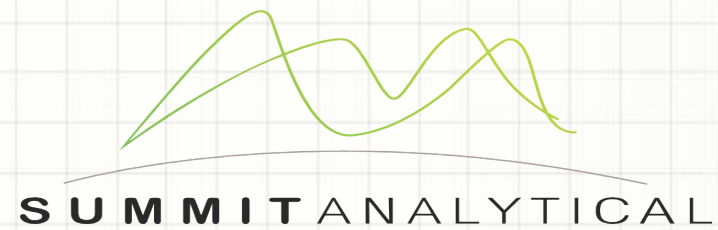


VISUALIZING MULTIPLE ENDPOINTS: EXTENDING THE USE OF FOREST PLOTS IN CLINICAL TRIALS

2017 PhUSE Annual Meeting
Edinburgh, Scotland
October 8-11, 2017

Paper: DV09

James R. Johnson, PhD
Mark J. Jaros, PhD



Programmers Produce
Tables Lots of Tables

The life of a programmer:



YES! The code is working again!

Table 1:

Statistic	<i>N</i>	<i>Mean</i>	<i>St. Dev.</i>	<i>Min</i>	<i>Max</i>
rating	30	64.633	12.173	40	85
complaints	30	66.600	13.315	37	90
privileges	30	53.133	12.235	30	83
learning	30	56.367	11.737	34	75
raises	30	64.633	10.397	43	88
critical	30	74.767	9.895	49	92
advance	30	42.933	10.289	25	72

How do I
interpret
this mess?

Medical Writers
Interpret Tables
(Maybe)



Σ

**KEEP
CALM
BECAUSE
I'M A
STATISTICIAN**

Welcome to Results Interpretation and Presentation with Forest Plots

Themes for Extending the Use of Forest Plots in Clinical Trials

1

- Forest Plots (FP) are not just for Meta-Analysis. Great tool for visualizing endpoint results in a study

2

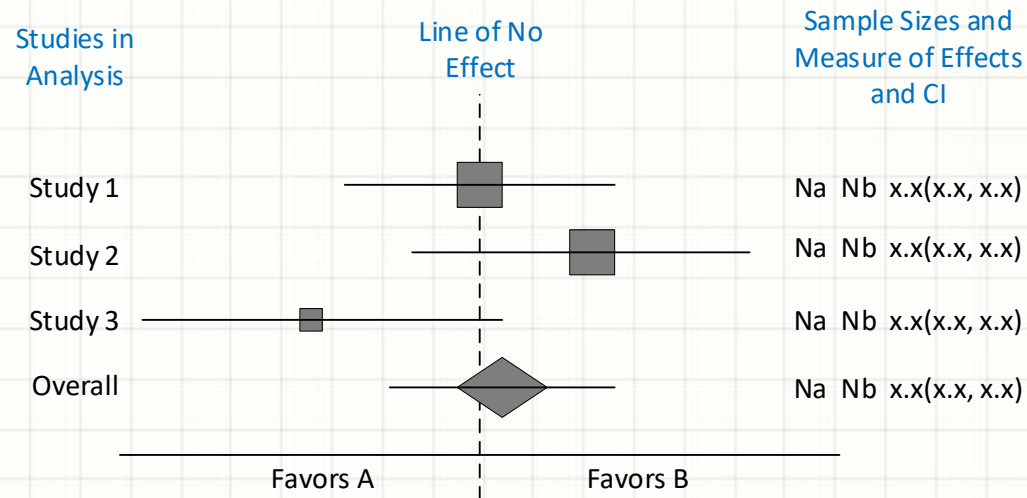
- Standardized Analysis Results Data and Meta-Data will facilitate production of publication ready FP

3

- FP usage and utility can be extended to include multiple endpoints, over multiple sampling time points, and used to supplement traditional visual displays

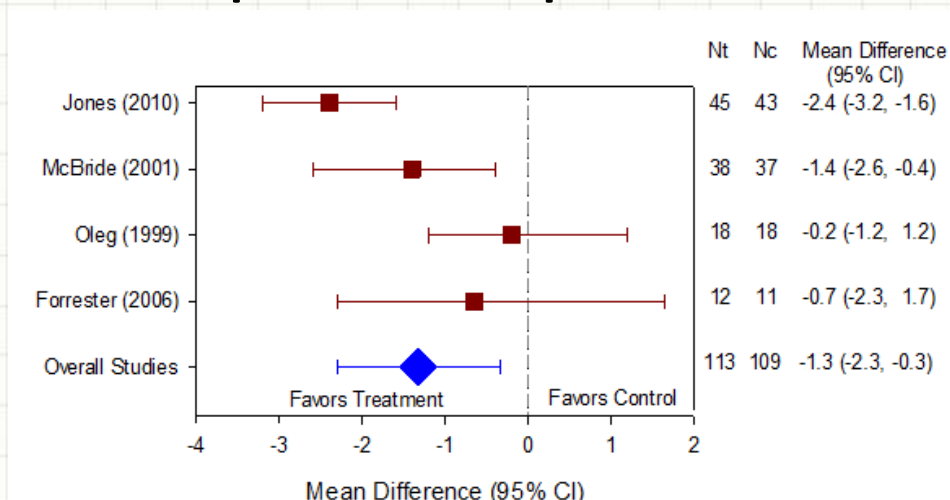
Forest Plot Basics

- General Structure in Meta-Analysis

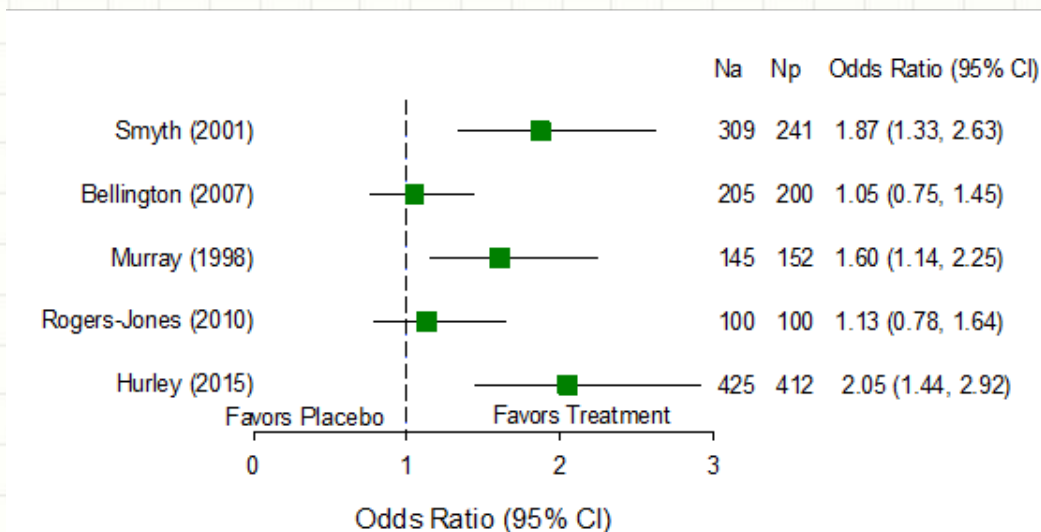


Forest Plot Basics

- Simple Examples



(B): Odds Ratios



Forest Plot Basics

- Minimum Information Required to put together a Forest Plot

Variable	Char/Num	Description
YORDER	Numeric	Study sequence number
STUDY	Char	Study reference
NA	Numeric	Number in Active Treatment
NC	Numeric	Number in Control Treatment
PE	Numeric	Point Estimate
LCL	Numeric	Lower Bound of Confidence Interval
UCL	Numeric	Upper Bound of Confidence Interval
YLABEL	Char	Concatenation of PE, LCL, UCL

- YORDER and YLABEL are derived.
- Based on Cochrane Meta-Analysis Collaboration

Extending Forest Plots into Clinical Trials

- Tabular summaries: Main source of analysis information.

Time point/ Statistic	Treatment A (N=161)		Placebo (N=162)		Treatment B (N=161)	
	Change From		Change From		Change From	
	Observed	Baseline	Observed	Baseline	Observed	Baseline
Baseline						
n	161		162		161	
Mean (SD)	6.26 (0.933)		6.27 (0.980)		6.25 (0.901)	
Median	6.14		6.14		6.14	
Min ; Max	5.0 ; 8.5		5.0 ; 8.9		5.0 ; 9.0	
Week X						
n	160	160	162	162	161	161
Mean (SD)	4.40 (1.943)	-1.85 (1.723)	5.18 (1.797)	-1.09 (1.604)	4.13 (1.873)	-2.12 (1.824)
Median	4.43	-1.57	5.36	-0.57	4.17	-1.71
Min ; Max	0.2 ; 9.0	-6.2 ; 1.4	0.4 ; 8.4	-5.9 ; 1.4	0.3 ; 8.5	-6.6 ; 1.4
LSM (SE)		-1.90 (0.202)		-1.04 (0.200)		-2.13 (0.201)
95% CI		-2.30, -1.51		-1.43, -0.65		-2.52, -1.73
LSM Difference from Placebo		-0.86				
95% CI		-1.35, -0.38				
2-sided p-value		0.0005				
LSM Difference from Trt B		0.22				
95% CI		-0.26, 0.71				
2-sided p-value		0.3688				

- Often times many pages of tabular output to follow.

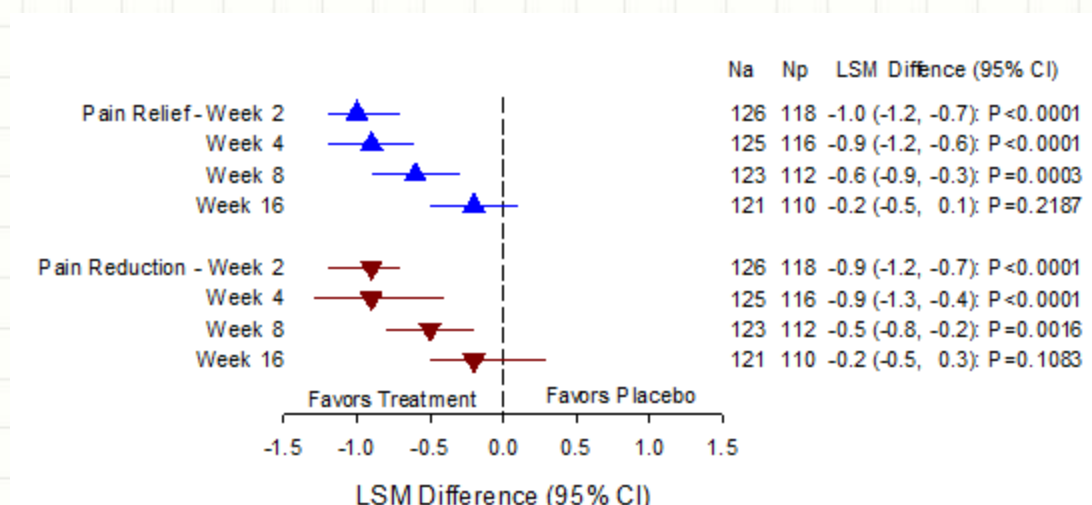
Extending Forest Plots into Clinical Trials

- We provide several extensions of the general structure of FPs for individual clinical trials with examples for:
 1. Multiple Endpoints Captured over Time,
 2. Multiple Treatment Comparisons with Multiple Endpoints,
 3. Single Endpoint Over Time: Combination Graphics: Bar Chart Means, FP LSM Difference.
 4. Pharmacokinetic Bioequivalence testing for multiple formulations.
 5. Standardized Effect Sizes

Extending Information Needed for FPs

Variable	Char/Num	Description
GRPID	Numeric	Grouping Identifier
GROUP	Char	Group Description
PARCAT1	Char	Parameter Grouping
PARAMCD	Char	Parameter Code
PARAM	Char	Parameter Description
YORDER	Numeric	Order on Y-Axis of FP
ENDPOINT	Char	Description of Analysis Endpoint
AVISIT	Char	Analysis Visit
AVISITN	Numeric	Analysis Visit (Numeric)
NA	Numeric	Number Active Treatment
NC	Numeric	Number Control Treatment
PE	Numeric	Point Estimate from Endpoint Analysis
PEB1	Numeric	Lower Confidence Interval of PE, or Measure of Dispersion
PEB2	Numeric	Upper Confidence Interval of PE
PVALUE	Numeric	P-Value from Endpoint Analysis
Y1LABEL	Char	Description of Endpoint/Time Analysis
Y2LABEL	Char	Description of NA NC PE (PEB1, PEB2): PVALUE
APROGRAM	Char	Name of the Analysis Program

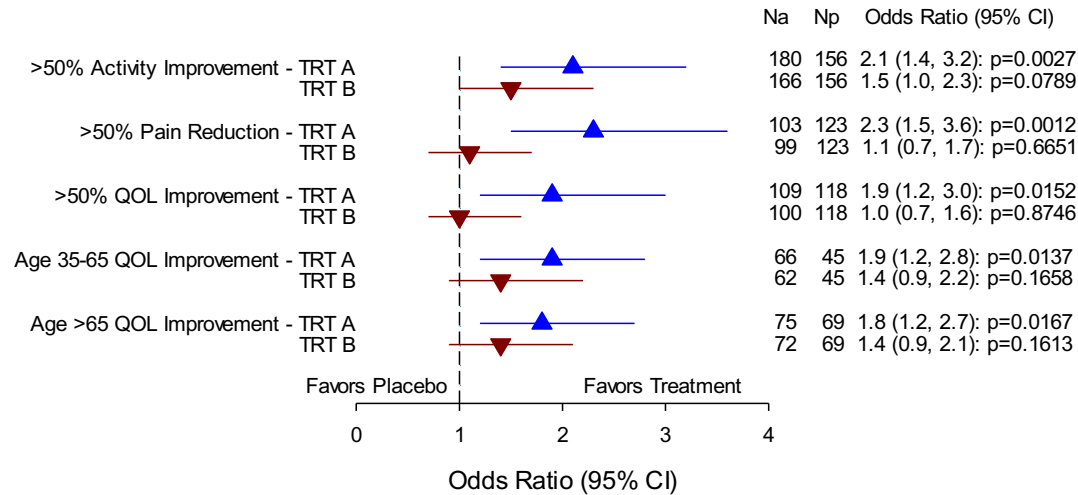
Multiple Endpoints Captured over Time



GRPID	GROUP	PARCAT1	PARAMC D	PARAM	YORDER	ENDPOINT	AVISIT	AVISITN	NA	NC	PE	PEB1	PEB2	PVALUE	Y1LABEL	Y2LABEL
1	Figure 1	1	QOLPR	Pain Relief	1	LSMDIFF	Week 2	2	126	118	-1	-1.2	-0.7	<0.0001	Pain Relief - Week 2	126 118 -1.0 (-1.2, -0.7): P<0.0001
1	Figure 1	1	QOLPR	Pain Relief	2	LSMDIFF	Week 4	4	125	116	-0.9	-1.2	-0.6	<0.0001	Week 4	125 116 -0.9 (-1.2, -0.6): P<0.0001
1	Figure 1	1	QOLPR	Pain Relief	3	LSMDIFF	Week 8	8	123	112	-0.6	-0.9	-0.3	0.0003	Week 8	123 112 -0.6 (-0.9, -0.3): P=0.0003
1	Figure 1	1	QOLPR	Pain Relief	4	LSMDIFF	Week 16	16	121	110	-0.2	-0.5	0.1	0.2187	Week 16	121 110 -0.2 (-0.5, 0.1): P=0.2187
1	Figure 1	2	QOLPRD	Pain Reduction	6	LSMDIFF	Week 2	2	126	118	-0.9	-1.2	-0.7	<0.0001	Pain Reduction - Week 2	126 118 -0.9 (-1.2, -0.7): P<0.0001
1	Figure 1	2	QOLPRD	Pain Reduction	7	LSMDIFF	Week 4	4	125	116	-0.9	-1.3	-0.4	<0.0001	Week 4	125 116 -0.9 (-1.3, -0.4): P<0.0001
1	Figure 1	2	QOLPRD	Pain Reduction	8	LSMDIFF	Week 8	8	123	112	-0.5	-0.8	-0.2	0.0016	Week 8	123 112 -0.5 (-0.8, -0.2): P=0.0016
1	Figure 1	2	QOLPRD	Pain Reduction	9	LSMDIFF	Week 16	16	121	110	-0.2	-0.5	0.3	0.1083	Week 16	121 110 -0.2 (-0.5, 0.3): P=0.1083

This FP reduces 2 tables (multiple pages) into a single graph

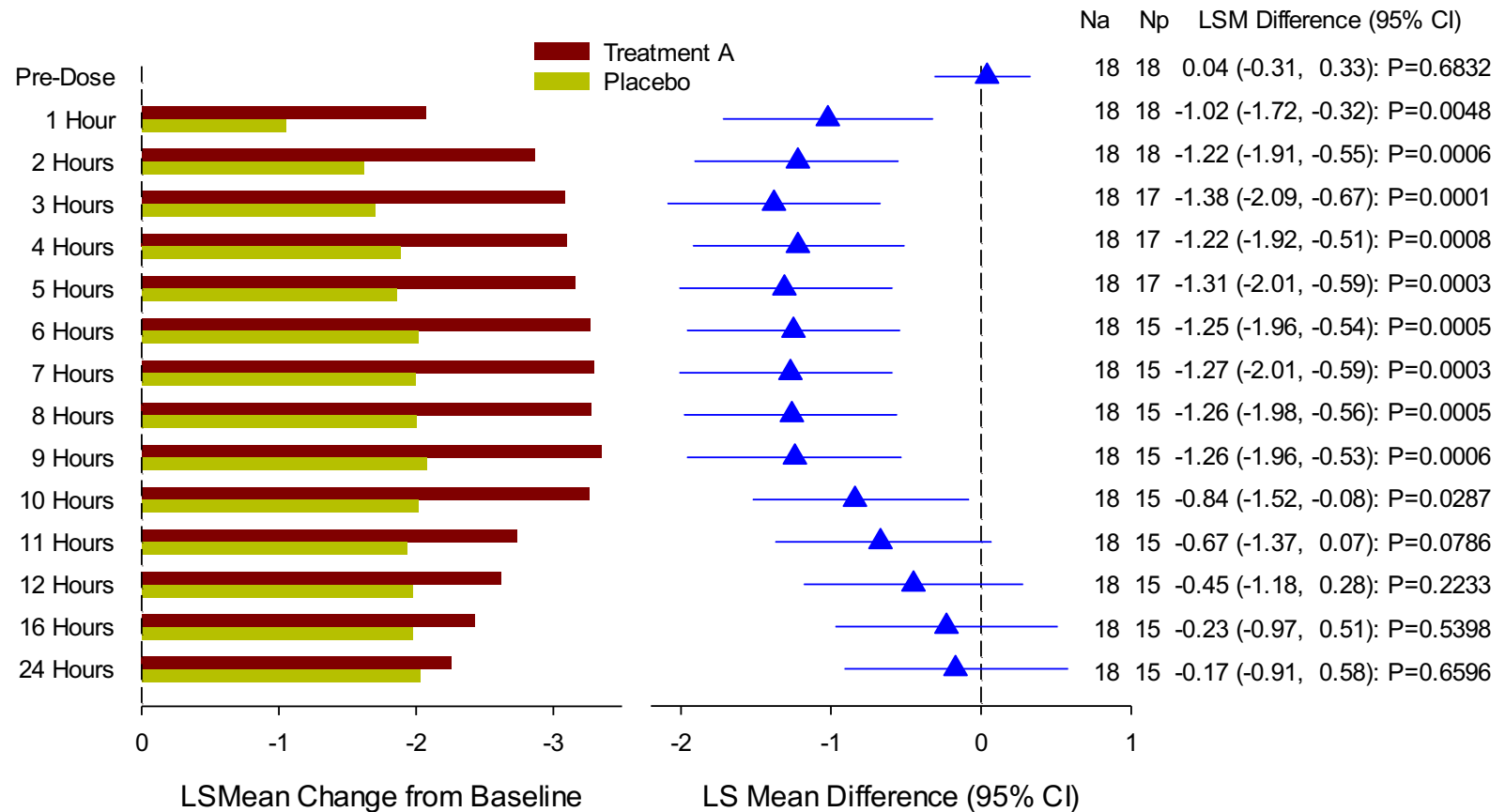
Multiple Treatment Comparisons with Multiple Endpoints



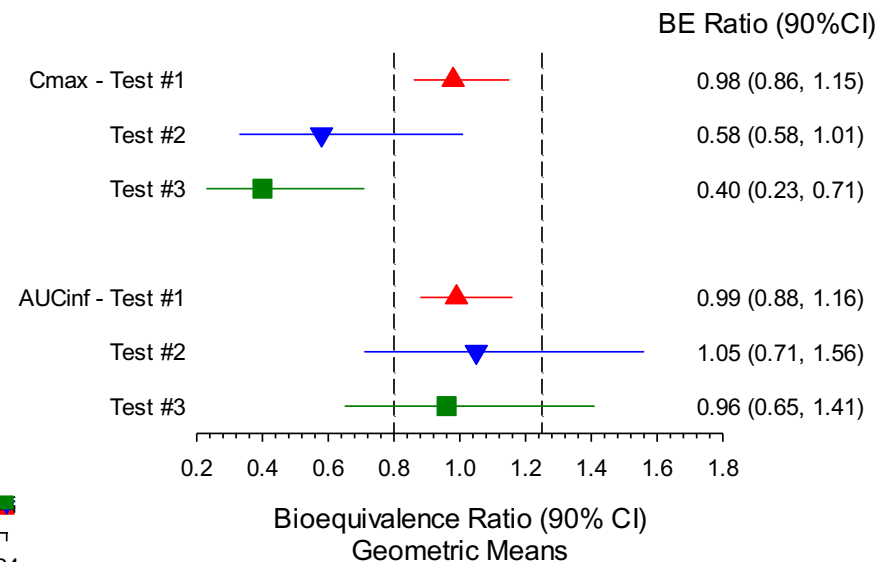
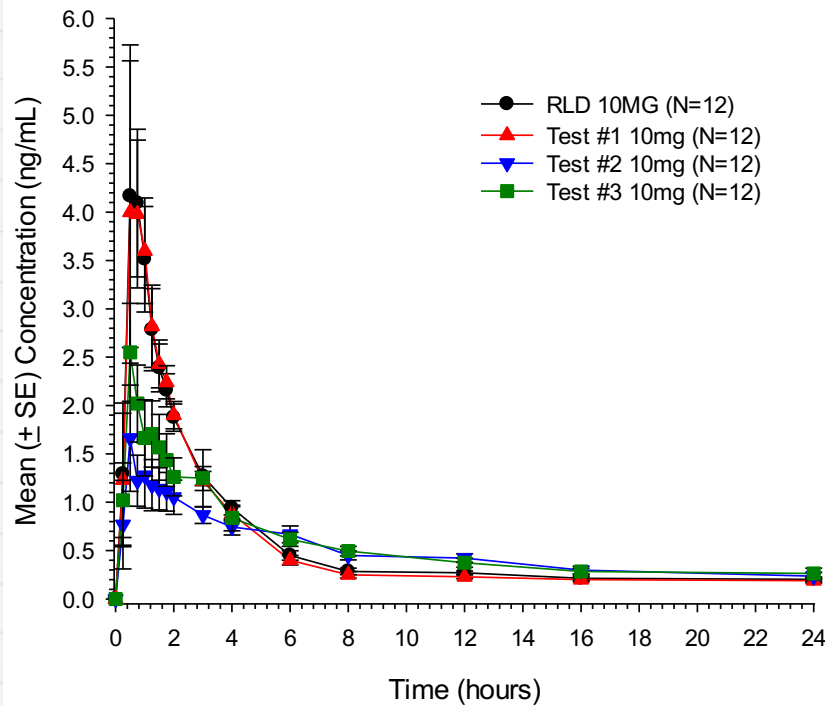
GRPID	GROUP	PARCAT			ENDPOIN										PVALUE	Y1LABEL	Y2LABEL
		1	PARAMCD	PARAM	YORDER	T	AVISIT	AVISITN	NA	NC	PE	PEB1	PEB2				
2	Figure 2	1A	QOLAI	>50% Activity Improvement	1	OR	Week 24	24	180	156	2.1	1.4	3.2	0.0027	>50% Activity Improvement - TRT A	180 156 2.1 (1.4, 3.2): p=0.0027	
2	Figure 2	1B	QOLAI	>50% Activity Improvement	2	OR	Week 24	24	166	156	1.5	1	2.3	0.0789	TRT B	166 156 1.5 (1.0, 2.3): p=0.0789	
2	Figure 2	2A	QOLPR	>50% Pain Reduction	4	OR	Week 24	24	103	123	2.3	1.5	3.6	0.0012	>50% Pain Reduction - TRT A	103 123 2.3 (1.5, 3.6): p=0.0012	
2	Figure 2	2B	QOLPR	>50% Pain Reduction	5	OR	Week 24	24	99	123	1.1	0.7	1.7	0.6651	TRT B	99 123 1.1 (0.7, 1.7): p=0.6651	
2	Figure 2	3A	QOLIMP	>50% QOL Improvement	7	OR	Week 24	24	109	118	1.9	1.2	3	0.0152	>50% QOL Improvement - TRT A	109 118 1.9 (1.2, 3.0): p=0.0152	
2	Figure 2	3B	QOLIMP	>50% QOL Improvement	8	OR	Week 24	24	100	118	1	0.7	1.6	0.8746	TRT B	100 118 1.0 (0.7, 1.6): p=0.8746	
2	Figure 2	4A	QOLIMP1	Age 35-65 QOL Improvement	10	OR	Week 24	24	66	45	1.9	1.2	2.8	0.0137	Age 35-65 QOL Improvement - TRT A	66 45 1.9 (1.2, 2.8): p=0.0137	
2	Figure 2	4B	QOLIMP1	Age 35-65 QOL Improvement	11	OR	Week 24	24	62	45	1.4	0.9	2.2	0.1658	TRT B	62 45 1.4 (0.9, 2.2): p=0.1658	
2	Figure 2	5A	QOLIMP2	Age >65 QOL Improvement	13	OR	Week 24	24	75	69	1.8	1.2	2.7	0.0167	Age >65 QOL Improvement - TRT A	75 69 1.8 (1.2, 2.7): p=0.0167	
2	Figure 2	5B	QOLIMP2	Age >65 QOL Improvement	14	OR	Week 24	24	72	69	1.4	0.9	2.1	0.1613	TRT B	72 69 1.4 (0.9, 2.1): p=0.1613	

Single Endpoint Over Time: Combination

Graphics: Bar Chart Means, FP LSM Difference



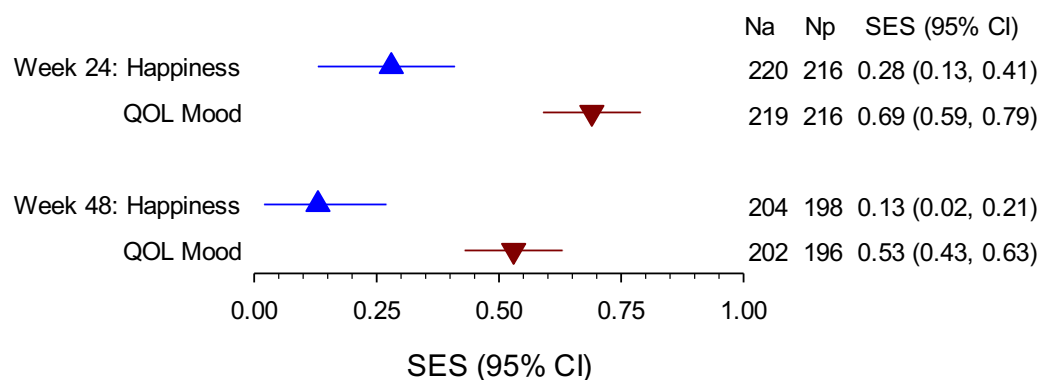
Pharmacokinetics Endpoints: BE Ratios



Standardized Effect Sizes

- A standard method to quantify the magnitude of difference between two treatment groups.

$$SES = \frac{LSM_{Active\ Trt} - LSM_{Placebo}}{\sqrt{\frac{[(N_{Active\ Trt} - 1)(SD_{Active\ Trt})^2] + [(N_{Placebo} - 1)(SD_{Placebo})^2]}{(N_{Active\ Trt} + N_{Placebo})^2}}}$$



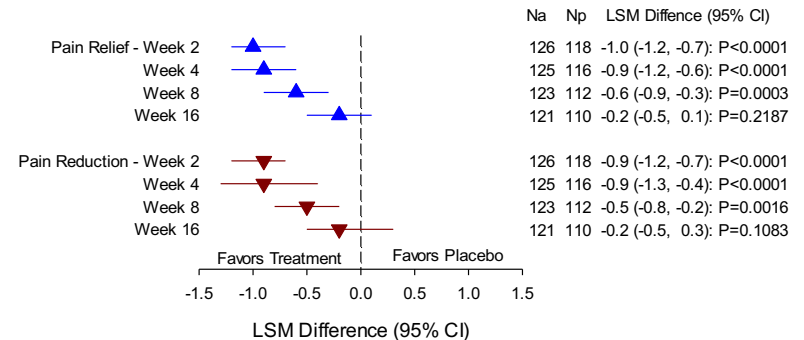
Software

- Multiple Software Packages are available for creating FPs:
 - SAS® Software
 - Sigma Plot®
 - NCSS®
 - R language
- FP examples in this paper were generated with Sigma Plot Version 13.0 and the analysis dataset generated using SAS® Software

Programmers Produce Tables Lots of Tables

Time point/ Statistic	Treatment A (N=161)		Placebo (N=162)		Treatment B (N=161)	
	Observed	Change From Baseline	Observed	Change From Baseline	Observed	Change From Baseline
Baseline						
n	161		162		161	
Mean (SD)	6.26 (0.933)		6.27 (0.980)		6.25 (0.901)	
Median	6.14		6.14		6.14	
Min ; Max	5.0 ; 8.5		5.0 ; 8.9		5.0 ; 9.0	
Week X						
n	160	160	162	162	161	161
Mean (SD)	4.40 (1.943)	-1.85 (1.723)	5.18 (1.797)	-1.09 (1.604)	4.13 (1.873)	-2.12 (1.824)
Median	4.43	-1.57	5.36	-0.57	4.17	-1.71
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LSM Difference from Trt B		0.22				
95% CI		-0.26, 0.71				
2-sided p-value		0.3688				

How do I
interpret
this mess?
Give me an FP



Forest Plots can efficiently and accurately summarize
in a graph most analyses that make comparisons.

Conclusion and Recommendation

- Implementing the use of FPs as a data visualization tool requires some planning on the part of the statistician and statistical programmer.
- Identifying key endpoints, planned analyses, and messages to be presented from the statistical analysis plan is the first step in this process.
- The second step is to develop a standard data structure for capturing the results from different endpoints and analyses and capturing these results during the programming and tabular display of results.
- The general structure can be customized to meet individual programming methods and standards, yet all the elements needed for a FP are present.
- A forest plot (FP) should be considered an important and useful analysis results visualization tool that programmers and statisticians use in daily practice.

Questions

