Communicating Clinical Trial Results the Statistical Graphic Way

Mat Soukup, Ph.D.

FDA/CDER/OTS/OB/Division of Biometrics 3

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Disclaimer

- The views expressed in this presentation are those of the presenter and must not be taken to represent policy or guidance on behalf of the Food and Drug Administration.

Outline

1 Introduction

2 Application of Statistical Graphics: The Good & The Bad in Clinical Trials

3 Developing Standard Views of Safety Data

4 Concluding Remarks
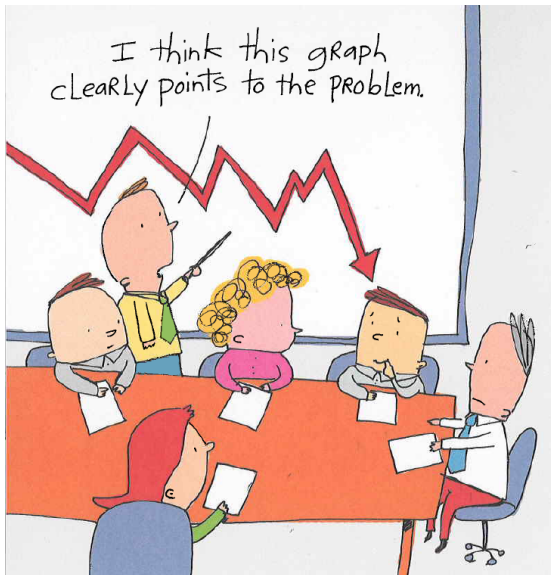
By: David Walker

Quotation

"Information, that is imperfectly acquired, is generally as imperfectly retained; and a man who has carefully investigated a printed table, finds, when done, that he has only a very faint and partial idea of what he has read; and like a figure imprinted on sand, is soon totally erased and defaced."

   - William Playfair (1786 English Economist)

Motivation

Reasons to Include Graphic Summaries

- Complex statistical concepts and data structures can be conveyed at a level which is within reach to those with little statistical training.
- Ability to highlight key safety signals and depict efficacy characteristics from both small and large databases.
- Paradigm is to actively assess the data in a manner that is visual, intuitive, and geometric - then use this assessment to guide our communication of the data.
- Improves retention of information displayed.

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The Good

Whenever possible:

- Depict subject-level data
- Depict multivariate structures in the data
- Use graphical displays rather than tables
- Incorporate tabular values into the displays
- Account for temporal relationships

Depicting Subject-Level Data

Lancet **Article on T4N5 to Treat XP**

- XP is life-threatening disease occurring in approximately 1 out of 250,000 people in the US. Average age of developing skin cancer is 8 years.

- Study objective is to see if T4N5 reduces number of AK and BCC lesions.

- Study enrolled 29 subjects, 20 randomized to T4N5.

- Data is publicly available on journal website: Vol. 357, Issue 9260, March 2001, pages 926-929.

- Objective: Visualize the data.

Xeroderma Pigmentosum

The Lancet **Data Plot of Means**
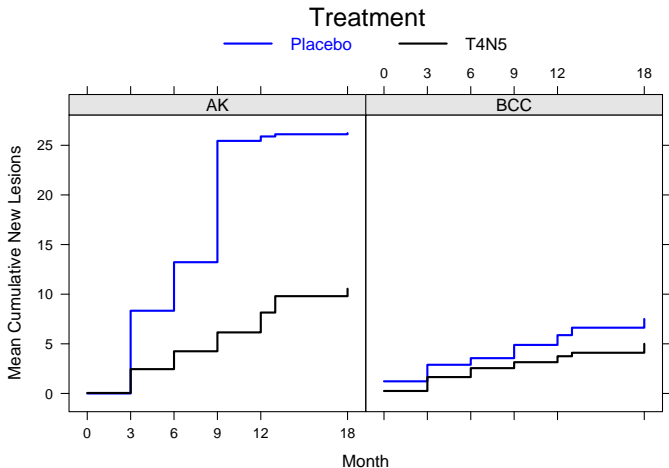
The Lancet **Data Plot of Subject Profiles**
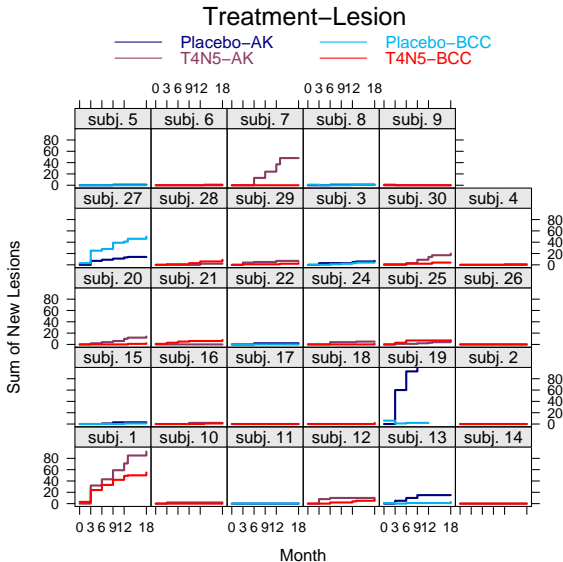
Displays Versus Tables

Tabular Summary of SBP

		Active Drug				Control Drug		
Visit	N	Mean	SD	95% CI	N	Mean	SD	95% CI
1	112	118.1	1.3	(115.9, 120.3)	113	119.1	1.2	(117.0, 121.2)
2	112	122.7	1.4	(120.4, 125.0)	112	119.1	1.1	(117.0, 121.2)
3	111	125.6	1.0	(123.6, 127.6)	110	114.4	1.2	(112.3, 116.5)
4	110	133.1	1.2	(131.0, 135.2)	108	124.2	1.4	(121.9, 126.5)
5	110	136.7	1.2	(134.6, 138.8)	108	123.8	1.2	(121.7, 125.9)
6	108	134.2	1.1	(132.1, 136.3)	108	114.9	1.1	(112.8, 117.0)
7	106	131.0	1.2	(128.9, 133.1)	104	120.1	1.2	(118.0, 122.2)
8	105	126.2	1.3	(124.0, 128.4)	103	121.6	1.2	(119.5, 123.7)
9	104	124.3	1.2	(122.2, 126.4)	100	118.6	1.1	(116.5, 120.7)
10	102	125.1	1.2	(123.0,127.2)	100	117.7	1.3	(115.5, 119.9)

Identify the Signal!

Graphical Approach to Summarize SBP
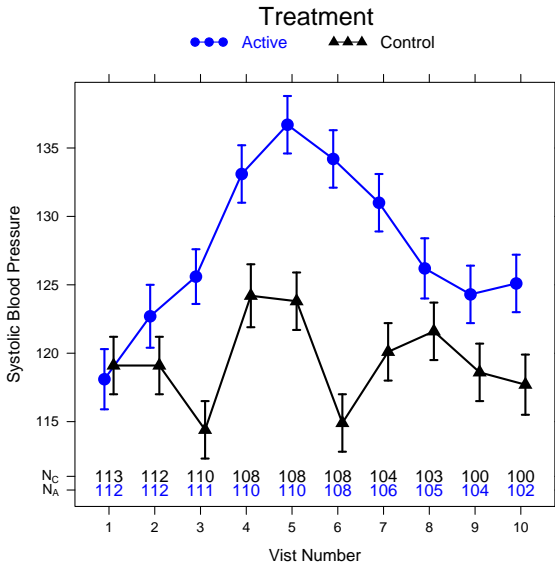
Incorporating Table Info Into Graphical Display

Aldara Label for sBCC

	Aldara Cream n=184		Vehicle n=178	
	Overall*	Severe	Overall*	Severe
Erythema	184 (100%)	57 (31%)	173 (97%)	4 (2%)
Flaking/Scaling	167 (91%)	7 (4%)	135 (76%)	0 (0%)
Induration	154 (84%)	11 (6%)	94 (53%)	0 (0%)
Scabbing/Crusting	152 (83%)	35 (19%)	61 (34%)	0 (0%)
Edema	143 (78%)	13 (7%)	64 (36%)	0 (0%)
Erosion	122 (66%)	23 (13%)	25 (14%)	0 (0%)
Ulceration	73 (40%)	11 (6%)	6 (3%)	0 (0%)
Flaking/Scaling	57 (31%)	3 (2%)	4 (2%)	0 (0%)

*Mild, Moderate, or Severe

Dotplot of Aldara Data

The Bad

Whenever possible, avoid the following:

- Creating discrete variables from continuous
- Non-optimal data to ink ratio
- Misuse of scaling
- Using unneeded dimensions

Creating Discrete Variables from Continuous and Non-Optimal Data to Ink Ratio
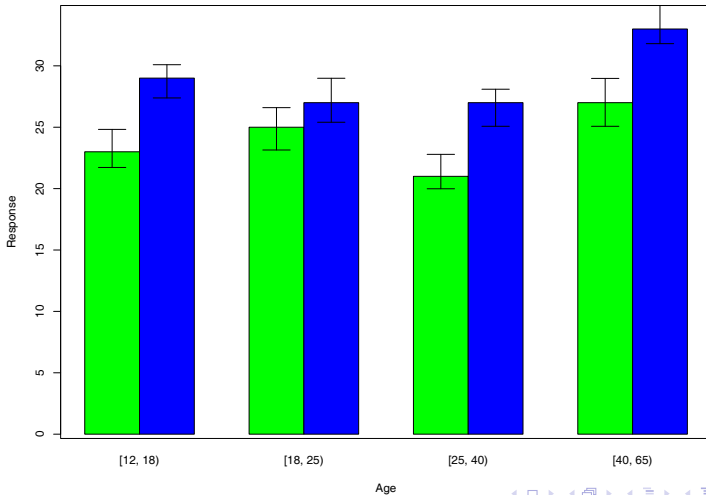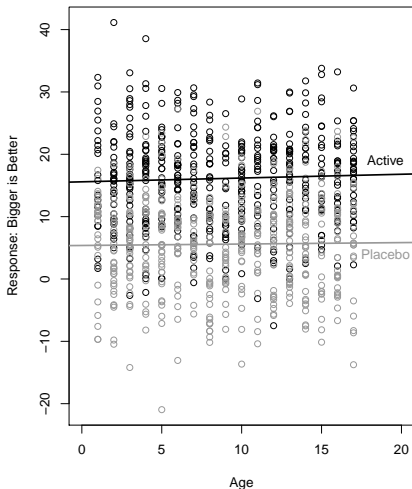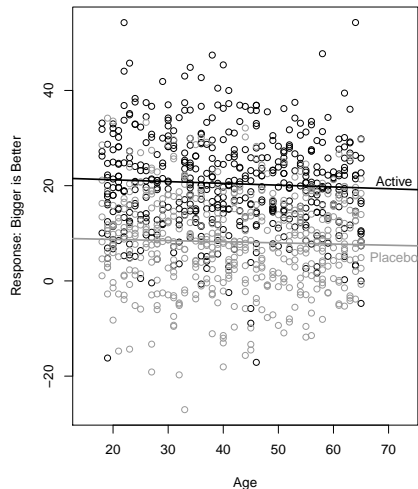
Misuse of Scaling

Misuse of Scaling, cont.
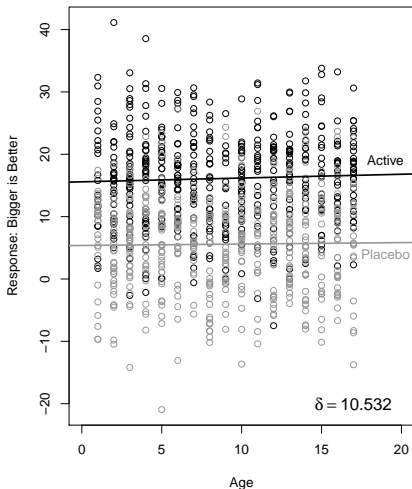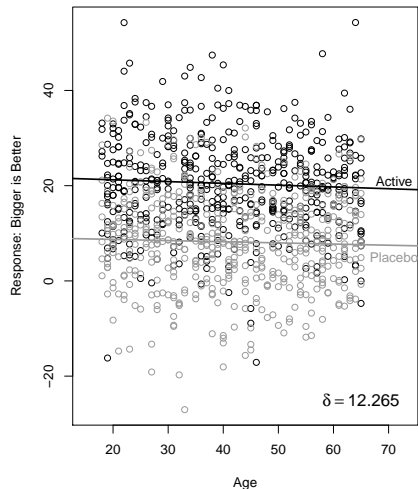
Using Unneeded Dimensions
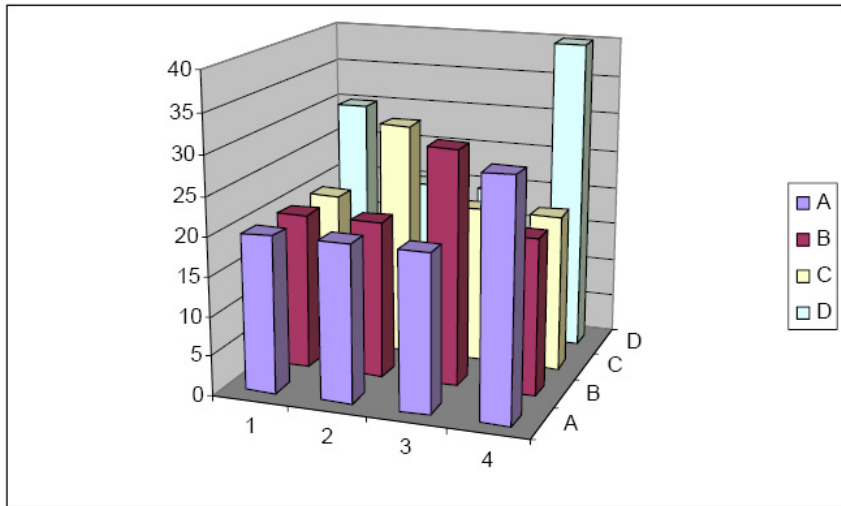
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FDA/Industry/Academia Working Group

Background

- Formed in Fall of 2009
- Members are affiliated with:
    - Regulatory: FDA (21 members) and Health Canada (1 member)
    - Academia: Vanderbilt (1 member), UC-Davis (1 member)
    - Industry: Schering-Plough, Pfizer, GSK, Johnson and Johnson, Novartis, Bayer, Eli Lilly, Merck, Sanofi-Aventis, Roche, Amgen (13 members)
- **Goal: To develop a palette of graphics for visualizations of clinical trial safety data**

Project Objectives

1. Identify areas particularly applicable or useful to regulatory review in which graphics can enhance understanding of safety information.

2. Develop a palette of statistical graphics for reporting on clinical trials safety data.

3. Recommend graphics for clinical data based on good scientific principles and best practices.

4. Create a publicly-available repository of sample graphics (ensuring appropriate credits are given for contributions), including data sets and code.

5. Educate and engage stakeholders through outreach activities.

6. Consider publishing with authorship/acknowledgments as is consistent with contributions and policy of the affiliated institution.

Project Scope

Includes

- Graphics to convey pre-approval clinical safety information, typically submitted in support of an ISS
- Static graphics represented in; color, black and white; and grayscale
- Graphs for both descriptive and inferential purposes
- Static graphics should be printable
- Develop tools that will aid in the production of new graphics

Excludes

- Spontaneous reporting or epidemiological case control studies
- Dynamic graphics

Working Group Structure

Invited membership and time/resources are based upon a volunteer basis.

Subgroups

- ECG/Vitals (10 members)
- General Adverse Events (11 members)
- General Principles (9 members)
- Labs/Liver (7 members)

Describing Graphic Entries

Metadata included in Graphic Repository

> **Required Fields:** Title, description, background, image, author, dates, use/suitability, software, code, keywords
>
> **Optional Fields:** references, data description
>
> **Categorizations:** Evaluation (e.g. safety, efficacy), Graph Type (e.g. scatterplot, dotplot), Variable relationship (e.g. categorical vs. categorical), Data type (e.g. continuous)

Distribution of Content

- Information will be presented at: http://ctspedia.org
- Currently, materials require administration authorization as:
    - Group is discussing site structure
    - Content for safety is in early stages
    - Infrastructure for registration of graphics is being developed; desire for easy entry.
- All content is intended to be provided publicly in the near term

CTSpedia Screenshot

CTSpedia Graphics Homepage Screenshot

CTSpedia Graphic Example Screenshot, 1

CTSpedia Graphic Example Screenshot, 2

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Potential Results using Effective Graphics

- Clinical trial results are more transparent (hard to hide the data if it is all shown).
- Increases the likelihood of detecting safety signals and understanding efficacy characteristics.
- Improves the ability to make clinical decisions
- Allows for more productive interactions with the FDA.
- Improves communication to the public.

EVERYONE CAN BENEFIT!!!

Community of Users Can Aid in Widespread Application

- Sharing of information in a **public domain**:
    - Increases the talent pool for developing new approaches
    - Allows one to share code for ease of implementation
    - Evolves towards best practices in graphic usage for reporting clinical trial results
- Get involved: register at http://ctspedia.org

Special Thanks

The following members of the FDA/Industry/Academia Working Group

- Regulatory: George Rochester, Bruce Weaver, Stephine Keeton, Janelle Charles, Chuck Cooper, Suzanne Demko, Robert Fiorentino, Richard Forshee, Eric Frimpong, Ted Guo, Pravin Jadjav, Leslie Kenna, Joyce Korvick, Antonio Paredes, Jeff Summers, Mark Walderhaug, Yaning Wang, Markus Yap, Hao Zhu, Catherine Njue

- Industry: Ken Koury, Rich Anziano, Susan Duke, Mac Gordon, Fabrice Bancken, Navdeep Boparai, Andreas Bruckner, Brenda Crowe, Sylvia Engelen, Larry Gould, Matthew Gribbin, Liping Huang, Qi Jiang

- Academia: Frank Harrell, Mary Banach

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