Decision Making and Safety in Clinical Trials – Graphs make a Difference!

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Signal Detection, Strengthening, and Management Based on Clinical Trial, Spontaneous, Claims, and EHR Data

Session Abstract:

- This symposium will review many aspects of signal detection. The symposium will demonstrate practical mechanisms for signal detection, and how to assess, triage, strengthen, and manage signals and safety concerns. The presentations will show how to detect and manage signals from multiple data sources including clinical trial data, spontaneous adverse event reports, claims data, and electronic health records used in Integrated Delivery Networks.

Objectives of this Talk

1. Offer convincing evidence that graphs make a difference in understanding safety results
   - What is it about the human brain?
   - ECG example
2. Given that graphs make a difference, why aren't they used more?
   - Process, Standards, Software

Is Your Brain Frozen?

- A recent article in Newsweek confirms what we all experience
- From brain scans - parts of the brain best at decision-making can get overloaded
- Too much information results in poorer decisions

The Science of Making Decisions Newsweek 27 Feb 2011

Is Your Brain Frozen?

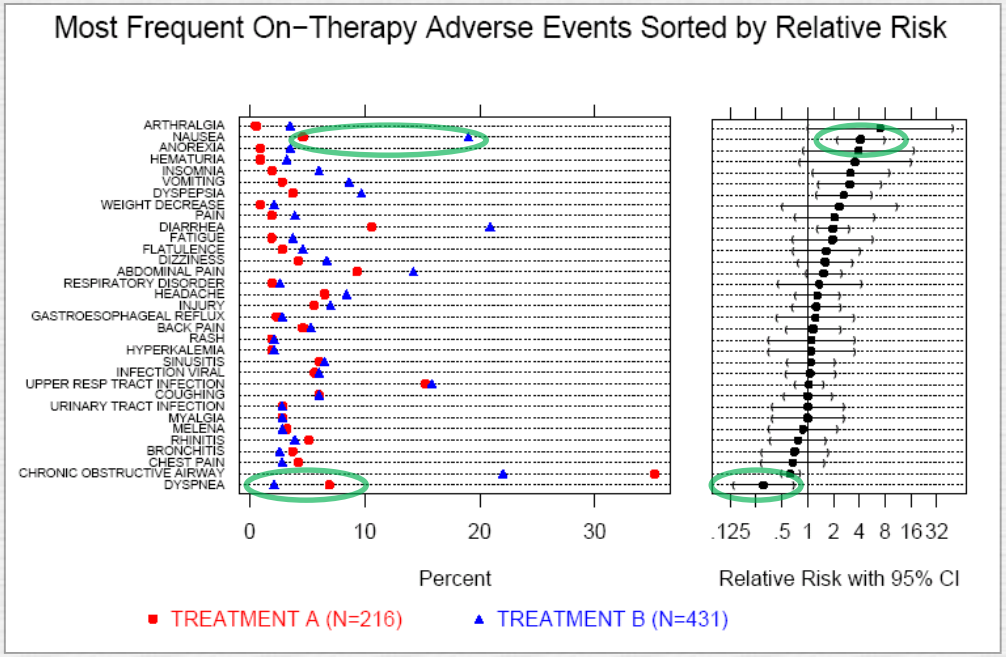
- *40-60% of the human brain is devoted to visualization*
- *Human visual capability is far ahead of the computer*

Data in Table Format

Event	Drug A (%)	Drug B (%)	RelRisk	Low95%	Up95%
ARTHRALGIA	3.5	0.5	7.0	1.6	31.5
NAUSEA	19.0	4.6	4.1	2.5	6.9
ANOREXIA	3.5	0.9	3.9	1.2	13.1
HEMATURIA	3.2	0.9	3.6	1.0	12.2
INSOMNIA	6.0	1.9	3.2	1.3	7.5
VOMITING	8.6	2.8	3.1	1.5	6.2
DYSPEPSIA	9.7	3.7	2.6	1.4	4.9
WEIGHT DECREASE	2.1	0.9	2.3	0.6	9.0
PAIN	3.9	1.9	2.1	0.8	5.3
DIARRHEA	20.9	10.6	2.0	1.4	2.9
FATIGUE	3.7	1.9	1.9	0.7	5.1
FLATULENCE	4.6	2.8	1.6	0.7	3.7
DIZZINESS	6.7	4.2	1.6	0.8	3.1
ABDOMINAL PAIN	14.2	9.3	1.5	1.0	2.4
RESPIRATORY DISORDER	2.6	1.9	1.4	0.5	4.0
HEADACHE	8.4	6.5	1.3	0.7	2.3
INJURY	7.0	5.6	1.2	0.7	2.3
GASTROESOPHAGEAL REFLUX	2.8	2.3	1.2	0.4	3.3
BACK PAIN	5.3	4.6	1.2	0.6	2.3
HYPERKALEMIA	2.1	1.9	1.1	0.4	3.4
RASH	2.1	1.9	1.1	0.4	3.4
SINUSITIS	6.5	6.0	1.1	0.6	2.0
INFECTION VIRAL	6.0	5.6	1.1	0.6	2.1
UPPER RESP TRACT INFECTION	15.8	15.3	1.0	0.7	1.5
MYALGIA	2.8	2.8	1.0	0.4	2.6
URINARY TRACT INFECTION	2.8	2.8	1.0	0.4	2.6
COUGHING	6.0	6.0	1.0	0.5	1.9
MELENA	2.8	3.2	0.9	0.3	2.2
RHINITIS	3.9	5.1	0.8	0.4	1.7
BRONCHITIS	2.6	3.7	0.7	0.3	1.8
CHEST PAIN	2.8	4.2	0.7	0.3	1.6
CHRONIC OBSTRUCTIVE AIRWAY	22.0	35.2	0.6	0.5	0.8
DYSPNEA	2.1	6.9	0.3	0.1	0.8

Where is the signal?

Identical Data in Graph



Signals easily identified
(the human brain is good at pattern recognition)

Graphical Perception

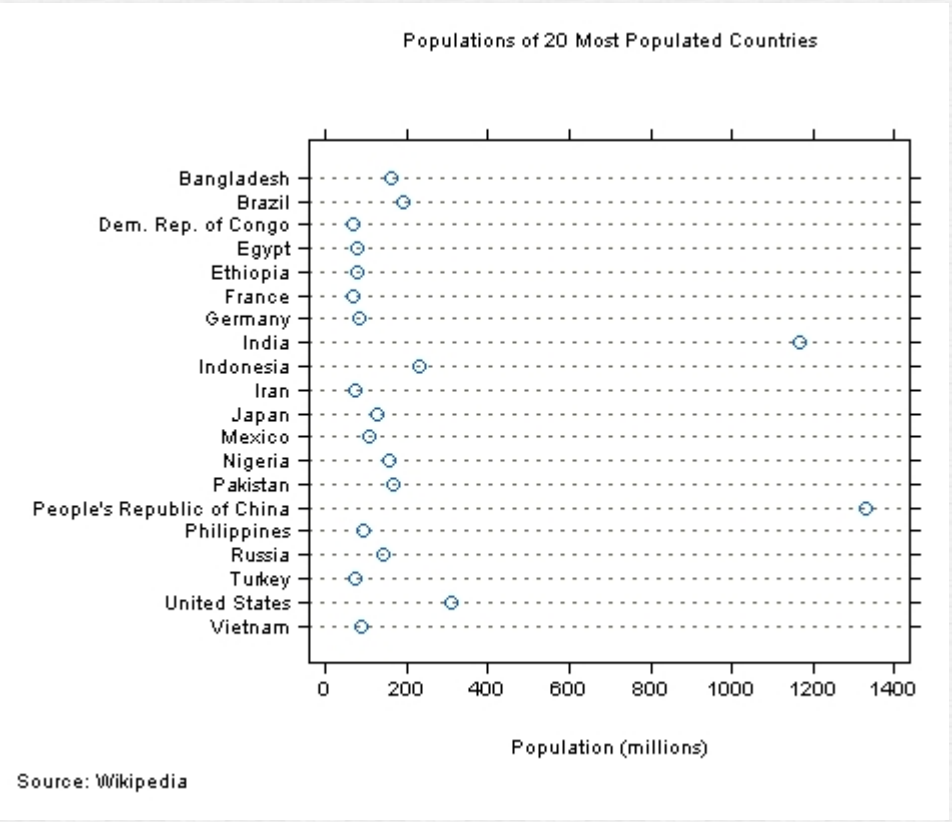
"When a graph is constructed, information is *encoded*. The *visual decoding* of this encoded information is *graphical perception*.

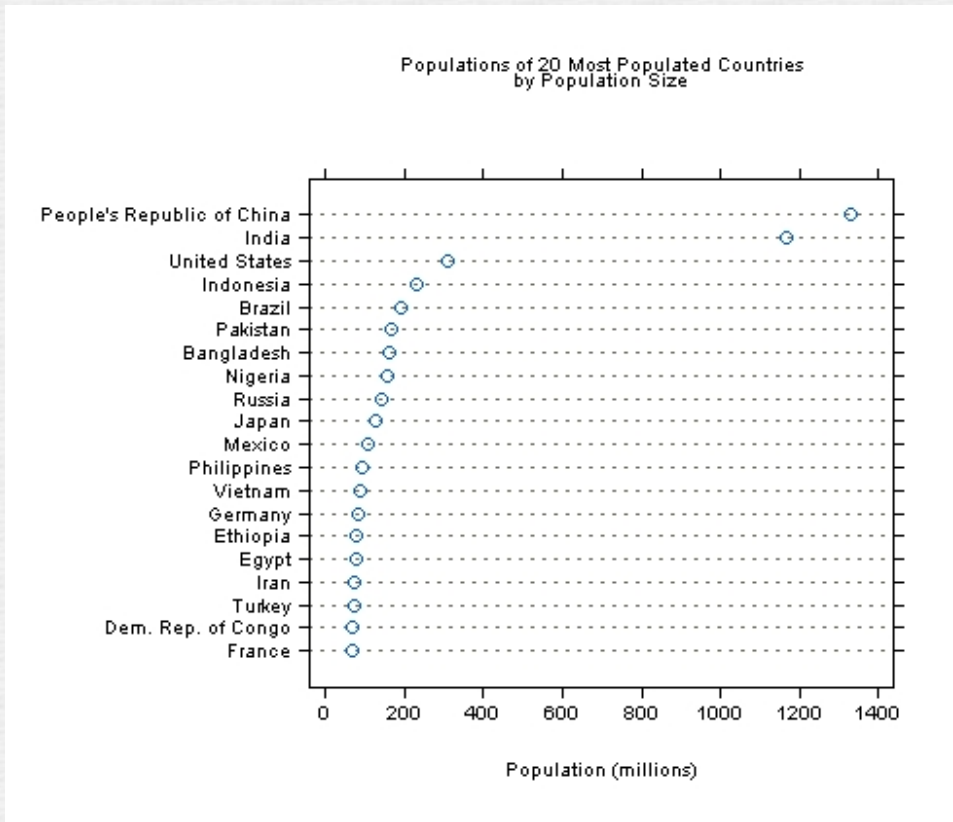
The decoding is the vital link …

No matter how ingenious the encoding … and no matter how technologically impressive the production, a graph is a failure if the visual decoding fails."

William Cleveland, The Elements of Graphing Data

Table Look-Up and Pattern Perception





Concept from William Cleveland, *The Elements of Graphing Data*

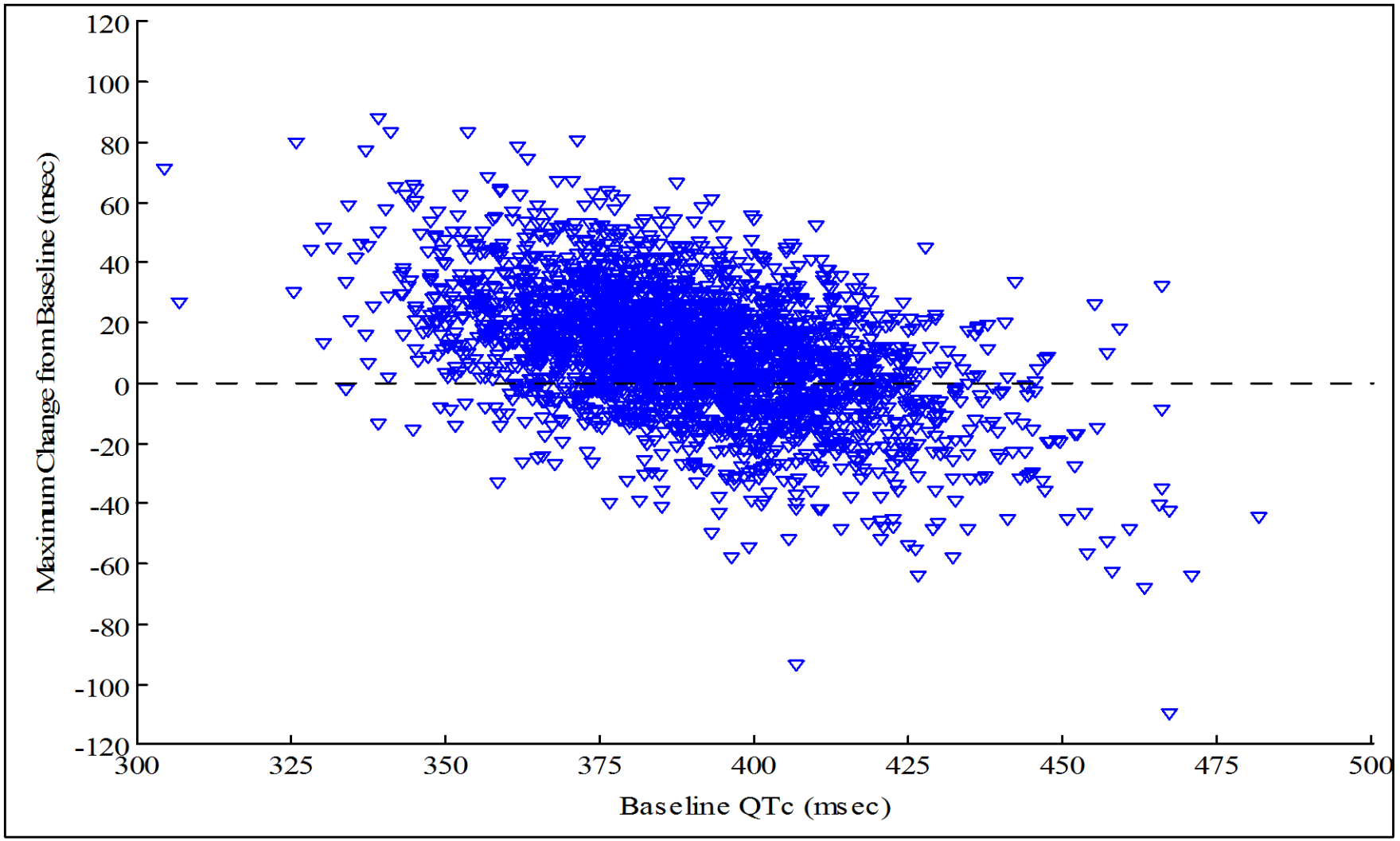
Advisory Committee Example

- Context: Experimental drug had shown approx. 4 msec increase in ECG QTc for the overall phase 2/3 population
- Concern Expressed: Subjects with a high baseline would be pushed over the critical 500 msec boundary.

Maximum Change from Baseline vs. Baseline QTc
(Baseline Correction)
Phase II/III Data

The mean change of 4 msec alone doesn't show the whole story, there is also a strong relationship with change from the starting value

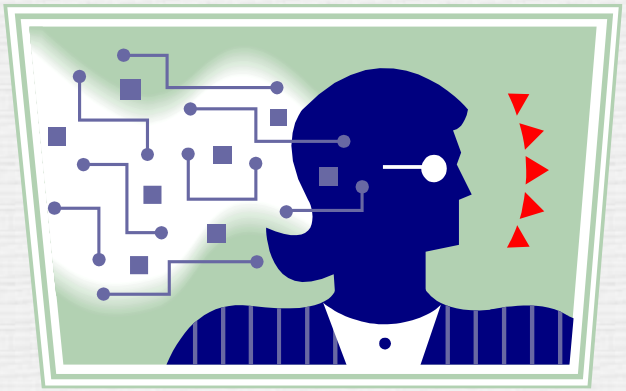
Experimental Drug



We All Would Agree

Study teams
Decision-makers
Prescribers
Patients

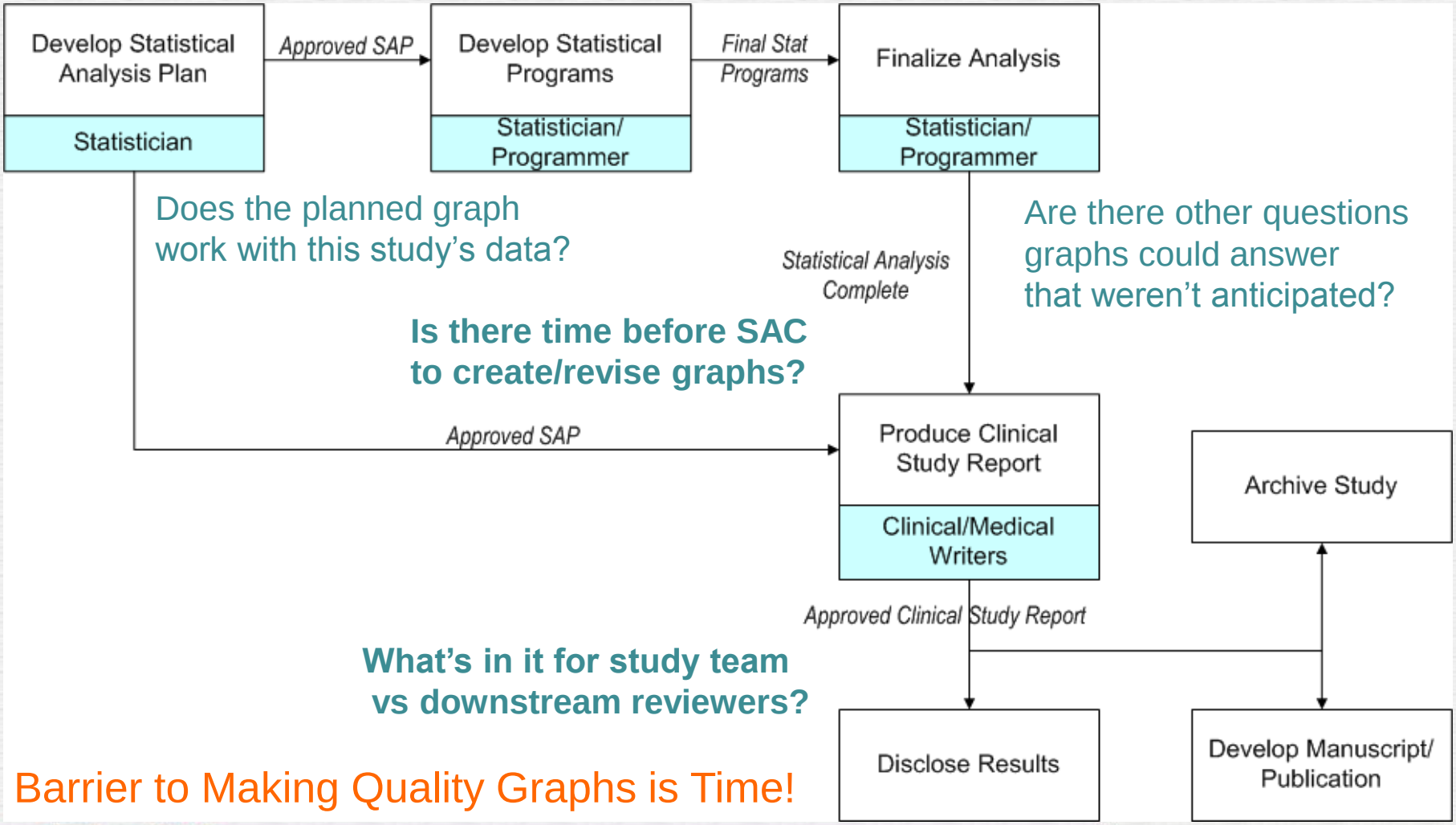
Benefit from easy ways to understand results



Obvious?

Then why aren't there more graphs in submissions?

Let's Take a Look at the Clinical Study Analysis Process…



#1 Barrier to Making Quality Graphs is Time!

Understanding the Problem Space, Identifying and Implementing Solutions

Standards

Process

Technology

Culture

A. Understand the problem space:
   - Graphs take time to make and authors have many activities competing for their time
   - Primary value of graphs may be downstream from those who create them

B. Solve the problems:
   - Faster ways to make graphs
   - Better understanding of graph usage downstream

C. Solutions:
   1. Improve graphics software
   2. Standard Graphs for Common Safety Questions

How to Make Quality Graphs More Quickly?

Standards

Process

Technology

Culture

1. Improve Statistical Graphics Software
   Important, but not the focus of this talk

2. **Standard Graphs for Common Safety Questions**
   - To address safety questions that occur time and again
   - Many become familiar with using the same figure for the same question, know how to interpret

How to Make Quality Graphs More Quickly?

Use Standard Graphs for Common Safety Questions

- *FDA/Industry/Academia Safety Graphics Wiki Goals*

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

How to Make Quality Graphs More Quickly?

Use Standard Graphs for Common Safety Questions

- *FDA/Industry/Academia Safety Graphics Wiki*
  - Has common graphs for
    - Adverse Events
    - ECG
    - Labs/Liver Events
  - And some General Principles and tips for creating effective graphics
- See slides for:

#163 TRACK 12: STATISTICS

3:30 PM – 5:00 PM LEVEL: ■ Format: **SESSION**

Room W181bc

Innovative Graphical Approaches to Display Safety Data Collected in Clinical Trial Research

CHAIRPERSON

Mat Soukup, PhD

Team Lead, Office of Translational Sciences, CDER, FDA

The session will present efforts of a collaborative working group that is developing graphical approaches to enhance transparency and understanding of safety data collected in clinical trial research.

How to Make Quality Graphs More Quickly?

Use Standard Graphs for Common Safety Questions

- Industry-wide: FDA/Industry/Academia Safety Graphics Wiki

CTSPedia: CTSpedia.StatGraphHome

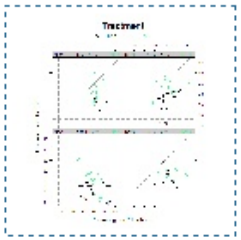
Welcome to the CTSpedia section on statistical graphics.

I WANT TO:

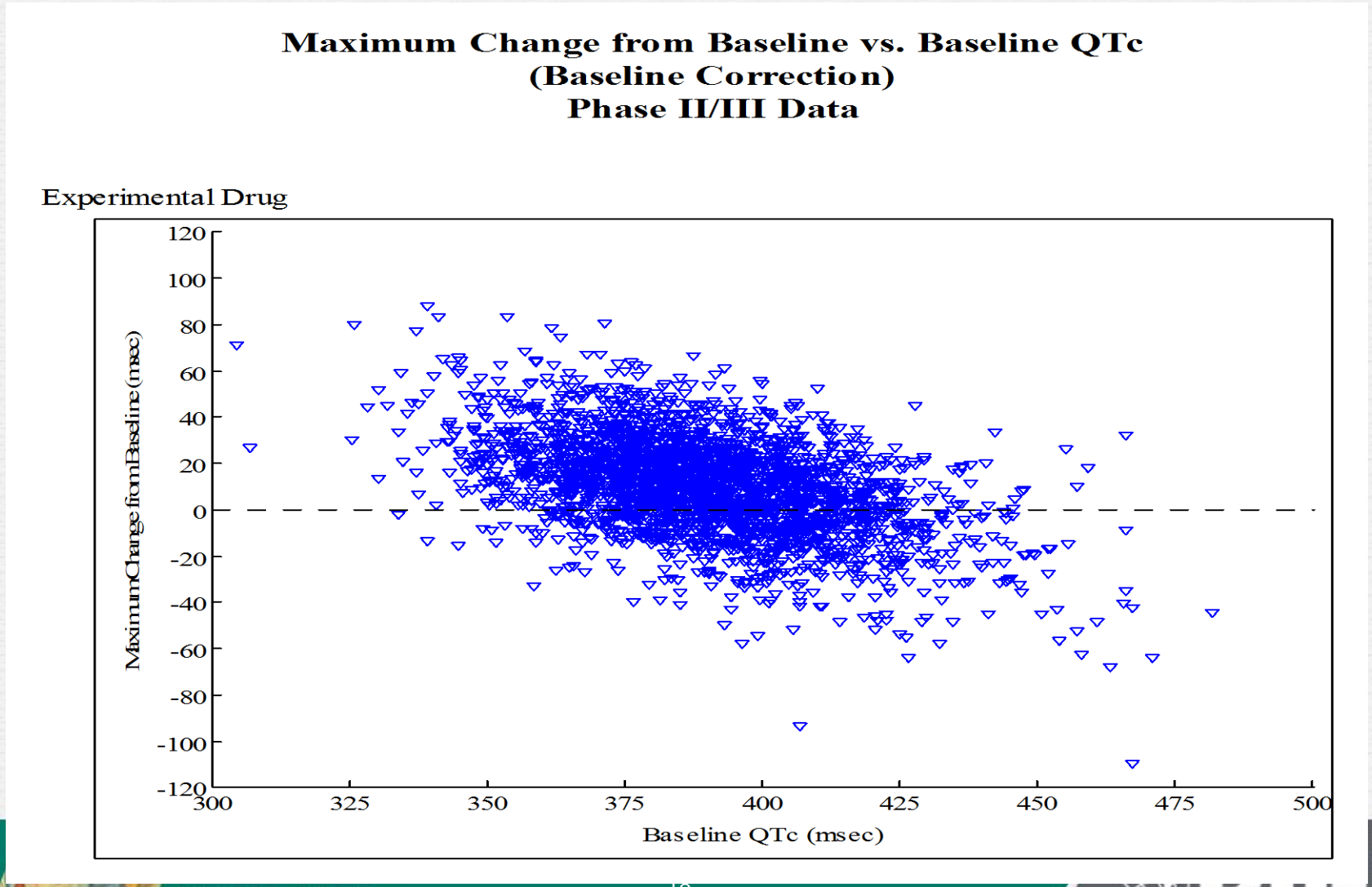
- **Select the right graph for my question:**
  - Data Visualization
  - Labs/Liver (Links to listings: Labs Liver Clinical Question Listings)
  - ECG/Vitals
  - General Adverse Events
- See all graphical entries in the library
- Search for graphics
- Contribute a graphic to the library

LIBRARY SAMPLING

Three Highest Rated Graphs

Title of Graphic	Image-Click to Enlarge	Score-Stars
HPA Axis Suppression		5
Survival Plot		4.11

You'll Remember this Graph from Earlier in the Talk…



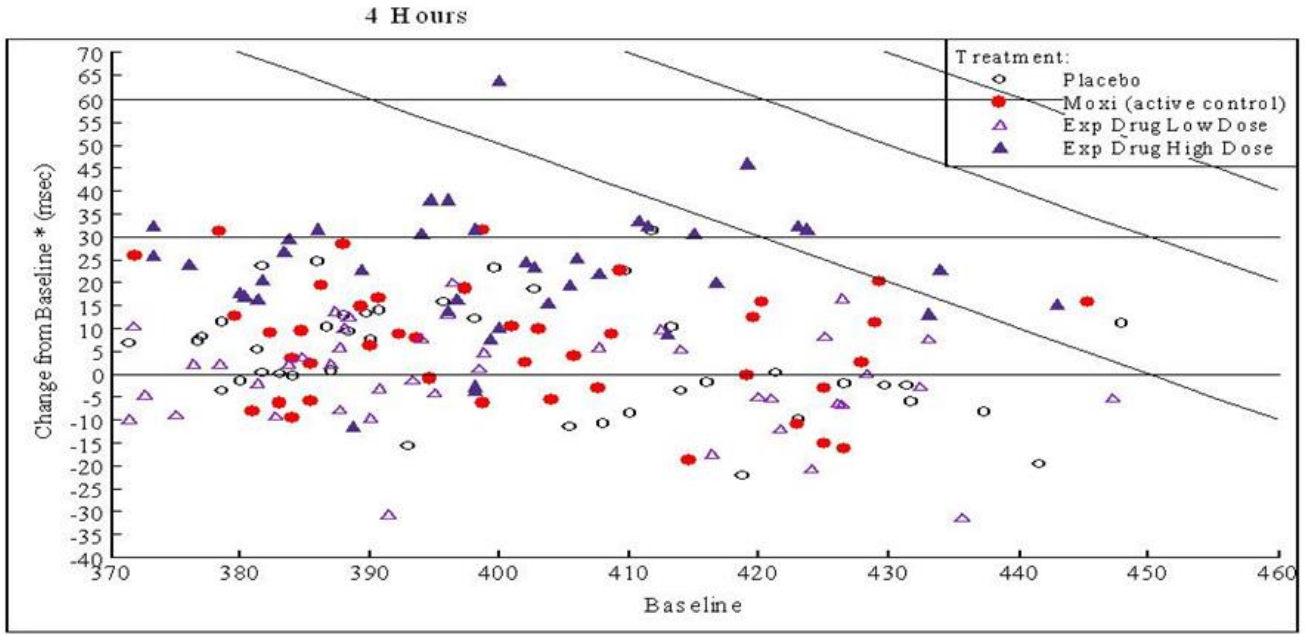
Safety Graphics Wiki ECG Subteam's Answer for a Standard Graph

- Typically Tabular summaries of Categorical QTc
  - Changes from Baseline: N's and % changes exceeding 30 and 60 msec
  - Raw/Absolute QTc values: N's and % exceeding 450, 470, and 500
- Problem: interpreting the changes without knowing the Baseline or absolute QTc value
- Plot shows relationship of change to the absolute

Safety Graphics Wiki ECG Subteam's Answer for a Standard Graph

Categorical QTc plot from CTSpedia

Individual Changes from Baseline (Day 0) by Baseline (Day 0) Value
Page by Hour Post Dose
TQT Study



* Changes from Baseline are defined as time matched changes from the baseline day.
Horizontal lines refer to 30 and 60 msec changes and diagonal lines refer to 450, 480, and 500 msec from lower left to upper righ

Interpretation of Categorical QTc plot

- Design shortcoming of this graph type: regression to the mean
  - The majority of large changes occur in subjects with low baseline
  - The majority of large absolute values started with a high baseline
- Values of real concern are large changes with large absolute values – upper right is area of concern
- This couldn't be assessed with a table where absolute and changes are presented separately – the dependence of one on the other is lost with tabular displays

How to Make Quality Graphs More Quickly?

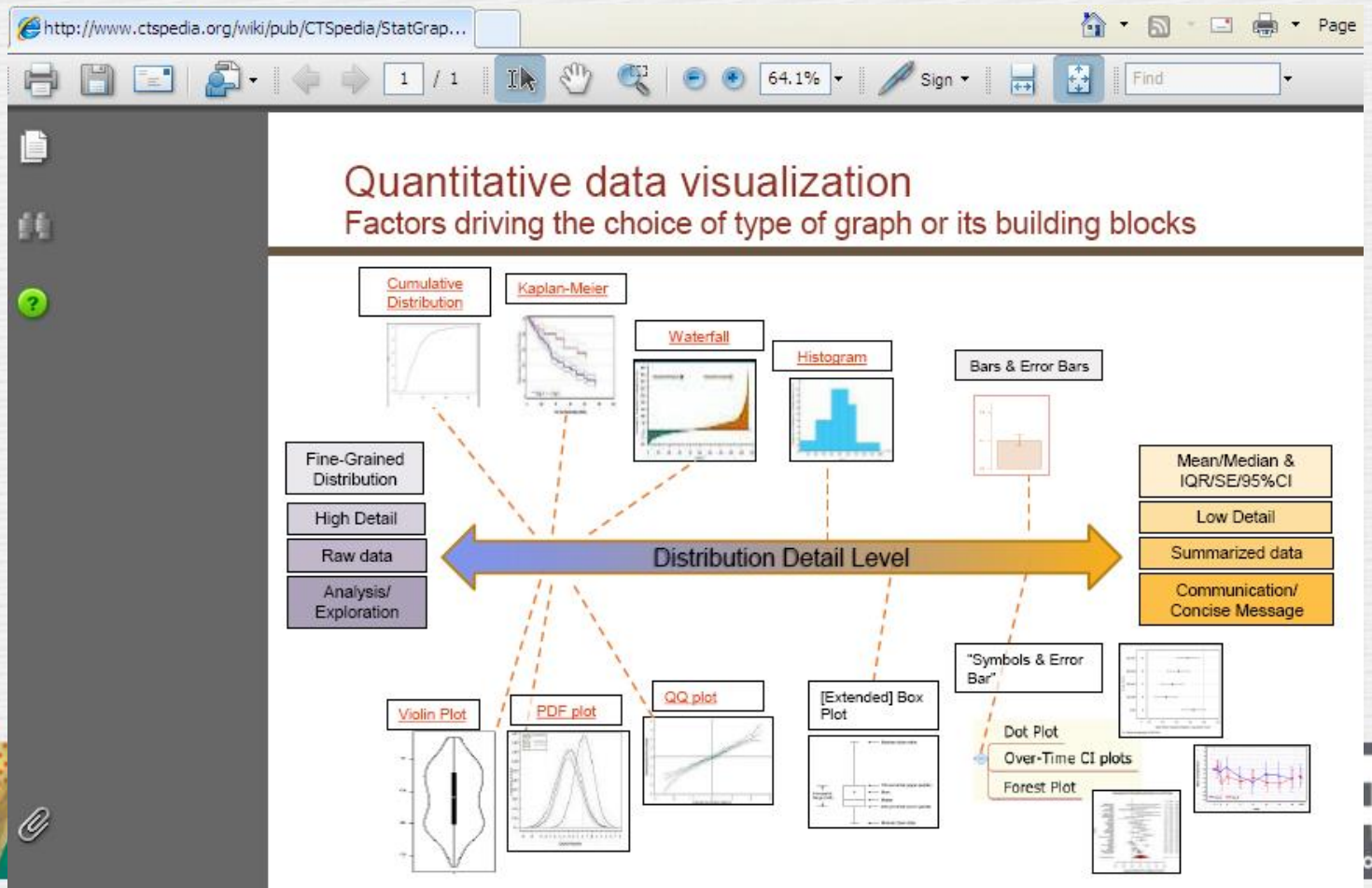
Use Standard Graphs for Common Safety Questions

- The ECG example is just one of many for ECG
  - The same is true for Adverse Events and Lab/Liver
- Each graph entry in the wiki has a description of use, sample program code & data
- The wiki is searchable, has a glossary and many other features

How to Make Quality Graphs More Quickly?

Industry-wide: FDA/Industry/Academia Safety Graphics Wiki

- … and if you're not sure what kind of graph you need, Safety Graphics Wiki has guidance to find the best graph type for your needs



How to Make Quality Graphs More Quickly?

Ensure Clinical Interpretation of Standard Graphs is Understood

- *At my company:*
  - Having standard safety graphs is not enough – must increase usage

Standards
Process
Technology
Culture

- "Effective Graphics Design for Clinical Development" course
  - 1/3 of course devoted to clinical interpretation, with great support

PHARMACEUTICAL STATISTICS
Pharmaceut. Statist. 2008; 7: 20–35
Published online 26 February 2007 in Wiley InterScience
(www.interscience.wiley.com) DOI: 10.1002/pst.254

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Graphical Approaches to the Analysis of Safety Data from Clinical Trials

MAIN PAPER

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How to Make Quality Graphs More Quickly?

Ensure Clinical Interpretation of Standard Graphs is Understood

Standards

Process

Technology

Culture

- *At my company:*
  - Having standard safety graphs is not enough – must increase usage
- "Effective Graphics Design for Clinical Development" course
  - 1/3 of course devoted to clinical interpretation, with great support from clinicians in safety and therapy areas
- Improve statistical graphics software
  - Standard safety templates at launch
  - Intuitive GUI interface / Quick ramp-up
  - High quality output with little fuss
  - Easy for users to change graphs, create new ones

Conclusions

- Graphs make a difference in understanding safety results
  - Pattern recognition of human brain far superior to computer
- Thoughtful consideration of
  - Process,
  - Standards, *and*
  - Software

will improve graphics usage in your organization

and across our industry

Acknowledgments

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  - Leads: George Rochester (FDA), Mat Soukup (FDA), Ken Koury (Merck), Brenda Crowe (Lilly)
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  - 30+ statisticians

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*special thanks to Rich & Wiki ECG subteam for the ECG example