PhUSE 2017

Paper DV09

Visualizing Multiple Endpoints: Extending the Use of Forest Plots in Clinical Trials

James R. Johnson, Summit Analytical, LLC., Cary, NC USA
Mark J. Jaros, Summit Analytical, LLC., Frankfort, IL USA

ABSTRACT

Forest plots (FPs) are graphical displays originally developed for meta-analyses to present results obtained from multiple clinical trials addressing the same question or endpoint.[1,2,10] Today FPs are considered one of the "gold standard" tools for the publication and presentation of meta-analyses of randomized controlled clinical trials. Often, the measurement of effect presented in the FP is an Odds Ratio, or mean difference, comparing treatment to control.[26]

The structure and format of FPs are very useful within a clinical trial for presenting analyses of multiple endpoints over a sampling time. This data visualization structure is an ideal tool to summarize key messages and endpoints from multiple tabular summaries into a single graph. In this paper, we present the structure and implementation of FPs, with suggestions for the structure of an analysis results dataset for presenting a FP. We provide several extensions of the general structure of FPs for individual clinical trials with examples. The use of FPs as a visual tool for summarizing multiple endpoint in a CSR offers a broad heuristic view of trial results, with enhanced understanding of overall treatment effects.

INTRODUCTION

The primary objective of graphing research data is to communicate key information visually in a rapid, accurate, transparent, and concise manner. [3,4,5,6,7,8,9] A visual display of research data is also a very useful tool for presentation of modeling results that take the form of many pages in tabular summaries, and serves a key role in translating multiple findings into conclusions or messages. If graphical summaries (visual displays) are implemented well then complex information from tabular summaries is reduced into a simple and easily interpretable display. Tabular data tables and listings are a requirement by regulatory guidance and critical to clinical trial reports, but they should supplement the primary graphical display of similar information.

Graphs are visual summaries of one or more endpoints in a study. Most graphs appearing in the literature or clinical study reports consist of the traditional line graphs, histograms, and bar charts for single endpoints. Over the past 20 years, graphing techniques have evolved beyond group means and confidence intervals to make data and results easier to read and interpret. These methods include extensions of horizontal bar charts, dot charts, stem-and-leaf plots, box plots (and notched box plots), surface plane plots, along with advanced scatter and line plots for modelled results.

Another graphical tool that has evolved over the past 20 years is the Forest Plot (FP).[13,14,15] FPs were originally developed for meta-analyses to present results obtained from multiple clinical trials addressing the same question or endpoint. FPs are graphs that visually display the results from the individual studies (treatment effect and confidence interval), as well as the estimate of overall treatment effect and associated confidence interval. Treatment effects are often provided in terms of standardized effect sizes, standardized mean differences, odds ratio, risk ratio, rate ratio or hazard ratio and are accompanied by the 95% confidence interval (CI) for the effect. FPs are also ideal graphical displays that have not been used on a regular basis to summarize data within a study.

In this paper, we present the structure and implementation of FPs, with suggestions for a general structure of an analysis results dataset for the FP. We provide several extensions of the general structure of FPs for individual clinical trials with examples for:

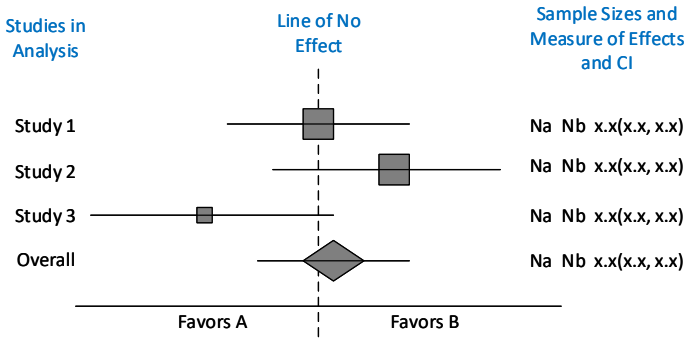
(1) Multiple endpoints at a fixed point in time within a clinical trial that are analyzed with similar statistical models (e.g. mixed model for repeated measures (MMRM) with endpoints of Least Squares (LS) mean change from baseline),
(2) An endpoint collected over multiple time points,
(3) Multiple endpoints with standardized effect sizes. In a clinical trial, the presentation of individual endpoints would typically be with individual summaries (tables and figures), and
(4) Pharmacokinetic Bioequivalence testing for multiple formulations.

The discussion and summaries in clinical study reports (CSR) of the treatment effect(s) for a drug are rarely limited to a single endpoint. The use of FPs as a visual tool for summarizing multiple endpoint in a CSR offers a broad heuristic view of trial results, with enhanced understanding of overall treatment effects.

STRUCTURE AND FUNCTION OF META-ANALYSIS FOREST PLOTS

Today FPs are considered one of the "gold standard" tools for the publication and presentation of meta-analyses of randomized controlled clinical trials. The generalized structure of FPs in meta-analyses is shown in Figure 1:

Figure 1 General Structure of a Forest Plot in Meta-Analyses



In the generalized structure of FPs for meta-analyses the studies are on the left side of the plot, the sample sizes and measurements of effects (with confidence intervals) for the endpoint on the right side.[26] The x-axis displays a scale of the treatment effects, with a vertical reference to the line of no effect. Optionally, the size of the symbol for each study is a measure of the weight of the study to the overall meta-analysis. The FP may also, optionally, display an overall studies effect. Often, the measurement of effect is an Odds Ratio, or mean difference, comparing Experimental Treatment to Control.[11, 15, 21] In a simple example one can collect data from multiple studies that examine a continuous endpoint to look at mean differences, perform the meta-analysis, and produce a forest plot as shown in Figure 2. In a second example, you can examine a binary response endpoint over multiple studies and examine the Odds ratios as seen in Figure 3.

Figure 2 Simple Example of a Meta-Analysis of 4 Studies: Mean Differences

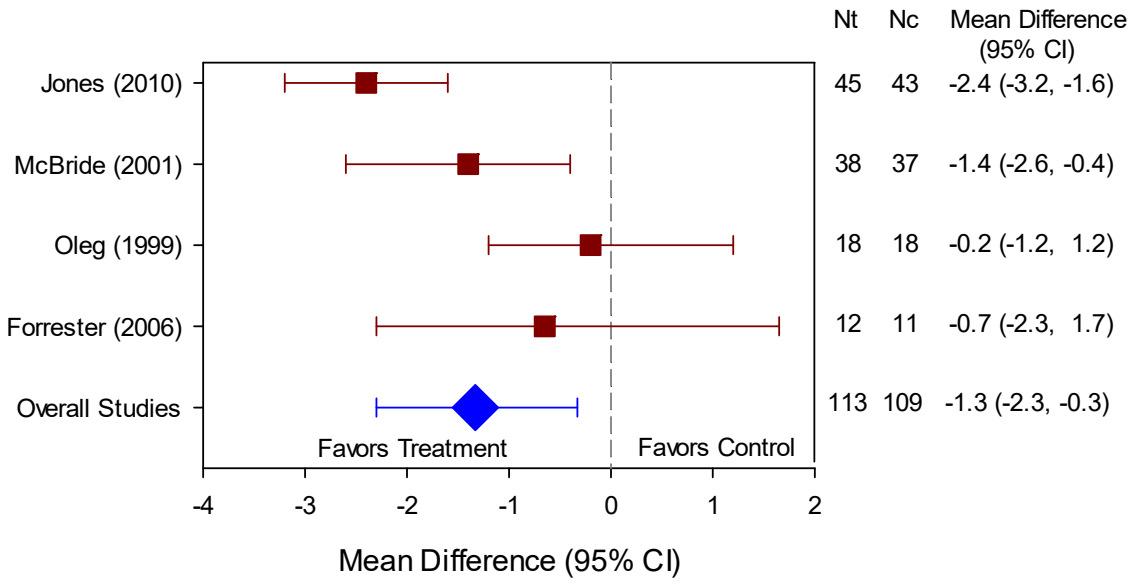
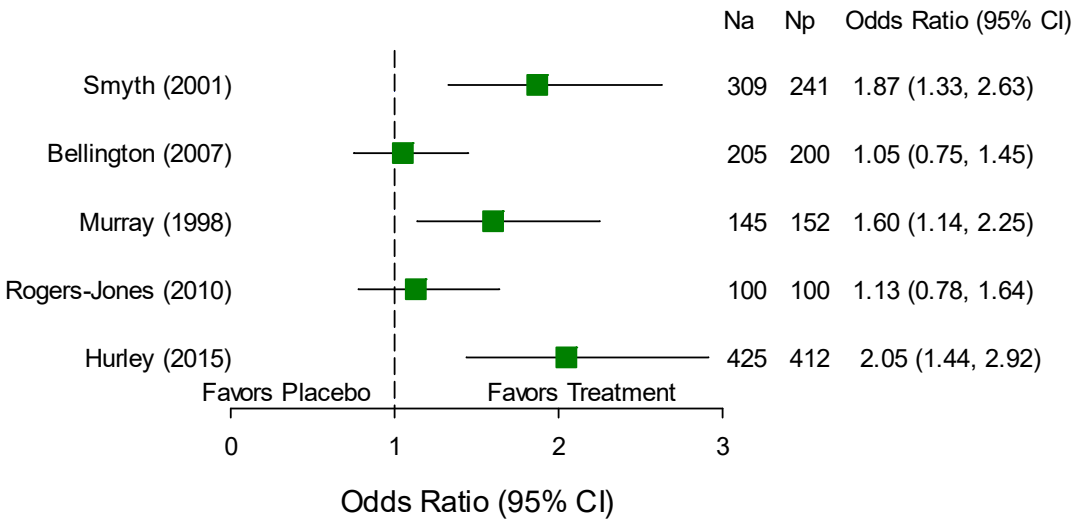


Figure 3 Simple Example of a Meta-Analysis of 5 Studies: Odds Ratios



In each example, the minimum structure of a simple analysis data set for the results presented in a FP will include variables as presented in Table 1.

Table 1 Minimum variables for Meta-Analysis FP Dataset

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

This logic and generic structure for a meta-analysis results dataset works whether the variable displayed is a mean difference, odds ratio, hazard ratio, standardized effect size, or risk ratio. These data requirements are what are normally seen with any Cochrane Meta-Analysis. [26, 27]

GENERAL STRUCTURE OF ANALYSIS RESULTS DATA SET FOR FOREST PLOTS

Extension of the generic structure in Table 1 for multiple endpoints, endpoints over time, subgroups, and other logical presentations of results in a FP must include meta-data about the endpoint and timing of the endpoint, meta-data about the sub-group, and information about the labeling to be applied for the FP. Additional graphics package specific information may also be included in the analysis results data set that describes the symbols to be used, color, line characteristics, and weighting of the symbol size. We propose a general structure of the analysis results dataset that can be used as input for presentation of a trial specific FP, independent of software package used to produce the FP.

The architecture of this analysis results dataset is predicated in using common ADaM nomenclature for some of the variables, along with additional graphics specific variables, and a program sourcing variable. With adequate planning for visual display of planned analyses the analysis programs that complete the statistical analyses and produce the tabular summaries can be extended to generate the results in a form for visual display as a FP.

The general structure for an analysis results dataset for capturing results from multiple analyses is presented in Table 2.

Table 2 General Structure for Analysis Results Data Set for a FP

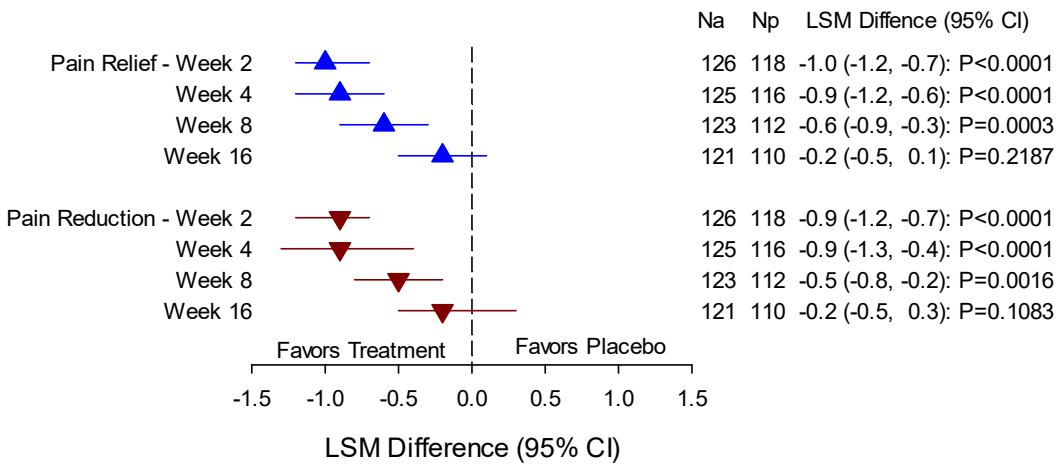
Variable	Char/Num	Description
GRPID	Numeric	Grouping Identifier
GROUP	Char	Group Description
PARCAT1	Char	Parameter Grouping
PARAMCD	Char	Parameter Code
PARAM	Char	Parameter Description
YORDER	Numeric	Order on Y-Axis of FP
ENDPOINT	Char	Description of Analysis Endpoint
AVISIT	Char	Analysis Visit
AVISITN	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

An example dataset for a representative sample of the FP examples in subsequent sections is presented in the Appendix. Note that this standardized structure can be set up with standardized programming (e.g. macros) to capture individual analysis results from multiple analysis models. Additional variables may also be added to provide additional meta-data (e.g. STUDYID, cross reference TLF numbers, etc.) if the dataset is to be submitted with a data package to regulatory authorities.

MULTIPLE ENDPOINTS FOREST PLOTS

Multiple endpoints at a fixed timepoint, or over multiple times, within a clinical trial that are analyzed with similar statistical models (e.g. MMRM with endpoints of LS Mean Difference between treatments on a Change from Baseline) typically will produce tabular summaries for each individual endpoint at each individual time point. These summaries will provide descriptive as well as modelled results from the planned statistical model. Capturing the key information for the endpoint(s) of interest that compare treatment to control is usually the topic of results presentation in the clinical study reports, with reference to the tabular summaries in section 14 of a CSR. Adding the use of a FP to display multiple endpoints over a sampling time that summarizes the modeled statistics produces a clinically meaningful, and easily interpretable summary for the CSR. Consider the example in Figure 4, where two endpoints are captured over a 16-week period and the treatment difference from placebo at each time point for each correlated endpoint is of interest.

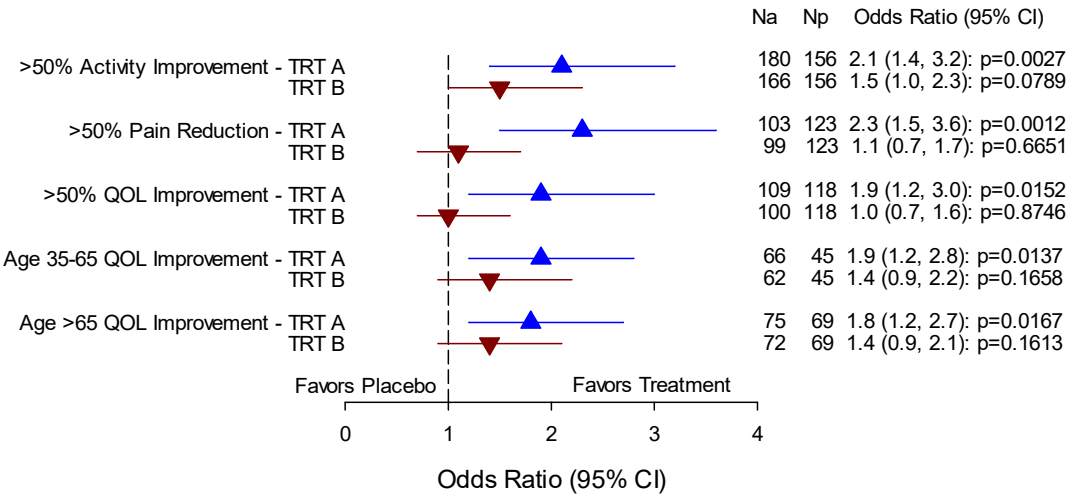
Figure 4 Multiple Endpoints Captured over Sequential Time Points



In this example, we have taken two distinct, but related endpoints, captured over multiple time points, and demonstrated the endpoint (Change from baseline) comparison of treatment to control over time.

This extension is not limited to just a single treatment comparison. The data structure supports multiple treatment comparisons at a single time point or at multiple time points. Consider the extension of a FP where two treatment comparisons (TRT A and TRT B) are made against Placebo for 5 endpoints at a single time point (Figure 5).

Figure 5 Multiple Treatment Comparisons with Multiple Endpoints

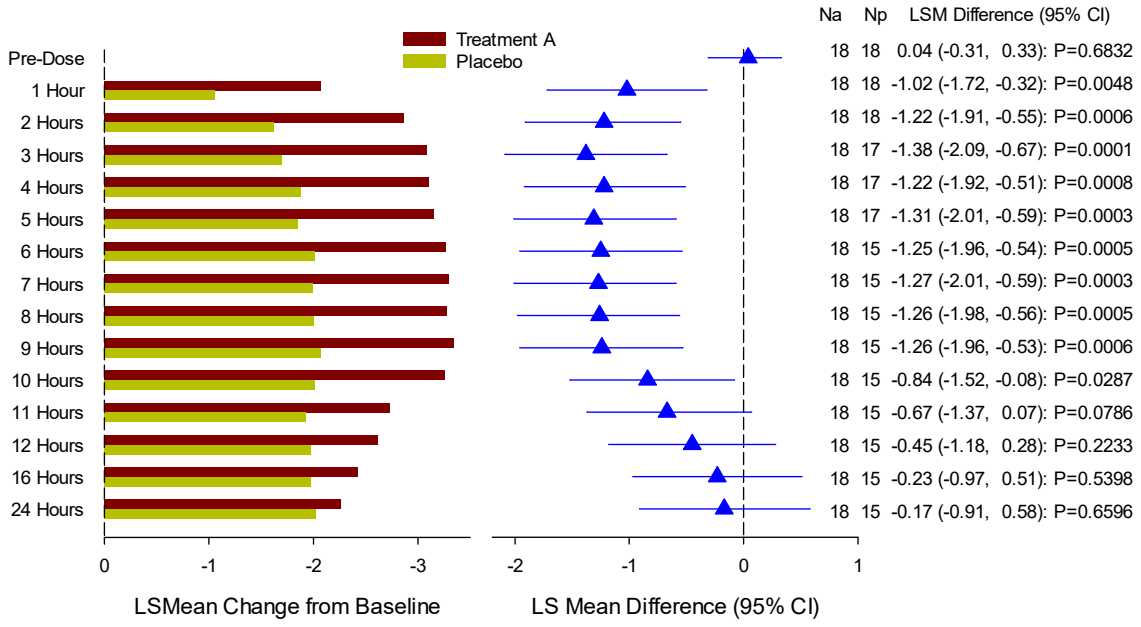


The same principle for visual display of multiple endpoints, over multiple treatments, compared to a control is summarized using the same analysis results data set architecture.

SINGLE ENDPOINT OVER TIME FOREST PLOTS

Single endpoints such as change from baseline (or pre-dose) collected over a sampling interval are common in early development studies. Typically, a simple x-y scatter plot or bar chart of the means (or some other descriptive statistic) at each serial time point is presented to visualize the temporal changes from baseline for each treatment. The extension of using the FP in this setting provides a mechanism to visualize the modelled difference in treatment along with the actual change from baseline. Combining a FP with a scatter plot or bar chart provides an ideal visualization tool consolidating tabular summaries of these analyses as seen in the example in Figure 6.

Figure 6 Single Endpoint over Time



The standard data structure will hold the individual means for each time as well as the LS Mean difference, providing an input source to the graphics package of choice.

STANDARDIZED EFFECT SIZES, MULTIPLE ENDPOINTS, AND FOREST PLOTS

Multiple endpoints in a clinical trial come with different units of measurement that are often arbitrary, in the sense that there is no necessary reason why the measurement instrument is based on a particular scaling. The resulting inferential statistic can be predicated on both the measurement unit and the sample size for the endpoint. Generally, these analyses stand alone in a clinical trial in tabular summaries. Standardizing effect size is a straightforward way of quantifying the differences between two groups that has many advantages over the use of inferential testing alone. This is a very common and useful method used in Meta-analysis that can be extended to an individual clinical trial.[25, 28,29]

Standardized Effect Size (SES is a standard method to quantify the magnitude of difference between two treatment groups. SES are methods where the difference between mean for the active treatment and placebo treatment are examined using pooled standard deviation to qualify the magnitude of treatment effects. Another words, the effect size is the standardized mean difference between the active and placebo treatment groups. A general form of an SES to examine LS means is as follows[26, 27, 28, 29]:

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

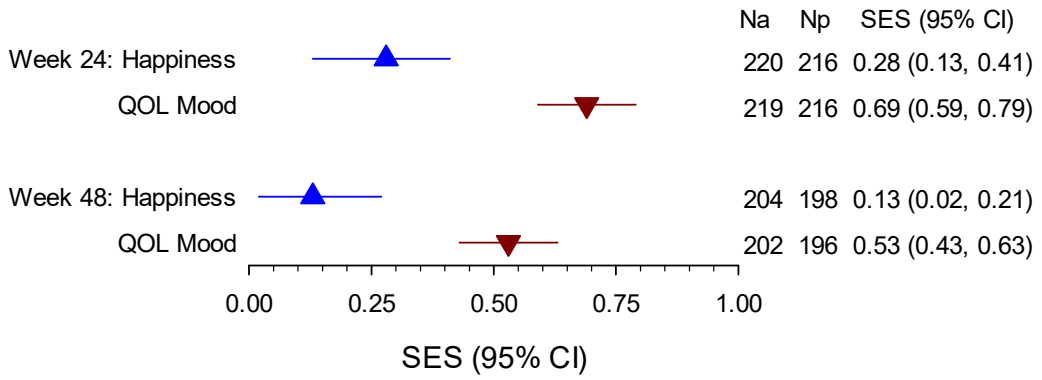
Standardized Effect Size (SES) emphasizes the magnitude of the difference rather than confounding this with sample size, is unit-less, and has a scale between 0 and 1. The larger the SES value the more robust the magnitude of treatment effect.

The utility of this measure includes:

(1) Standardized effect sizes (and confidence interval) help you evaluate how big or small an effect is when the units of measurement aren't intuitive.
(2) Standardized effect sizes (and confidence interval) can help you compare results both within and across studies.
(3) Standardized effect sizes (and confidence interval) can help you compare results from multiple endpoints with different measurement criteria within and across studies.

Editors of journals, and in many cases regulators, are requiring SES to be calculated. But the real reason for looking at SES is that it can greatly assist in understanding both the data analysis and results presented. FP is an ideal tool for presenting SES from multiple endpoints over time. Consider an example a subject in a clinical trial measures their daily happiness on an NRS, 0-10 scale, and then at scheduled visits completes a QOL questionnaire, with a happiness component, using a Likert scale (0-4). Both endpoints are analyzed using a MMRM. The measurement scale and units are different for each endpoint, and interpreting the MMRM LS Mean differences for each endpoint can be challenging due to different scales, yet these results are highly correlated and it is useful to examine results together for both endpoints, using an SES (95% CI) and a FP, as shown in Figure 7.

Figure 7 **SES (Confidence Interval) for Multiple Endpoints over Time**

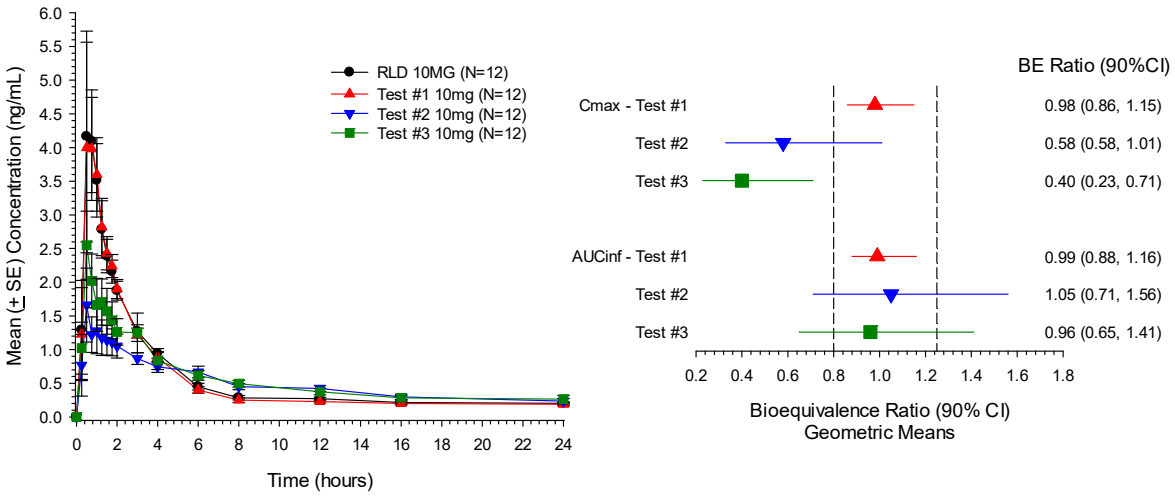


Converting results to an SES allows for direct comparison of multiple endpoints with different scales over time.

PHARMACOKINETIC ENDPOINTS, AND FOREST PLOTS

In the early development of drug products, bioequivalence studies may be conducted on one or more formulations in controlled cross-over clinical trials. Bioequivalence is generally evaluated as a ratio of the geometric means with 90% confidence intervals of pharmacokinetic parameters such as C_{max} and $AUC_{0\text{-}inf}$ (or other PK parameters as defined for a study). Evaluation of the mean concentration versus time profile for treatment arms provides a visual display of the profile for the treatment arms, and BE evaluation of the PK parameters provide estimates of the relationship of the profile and is usually in tabular form. Both are informative, and both are ideal for visualization displays to provide a complete understanding of the bioequivalence trial when combined using a FP. Consider the example in Figure 8.

Figure 8 **Pharmacokinetic Endpoints Combination Plot**



SOFTWARE FOR PRODUCING FOREST PLOTS

Forest Plots can be generated with many different commercial software packages. The FP examples in this paper were generated with Sigma Plot Version 13.0 and the analysis dataset generated using SAS® Software. However, these are not the only options available. The following software packages (with reference number) are available to create FPs in either a meta-analysis or multiple endpoints setting.

- SAS® Software[30]
- Sigma Plot®[31]
- NCSS®[33]
- R language[32]

CONCLUSION AND RECOMMENDATION

A forest plot (FP) should be considered an important and useful analysis results visualization tool. In this paper we have demonstrated, through example, the use of FPs as a tool for summarizing multiple endpoints, with diverse types of analyses, over multiple temporal periods of time. When appropriately implemented in a Clinical Study Report FPs provide a broad heuristic view of trial results, with an enhanced understanding of overall treatment effects. The general structure of the FP has been extended from use in meta-analyses to a general usage across individual clinical studies. Bijnens et al. (1996)[34] first described the use of a FP and described its use as an optimal tool for summarizing results for meta-analyses. This description is valid today as the use of a FP clearly provides a mechanism for easy review of trial results. The old adage "*A picture paints a thousand words*" probably can be extended to "*A FP presents a complete picture of many analyses from many tabular summaries*".

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. In this paper, we offer a standardized analysis results data structure for capturing information to be presented in FPs. The general structure can be customized to meet individual programming methods and standards, yet all the elements needed for a FP are present.

REFERENCES

1. Lewis S, Clarke M. *Forest plots: trying to see the wood and the trees*. BMJ. 2001;322:1479-1480.
2. Pocock SJ, Travis on TG, Wrack LM. *Figures in clinical trial reports: current practice and scope for improvement*. Trials. 2007;8(36):1-17.
3. Tufte ER. *The Visual Display of Quantitative Information*. Graphics Press. 1983. 197pages.
4. Tufte ER. *Envisioning Information*. Graphics Press. 1990. 125 pages.
5. Tufte ER. *Visual Explanations: Images and Quantities, Evidence and Narrative*. Graphics Press 1997. 156 pages.
6. Chambers JM, Cleveland WS, Kleiner B, Tukey PA. *Graphical Methods for Data Analysis*. Wadsworth Publishing 1983.
7. Cleveland WS, McGill R. *Graphical Perception: Theory, Experimentation, and Application to the Development of Graphical Methods*. Journal of Am Statistical Assoc. 1984;79:531-554.
8. Cleveland WS, McGill R. *The many faces of a Scatterplot*. Journal of Am Statistical Assoc. 1984;79(388):807-822.
9. Amit O, Heiberger RM, Lane PW. *Graphical Approaches to the Analysis of Safety Data from Clinical Trials*. Pharmaceutical Statistics 2008;7:20-35.
10. Schriger DL, Cooper RJ. *Achieving Graphical Excellence: Suggestions and methods for Creating High-Quality Visual Displays of Experimental Data*. Annals of Emergency Medicine. 2001;37(1):75-87.
11. Bax L, Ikeda N, Fukui N, Yaju Y, Tsuruta H, Moons KGM. *More than Numbers: The Power of Graphs in Meta-Analysis*. American Journal of Epidemiology. 2008;169(2):249-255.
12. Cooper RJ, Schriger DL, Close RJH. Graphical Literacy: *The Quality of Graphs in a Large-Circulation Journal*. Annals of Emergency Medicine. 2002;40(3):317-322.
13. Bogaty P, Brophy J. *Forest Plots and the Interpretation of Subgroups*. Lancet. 2005;365:1308.
14. Guddat C, Grouven U, Bender R, Skipka G. *A Note on the graphical presentation of prediction intervals in random-effects meta-analysis*. Systematic Reviews. 2012;1:34.
15. High R. *Plotting Differences among LSMEANS in Generalized Linear Models*. SUGI. Paper 1902-2014. 2014.
16. Kaur A. *Use of Graphics in Clinical Trials: A Discussion*. Presentation at Joint Statistical Meetings, Vancouver Canada. August 2010.
17. Krause A, O'Connell M. *A Picture is worth a Thousand Tables: Graphical Display of Clinical Data*. Presentation at AAPS Annual Meeting. San Antonio, TX. November 1, 2006.
18. O'Connell M, Knudsen S. *Statistical Graphics and Reporting in Drug Development*. PhUSE Annual Meeting 2006. Paper TS04. October 2006.
19. Paniello RC, Neely JG, Rich JT, Slattery EL, Voelker CCJ. *Practical Guide to Choosing an Appropriate Data Display*. Otolaryngology Head and Neck Surgery 2011;145(6):886-894.
20. Pietzko K, O'Connell M. *Statistical Graphics for Review and Reporting in Clinical Development*. PhUSE Annual Meeting 2010. Paper PO03. October 2010.
21. Schild AH, Voracek M. *Finding your way out of the forest without a trail of bread crumbs: development and evaluation of two novel displays of forest plots*. Res Synth Methods. 2015 Mar;6(1):74-86.
22. Stengel D, Calori GM, Giannoudis PV. *Graphical Data Presentation*. Injury. 2008 Jun;39(6):659-65.

23. Van Wetten P. Forest Plot: W3 + H2 What it is, Why use it, When to use it + How to generate and How to interpret. PhUSE Annual Meeting 2014. Paper SP08. October 2014.
24. Thompson B. *What Future Quantitative Social Science Research could Look Like: Confidence Intervals for Effect Sizes*. Educational Researcher, 2008;31:25–32.
25. Kelly K. *Confidence Intervals for Standardized Effects Sizes: Theory, Application, and Implementation*. Journal of Statistical Software. 2007;20(8).
26. Cochrane Handbook for Systematic Reviews of Interventions, Version 5.0.2, 2009; Available at: http://www.mrc-bsu.cam.ac.uk/cochrane/handbook.
27. Chinn S. *A simple method for converting an odds ratio to effect size for use in meta-analysis*. Statistics in Medicine. 200;19:3127-3131.
28. Fritz CO, Morris PE, Richler JJ. *Effect Size estimates: Current use, calculations, and interpretation*. Journal of Experimental Psychology. 2012;141(1):2-18.
29. Baguley T. *Standardized or Simple Effect Size: What should be reported?* British Journal of Psychology. 2009;100(3):603-617.
30. Bursac Z. Creating Forest Plots from pre-computed Data using PROC SGPLOT and Graphics Template language. SAS Global Forum 2010. paper 195-2010. (https://support.sas.com/resources/papers/proceedings10/195-2010.pdf).
31. Sigma Plot V13.0. (https://systatsoftware.com/products/sigmaplot/)
32. R language. Forest Plots Package. https://cran.r-project.org/web/packages/forestplot/vignettes/forestplot.html
33. NCSS 11 Statistical Software (2016). NCSS, LLC. Kaysville, Utah, USA, www.ncss.com/software/ncss.
34. Bijnens L, Collette L, Ivanov A, Hoctin-Boes G, Sylvester R. *Optimal graphical display of the results of meta-analyses of individual patient data*. In: Proceedings of the 4th Cochrane colloquium, Adelaide, Australia, 1996. Oxford: Cochrane Collaboration, 1996.

ACKNOWLEDGMENTS

We would like to thank all our colleagues who reviewed and provided valuable comments. We would especially like to thank the many sponsors who we, at Summit Analytical, have had the privilege of providing statistics and pharmacokinetics consulting and support. It was through these collaborations that we have refined our use of graphics and forest plots to provide a better and more comprehensive understanding of trial results.

CONTACT INFORMATION

Your comments and questions are valued and encouraged. Contact the author(s) at:

James R. Johnson, PhD (“Jim”)
Summit Analytical, LLC
104 Lutterworth Court
Cary, North Carolina 27519-8682 USA
Work Phone: +1 (919) 244-4756
Email: jrjphd@gmail.com or jjohnson@summitanalytical.com

APPENDIX

Example Analysis results dataset for FP

GRPID	GROUP	PARCAT1	PARAMCD	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
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
3	Figure 3	1	NRS	Numerical Rating Scale (0-10)	1	LSMDIFF	Pre-Dose	1	18	18	0.04	-0.31	0.33	0.6832	Pre-Dose	18 18 0.04 (-0.31, 0.33): P=0.6832
3	Figure 3	1	NRS	Numerical Rating Scale (0-10)	1	LSMDIFF	1 Hour	1	18	18	-1.02	-1.72	-0.32	0.0048	1 Hour	18 18 -1.02 (-1.72, -0.32): P=0.0048
3	Figure 3	1	NRS	Numerical Rating Scale (0-10)	2	LSMDIFF	2 Hours	2	18	18	-1.22	-1.91	-0.55	0.0006	2 Hours	18 18 -1.22 (-1.91, -0.55): P=0.0006
3	Figure 3	1	NRS	Numerical Rating Scale (0-10)	3	LSMDIFF	3 Hours	3	18	17	-1.38	-2.09	-0.67	0.0001	3 Hours	18 17 -1.38 (-2.09, -0.67): P=0.0001
3	Figure 3	1	NRS	Numerical Rating Scale (0-10)	4	LSMDIFF	4 Hours	4	18	17	-1.22	-1.92	-0.51	0.0008	4 Hours	18 17 -1.22 (-1.92, -0.51): P=0.0008
3	Figure 3	1	NRS	Numerical Rating Scale (0-10)	5	LSMDIFF	5 Hours	5	18	15	-1.31	-2.01	-0.59	0.0003	5 Hours	18 17 -1.31 (-2.01, -0.59): P=0.0003
3	Figure 3	1	NRS	Numerical Rating Scale (0-10)	6	LSMDIFF	6 Hours	6	18	15	-1.25	-1.96	-0.54	0.0005	6 Hours	18 15 -1.25 (-1.96, -0.54): P=0.0005
3	Figure 3	1	NRS	Numerical Rating Scale (0-10)	7	LSMDIFF	7 Hours	7	18	15	-1.27	-2.01	-0.59	0.0003	7 Hours	18 15 -1.27 (-2.01, -0.59): P=0.0003
3	Figure 3	1	NRS	Numerical Rating Scale (0-10)	8	LSMDIFF	8 Hours	8	18	15	-1.26	-1.98	-0.56	0.0005	8 Hours	18 15 -1.26 (-1.98, -0.56): P=0.0005
3	Figure 3	1	NRS	Numerical Rating Scale (0-10)	9	LSMDIFF	9 Hours	9	18	15	-1.24	-1.96	-0.53	0.0006	9 Hours	18 15 -1.26 (-1.96, -0.53): P=0.0006
3	Figure 3	1	NRS	Numerical Rating Scale (0-10)	10	LSMDIFF	10 Hours	10	18	15	-0.84	-1.52	-0.08	0.0287	10 Hours	18 15 -0.84 (-1.52, -0.08): P=0.0287
3	Figure 3	1	NRS	Numerical Rating Scale (0-10)	11	LSMDIFF	11 Hours	11	18	15	-0.67	-1.37	0.07	0.0786	11 Hours	18 15 -0.67 (-1.37, 0.07): P=0.0786
3	Figure 3	1	NRS	Numerical Rating Scale (0-10)	12	LSMDIFF	12 Hours	12	18	15	-0.45	-1.18	0.28	0.2233	12 Hours	18 15 -0.45 (-1.18, 0.28): P=0.2233
3	Figure 3	1	NRS	Numerical Rating Scale (0-10)	13	LSMDIFF	16 Hours	16	18	15	-0.23	-0.97	0.51	0.5398	16 Hours	18 15 -0.23 (-0.97, 0.51): P=0.5398
3	Figure 3	1	NRS	Numerical Rating Scale (0-10)	14	LSMDIFF	24 Hours	24	18	15	-0.17	-0.91	-0.58	0.6596	24 Hours	18 15 -0.17 (-0.91, 0.58): P=0.6596
4	Figure 4	1A	NRSMOOD	Happiness NRS 0 to 10	1	SES	Week 24	24	220	216	0.28	0.13	0.41		Week 24: Happiness	220 216 0.28 (0.13, 0.41)
4	Figure 4	1B	QOLLIKERT	QOL Likert Mood Scale, 0-4	2	SES	Week 24	24	219	216	0.69	0.59	0.79		QOL Mood	219 216 0.69 (0.59, 0.79)
4	Figure 4	2A	NRSMOOD	Happiness NRS 0 to 10	4	SES	Week 48	48	204	198	0.13	0.02	0.21		Week 48: Happiness	204 198 0.13 (0.02, 0.21)
4	Figure 4	2B	QOLLIKERT	QOL Likert Mood Scale, 0-4	5	SES	Week 48	48	202	196	0.53	0.43	0.63		QOL Mood	202 196 0.53 (0.43, 0.63)
5	Figure 5	1A	PKCMAX	Cmax	1	BERATIO			12	12	0.98	0.86	1.15		Cmax - Test #1	0.98 (0.86, 1.15)
5	Figure 5	1B	PKCMAX	Cmax	2	BERATIO			12	12	0.58	0.33	1.01		Test #2	0.58 (0.58, 1.01)
5	Figure 5	1C	PKCMAX	Cmax	3	BERATIO			12	12	0.4	0.23	0.71		Test #3	0.40 (0.23, 0.71)
5	Figure 5	2A	PKAUCINF	AUC0-inf	5	BERATIO			12	12	0.99	0.88	1.16		AUCinf - Test #1	0.99 (0.88, 1.16)
5	Figure 5	2B	PKAUCINF	AUC0-inf	6	BERATIO			12	12	1.05	0.71	1.56		Test #2	1.05 (0.71, 1.56)
5	Figure 5	2C	PKAUCINF	AUC0-inf	7	BERATIO			12	12	0.96	0.65	1.41		Test #3	0.96 (0.65, 1.41)