An Update from the FDA / Industry / Academia Safety Graphics Working Group: Adverse Event Sub Team

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on Behalf of the Adverse Event Sub Team

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The Disclaimer

The views expressed herein represent those of the presenters and do not necessarily represent the views or practices of the presenters’ employers or any other party
How to Achieve This?

I think this graph clearly points to the problem.

By: David Walker
Motivations

• Information regarding adverse events in drug development is complex
• Communicating information effectively and efficiently is crucial in detecting safety signals and helping decision-making
Frequently Asked Questions Regarding Adverse Events

Decision Making
Risk Factors?
Relationship with Other AEs?
Withdraw/ Interruption?
Time to an Event?
Relationship with Dosage?

Any AEs?
What are they?
Are they safety signals?
Background Rate?
Comparison with other regimens
Relationship with efficacy?
Categories of Graph

- Demographics and incidence of AEs
- AE occurrence over time across treatment groups
- Dosage and exposure
- Potential risk factors and their temporal relationship to AEs
- Withdrawal and interruption of treatment in relation to the occurrence of AEs
- Patient profile
Graphical Displays Addressing Key Clinical and Safety Issues
Most Frequent On-Therapy AE Sorted by Risk Difference

- **Clinical Question:** Which AEs are elevated in treatment vs. control?
- **Type:** Grouped Dotplot
- **Contributed by:** Frank E Harrell, Jr. modification of Amit et al 2008
Alternative Approach: Which AE Could Be A Safety Signal?

Dot Plot: Adverse Event Sorted by Relative Risk to address which AE could be caused by the drug

Source: Amit, Lane, Heiburger
Another Alternative: Which AEs Were Elevated?

Dot Plot: Proportions of AE Occurrence Between Treatment and Placebo

Source: Michael O'Connell “Graphical Analysis and Reporting of Safety Data”
Adverse Event Occurrence Over Time

- **Clinical Question:** Is there a difference in the time to event across treatment groups?
- **Type:** Grouped Trellis Kaplan-Meier Plot
- **Software:** R
- **Contributed by:** Mat Soukup
Cumulative Incidence of AE by Time of Initial Onset

- Clinical Question:
  - Is there a difference in the time to event across treatment groups?
- Contributed by:
  - Liping Huang

Note: Gastrointestinal AE of Concern are: Nausea, Abdominal Pain, Diarrhea, and Vomiting
Summary of Safety Subjects Exposure to Treatment

- Clinical Question:
  - What is the safety profile of the drug? Are there any AEs associated with dropouts?
- Contributed by: Qi Jiang
A Few More Graphical Displays
Addressing Key Clinical and Safety Issues
Which AEs Were Elevated in Treatment vs. Placebo?

Grouped Trellis Dot Plot: AEs by Group of Special Interest

Source: Michael O'Connell “Graphical Analysis and Reporting of Safety Data”
Is There A Special Pattern of AE Onset?

Risk Over Time Plot for Adverse Event

Source: Qi Jiang, Amgen
Which AE Could be A Safety Signal?

Volcano Plot:
Relationship Between Risk Difference and P-Value for AEs by SOC Visualizations with different adjustments for multiplicity and shows impact of multiplicity adjustments

Source: Qi Jiang, Amgen
Conclusions

• Clear and informative graphs enhance the ability to understand the data
• Suitable graphical presentation for adverse events could increase the likelihood of detecting safety signals
• Graphs convey information more efficiently and better meet regulatory requirements for ongoing safety evaluation
Conclusions

CHINESE PROVERB
One picture is worth ten thousand words
Special Thanks

FDA / Industry / Academia Safety Graphics Working Group

Working Group Adverse Events Sub Team Members:
- Liping Huang (co-lead) - CSL Behring
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- Fabrice Bancken - Novartis
- Andreas Brueckner - Bayer Healthcare
- Larry Gould - Merck
- Kenneth Koury - Merck
- Mat Soukup - CDER

Former Sub Team Members:
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- Suzanne Demko - CDER
- Navdeep Boparai - Merck
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In addition, Amgen Safety Biostat Graphical Team
Thank You!