11TH ANNUAL MEETING OF ISMPP

"DEFINING BEST PRACTICE FOR ADVERSE EVENT REPORTING WITH INDUSTRY-SPONSORED CLINICAL TRIAL MANUSCRIPTS"

April 28, 2015

Hyatt Regency Crystal City

Arlington, VA, USA

AstraZeneca

Pfizer

Janssen

Takeda

Biogen

AMGEN

MERCK

Bristol-Myers Squibb

gsk GlaxoSmithKline

ISMPP International Society for Medical Publication Professionals

Disclaimer

Information presented reflects the personal knowledge and opinion of the presenter and does not represent the position of her current or past employers, or ISMPP.

About MPIP

MPIP Vision

To develop a culture of **mutual respect, understanding, and trust** between journals and the pharmaceutical industry that will support more **transparent and effective** dissemination of results from industry-sponsored trials

MPIP Objectives

- Understand issues and challenges in publishing industry-sponsored research
- Identify potential solutions to increase transparency and trust
- Promote more effective partnership between sponsors and journals to raise standards in medical publishing

MPIP Website

http://www.mpip-initiative.org/

MPIP's Peer-Reviewed Publications

THE INTERNATIONAL JOURNAL OF CLINICAL PRACTICE

Enhancing transparency and efficiency in reporting industry-sponsored clinical research: report from the Medical Publishing Insights and Practices initiative

Editor's Choice

- Call to action to raise standards and streamline publication process

BMC Medicine

Five-step authorship framework to improve transparency in disclosing contributors to industry-sponsored clinical trial publications

- Interim results presented at the Seventh Peer Review Congress in 2013
  - Only industry-led oral presentation selected by meeting organized by JAMA/BMJ

CMRO
Current Medical Research & Opinion

Commentary
Authors' Submission Toolkit: A practical guide to getting your research published

- Guide to submission "best practices" (translated into Chinese)

MAYO CLINIC PROCEEDINGS

Ten Recommendations for Closing the Credibility Gap in Reporting Industry-Sponsored Clinical Research: A Joint Journal and Pharmaceutical Industry Perspective

Serves as a platform for planning future MPIP activities

MPIP's Focus on Adverse Events

Ten Recommendations for Closing the Credibility Gap in Reporting Industry-Sponsored Clinical Research: A Joint Journal and Pharmaceutical Industry Perspective

Bernadette A. Mansi, BA, Juli Clark, PharmD, Frank S. David, MD, PhD, Thomas M. Gesell, PharmD, Susan Glasser, PhD, John Gonzalez, PhD, Daniel G. Haller, MD, Christine Laine, MD, MPH, Charles L. Miller, MA, LaVerne A. Mooney, DrPH, Maja Zecevic, PhD, MPH

- Reporting adverse event (AE) data more transparently and in a more clinically meaningful manner is part of our "Ten Recommendations" highlighted by editors to close the credibility gap

Better Reporting of Harms in Randomized Trials: An Extension of the CONSORT Statement

John P.A. Ioannidis, MD; Stephen J.W. Evans, MSc; Peter C. Gøtzsche, MD, DrMedSci; Robert T. O'Neill, PhD; Douglas G. Altman, DSc; Kenneth Schulz, PhD; and David Moher, PhD, for the CONSORT Group*

- While the CONSORT 2004 Harms Extension Statement provides guidance to help collect and report AEs[1], sub-optimal AE reporting continues to persist[2]

Why is this important?

- AE reporting provides practical information that clinicians need to know to safely optimize patient care
- Continued need to ensure AE claims made in publications are appropriately balanced and reflect limitations of the trial design

1 John P.A. Ioannidis et al., Better Reporting of Harms in RCT: An Extension of the CONSORT Statement, 2004.

2 Catia Bauer Maggi et al., Information on adverse events in RCTs assessing drug interventions published in four medical journals with high impact factors, 2014.

Audience Poll

For Adverse Event reporting in manuscripts, what aspects prompt the most feedback from editors/peer reviewers?

A. Balance of benefit to risk information **20% (13/63)**

B. Use of overly broad descriptive terminology **19% (12/63)**

C. Relevance of AE data to the clinical audience **17% (10/63)**

D. Statistical methodology **6% (4/63)**

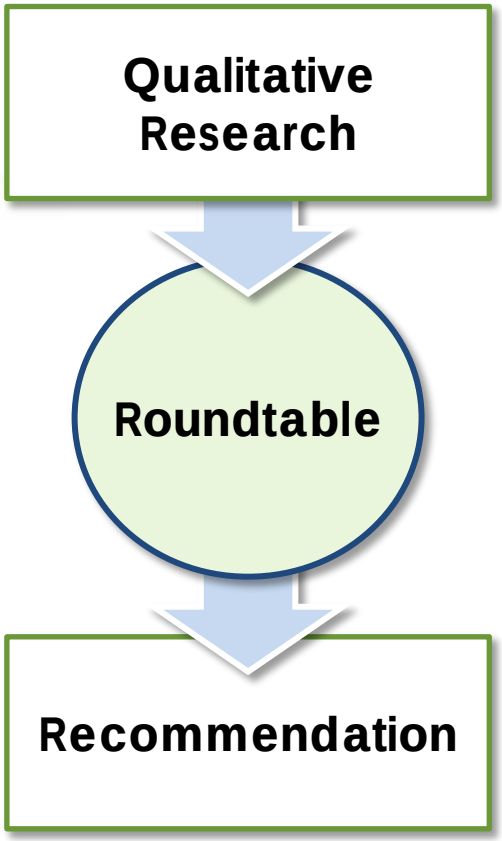
E. Requests for additional statistical analyses **38% (24/63)**

63 Respondents

MPIP Adverse Event Research Project

- ***Conducted qualitative interviews*** with journal editors, industry experts, and clinical investigators
- ***Convened a Round Table*** discussion with 9 journal editors and MPIP co-sponsors to obtain additional input
- Reach consensus on ***current challenges with adverse event/safety data*** communication in manuscripts, and:
  - Prioritize those challenges that allow for more clinically meaningful communication and increased transparency
  - Discuss recommendations that could address these challenges
- ***Collaborate with 7 senior journal editors who have agreed to serve as co-authors on this publication***

AE Roundtable Recommendations

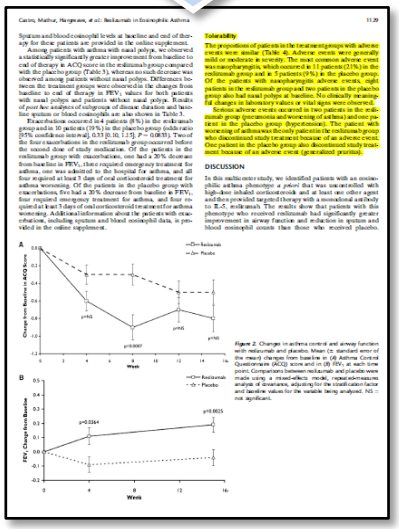


- Create more clinically relevant data outputs useful for clinical practice
  - Examples: relevant AE overview table, additional AE displays beyond incidence tables, clear data collection and analysis methods
- Help authors understand the limitations of reporting AEs from a single trial vs. an entire development program
- Avoid broad statements such as “generally safe” or “well tolerated”, which are uninformative for clinicians and often raise questions
- Understand the importance of patient-level data to detect rare or unexpected events from the larger clinical program as a means to build trust/credibility for manuscripts

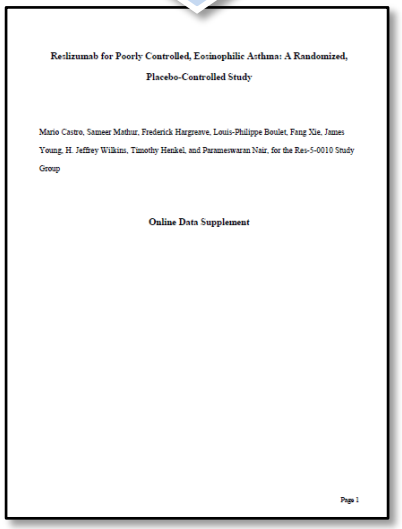
Discussion and Recommendations Centered on Three Core Areas of a Manuscript

1. **Manuscript Data**

2. **Text Descriptions**



3. **Supplemental Data**


Reslizumab for Poorly Controlled, Eosinophilic Asthma: A Randomized, Placebo-Controlled Study

Mario Castro, Sameer Mathur, Frederick Hargreave, Louis-Philippe Boulet, Fang Xie, James Young, H. Jeffrey Wilkins, Timothy Henkel, and Parameswaran Nair, for the Res-5-0010 Study Group

Online Data Supplement

Manuscript Data – Roundtable Summary

Call to Action

Where possible, provide additional AE data beyond traditional analyses

Journal Editor Insights

1. Consider including following data points in the manuscript body if relevant:
   - Mortality
   - Timing, duration, and frequency of selected relevant AEs
   - Discontinuations and supporting reason (e.g., due to study drug, patient choice)
   - Dose modifications and how AEs were managed
   - Adherence to study medication

2. New approaches with a more visual display of AE data can be helpful, where appropriate[1,2]

1 Amit O, Heiberger R, and Lane P, Graphical Approaches to the Analysis of Safety Data from Clinical Trials, 2009.

2 http://www.ctspedia.org/do/view/CTSpedia/StatGraphHome

Text Descriptions – Roundtable Summary

Call to Action

Eliminate overly general statements about AE profile to present a balanced and holistic risk profile in the manuscript text

Journal Editor Insights

1. Avoid using general language or phrases to summarize overall AE profile

2. In the results section, aim to explain in a concise manner the most relevant aspects of the risk/benefit profile seen in the trial(s)

3. For abstract :
   - Highlight the most relevant AE events; ensure results align with those presented in the main body of the manuscript

Statistical Analysis – Roundtable Summary

Call to Action

How to best incorporate statistical analyses of AE/safety data to ensure transparent and balanced representation of data

Journal Editor Insights

1. For AEs of particular interest, pre-specify analyses in statistical analysis plan

2. Confidence interval around the difference between treatments should be strongly considered

3. Absolute risk difference between treatment groups (with a confidence interval) is generally more informative than p-values , pre-specify if possible
   - If analyses, including sensitivity analyses, are performed retrospectively (e.g., at request of journal reviewer) note retrospective nature in manuscript and editorial communications

4. When p-values are provided (for pre-specified safety endpoints), marginally statistically insignificant results, such as a p-value = 0.06, should receive additional scrutiny, since they may represent informative and clinically relevant results

Next Steps

- Peer-reviewed publication in journal with wide audience for clinical trial manuscripts
- Written jointly between industry publication representatives, journals editors, and industry AE experts

- CONSORT considered the standard for AE/safety reporting guidance
- Consider other groups as needed

- Work with industry to map out approach and best practices for uptake and implementation
- Continue to educate key stakeholders about published recommendations and editor feedback

Key Takeaways

- MPIP is focused on developing a culture of mutual respect, understanding, and trust between journals and industry
- Past publications provide tangible recommendations, tools and guidance for industry publication professions
- Adverse Events reported in publications are not ideal for clinicians
- Through qualitative research and editor feedback a number of insights into AE reporting were identified
- MPIP intends to publish and disseminate recommendations on Adverse Events reported in medical journals

QUESTIONS?

Remembering Mary Whitman

- Passionate about transparency and ethics in medical publications, as well as a long-time member of ISMPP.
- Talented scientist and writer who has been a member of Janssen Biotech Immunology and Oncology Medical Affairs family for nearly 13 years, where she built a robust medical writing department.
- Took great pride in advancing science, while maintaining the highest quality, and compliance standards.
- Had a passion for training and educating others, and volunteered her time to speak around the country as an authority on medical writing best practices.

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