SESSION IV: BMPs: How do We Detect Adverse Events that We Weren’t Even Thinking About?

Kevin J. Bozic, MD, MBA
Associate Professor and Vice Chair
UCSF Department of Orthopaedic Surgery
Core Faculty, Philip R. Lee Institute for Health Policy Studies
Biases that Influence My Opinions

- **Research Support:**
  - AHRQ, NIH, RWJ, Yale Open Data Access Project

- **Consulting Income:**

- **Governance/Leadership Roles:**
  - AAOS (Council on Research and Quality)
  - AAHKS (Health Policy, EBPC)
  - American Joint Replacement Registry (Board of Directors)
  - COA (First Vice President)
  - OREF (Board of Trustees)
  - AHRQ (Effective Health Care Stakeholder Group)
  - UCSF Medical Center (HTAP)
Role of the Medical Device Industry

- Source of capital, infrastructure, risk for medical device innovation
- Platform for physician-industry collaboration
- Support for clinical trials
Concerns RE: Industry Funded Clinical Trials

- Influence over:
  - Investigators
  - Study design
  - Dissemination of results
Commercialization of rhBMP-2

- BMPs discovered
- InFUSE approved by FDA
- Industry-associated studies report no adverse events related to rhBMP-2
- Studies begin to report complications associated with rhBMP-2 use
- FDA issues Public Health Notification on BMP use in cervical spine
- FDA denies AMPLIFY
- Carragee et al. allege underreporting of adverse events
Selection of Investigators

- Biased interpretation of results by:
  - Consulting/design surgeons (conflicted)
    - rh-BMP2 PMA studies included paid consultants as authors
      - ~ $12 Million per study paid to authors (Carragee)
  - Readers (influence of ‘thought leaders’)
  - Role of Editorial Review Process?
- Public perception of bias
- Influence on Off-Label Use
### Study Design: Intended to Maximize Off-Label Use?

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Medtronic Biologic Sales

Sales (MM USD)

2005 2006 2007 2008 2009 2010 2011
Study Design: Biased Towards Favorable Results for BMP

1. Open-label study
2. Noninferiority trial design
3. BMP classified as a device, not as a drug
4. Compromised efficacy of ICBG
5. Under-report BMP complications
6. Over-report of ICBG complications
7. Financially conflicted researchers

Under-Reporting of Adverse Events?

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Under-Powered to Detect Adverse Events?¹

Mirza SK, Commentary: Folly of FDA-approval studies for bone morphogenetic protein, The Spine Journal, 2011
Over-reporting of Adverse Events in Control Group?


Editorial

Pseudomorbidity in iliac crest bone graft harvesting: the rise of rhBMP-2 in short-segment posterior lumbar fusion

Eugene J. Carragee, MD\textsuperscript{a,*}, Christopher M. Bono, MD\textsuperscript{b}, Gaetano J. Scuderi, MD\textsuperscript{c}
Dissemination of Results

- Industry-funded research is proprietary
  - No requirement for publication or dissemination

- Many clinical trials are conducted but never published
  - Public perception: Industry has a financial interest in promoting “supportive” research, not publishing rest

- Even when published, not all data is reported
  - *Patients, physicians, payors, and policymakers frequently make treatment decisions with access to only a fraction of clinical research data*
Yale Open Data Access Project

- New model for dissemination of industry-funded clinical trial results

- Goals:
  - To increase transparency, public trust in industry funded trials
  - To facilitate the independent assessment and dissemination of data relevant to the benefits and harms of drugs and devices

  - Physicians, patients, payors, and policymakers can base their decisions on the most comprehensive and contemporary evidence available
Project Governance

- **Funder**: Medtronic, Inc.
- **Coordinating organization**: Yale Center for Outcomes Research & Evaluation (CORE)
- **Principal Investigator**: Harlan Krumholz, MD, SM

**Clinical Steering Committee**:
- Kevin J. Bozic, MD, MBA (Chair)
- Marc Swiontkowski, MD
- Sohail Mirza, MD, PhD
- Regis O’Keefe, MD, PhD
- Dan Resnick, MD
Yale Model for Independent Data Evaluation and Transparency

- Designed to facilitate the release of data, ensure high quality reviews of the evidence, and provide the public with the scrutiny of independent review.
Why Should Industry Participate?

- Fair and objective assessment of product-specific research data, as opposed to speculative analysis based on incomplete data

- Promotes transparency

- Supports scientific competition, not marketing

- Untenable to withhold information about product effectiveness and safety
2011 YODA Project Accomplishments

- Contract signed with Medtronic, Inc (8/11)
- Request for Proposals (RFP) drafted & released (9/11)
- Steering and Clinical Committees selected (9-10/11)
- Applications received, scored and Centers selected (9-11/11)
- Data received from Medtronic, Inc and distributed to Centers (12/11)
- Centers commenced independent analyses (12/11)

JAMA

A Model for Dissemination and Independent Analysis of Industry Data

Harlan M. Krumholz, MD, SM
Joseph S. Ross, MD, MHS
A Look Ahead to 2012

- **Spring**
  - Conference at Institute of Medicine (IOM) in April

- **Summer**
  - Final Reports due from Independent Research Centers
  - Q & A period with Centers
  - Public release of data
Summary: Industry Funded Clinical Trials

- Industry-funded research is necessary for continued innovation

- Significant concerns RE influence on industry on:
  - Investigator bias
  - Study design
  - Selective dissemination of Results
  - Public health consequences!

- New models for dissemination of results from industry-funded trials offer hope to overcome current limitations, concerns
"Ties with industry are common in medicine. Some have produced important benefits, particularly through research collaborations that improve individual and public health."
“Ties with industry are common in medicine. Some have produced important benefits, particularly through research collaborations that improve individual and public health.”

“At the same time, widespread relationships with industry have created significant risks that individual and institutional financial interests may unduly influence professionals’ judgments about the primary interests or goals of medicine. Such conflicts of interest threaten the integrity of scientific investigations, the objectivity of medical education, and the quality of patient care. They may also jeopardize public trust in medicine.”
Thank You!!!