Sources of Bias in Meta-analysis of RCTs

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Disclaimer

- The views expressed in this talk are those of the presenter
- I am giving this talk as a private individual and not as an affiliate with an employer, and as such, the principles, ideas, and perspectives provided during the talk are my own and not necessarily those of my employer

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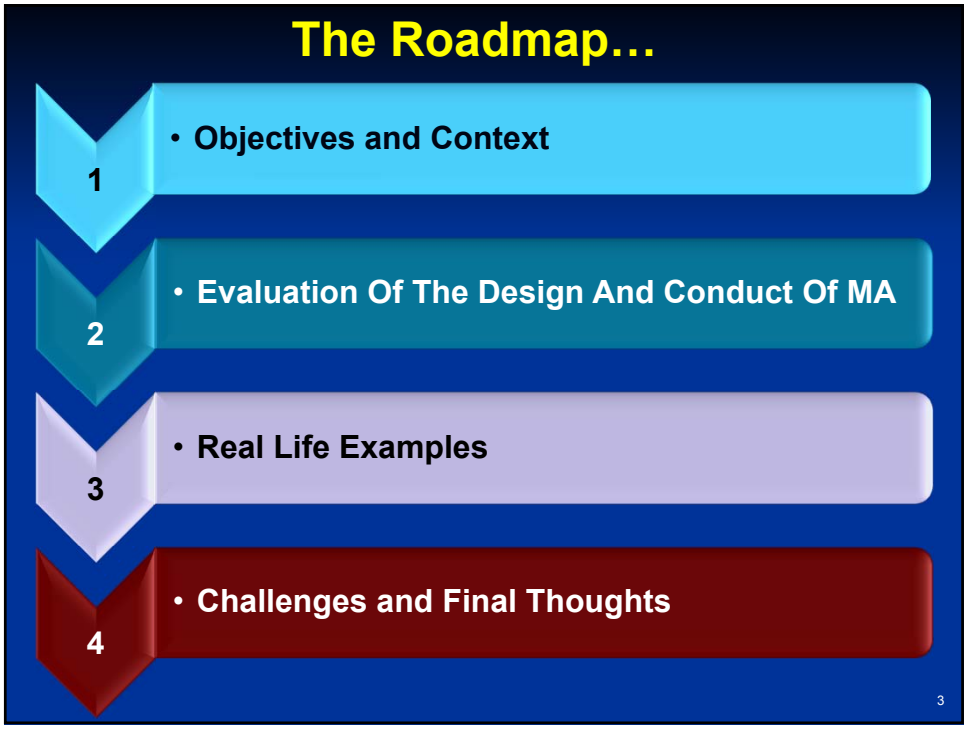
The Roadmap…
1
• Objectives and Context
2
• Evaluation Of The Design And Conduct Of MA
3
• Real Life Examples
4
• Challenges and Final Thoughts
3


The Roadmap…
1
• Objectives and Context
2
3
4
4

Objectives

- Examine sources of bias in meta-analyses of RCTs that may obscure or overestimate risk estimates of a safety signal
- Show that many challenges in MA are not statistical in nature
  - Meta-"Analysis", a misnomer?

Context…

- Nothing is "ground-breaking" in any of the issues that I will discuss, however:
  - Examining these aspects is rarely done/ reported in the published meta-analyses
  - The potential collective effect on risk estimates derived from meta-analysis of RCTs in drug safety

The Roadmap…

1. • Objectives and Context
2. • Evaluation Of The Design And Conduct Of MA
3.
4.

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Guest Editor's Introduction to Special Issue:

The Science and Practice of Research Synthesis

Julia H. Littell
Bryn Mawr College

Twenty years ago, Sir Iain Chalmers and his colleagues noted most research scientists

> *… operate on a double standard: they go to great lengths to define the methods they used to minimize biases and random errors in their reports on the results of new research, but they often do not attempt to apply scientific principles in their discussions of how the newly generated evidence accords with previously available information. Scientists also operate by this double standard when they conduct and report…[research] reviews* (Chalmers, Enkin, & Keirse, 1993, p. 411-412).

Future Directions

To build a reliable evidence base for practice and policy, we need more systematic reviews, better systematic reviews, more frequent updates of existing systematic reviews, and fewer nonsystematic reviews (Bastian et al., 2010). Chalmers and colleagues argued that systematic reviews should be conducted at the beginning and end of each new study to avert avoidable waste of research and related resources (Clarke, Hopewell, & Chalmers, 2010; Chalmers & Glasziou, 2009). Time and effort currently devoted to production of nonsystematic reviews could be greatly reduced or eliminated.

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If You … have to Inspect … Assembly …

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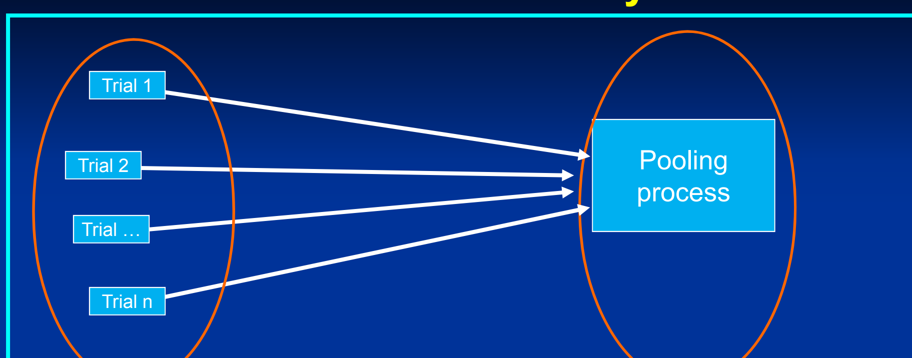
Sources of Bias in Meta-analysis of RCTs



I- Desi… …rials
A. Frai… …ing
B. Asc…
C. Asc…

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CLINICAL TRIALS ARTICLE

Clinical Trials 2011; **8:** 559–570

Secondary use of randomized controlled trials to evaluate drug safety: a review of methodological considerations

Tarek A Hammad, Simone P Pinheiro and George A Neyarapally

Background Randomized clinical trials (RCTs) are often positioned at the top of evidence hierarchies. Meta-analyses of RCTs aim to integrate the state of knowledge on a given scientific question, particularly for rare drug-related outcomes. However, although RCTs are valuable tools in our armamentarium, they are rarely designed to evaluate drug safety and are thus susceptible to limitations that may hamper the ability of both RCTs and meta-analyses to fully characterize the safety profiles of drugs. Their potential limitations might be exacerbated in the study of rare outcomes, often encountered in drug safety assessment, when even minor deviations from the intended randomization could impact the stability of the risk estimates.

Purpose This article considers the methodological caveats of both RCTs and meta-analyses of RCTs pertinent to the study of drug-related harms. It is intended to stimulate discussion about the impact of these caveats on interpreting findings of RCTs and meta-analyses for drug safety, which would foster more robust, critical evaluations, and thus enhance clinical and regulatory decision-making.

Methods Pertinent issues that can influence the interpretation of drug-related harms discussed in this article were based on authors' expertise and review of the literature.

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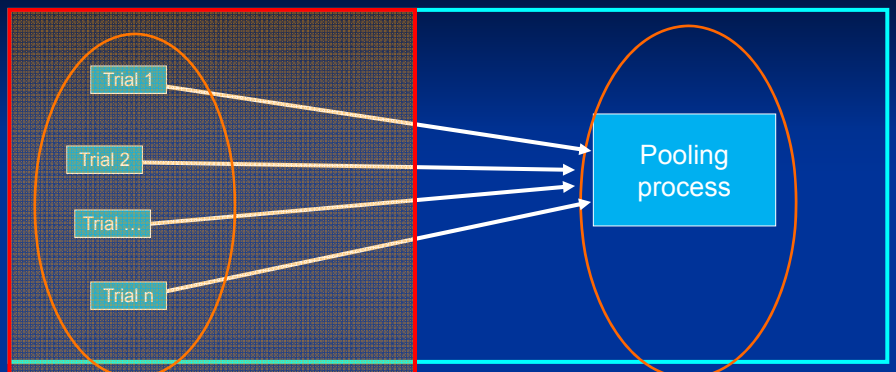
Sources of Bias in Meta-analysis of RCTs



I- Design and conduct of individual trials
A. Frailty of randomization and blinding
B. Ascertainment of AEs
C. Ascertainment of drug exposure

II- Design and conduct of meta-analyses
A. Selection of trials
B. Suitability of trials for integration
C. Subgroup analyses
D. Use of simple pooling approach
E. Pertinent statistical issues

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I- Design and Conduct of Individual Trials

A. Frailty of Randomization and Blinding

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Theory

Randomization Creates Equal Distribution of Known and Unknown Factors That Might Affect the Comparison

Practice

- Dropout rate can be significant in some trials, more than 50% sometimes

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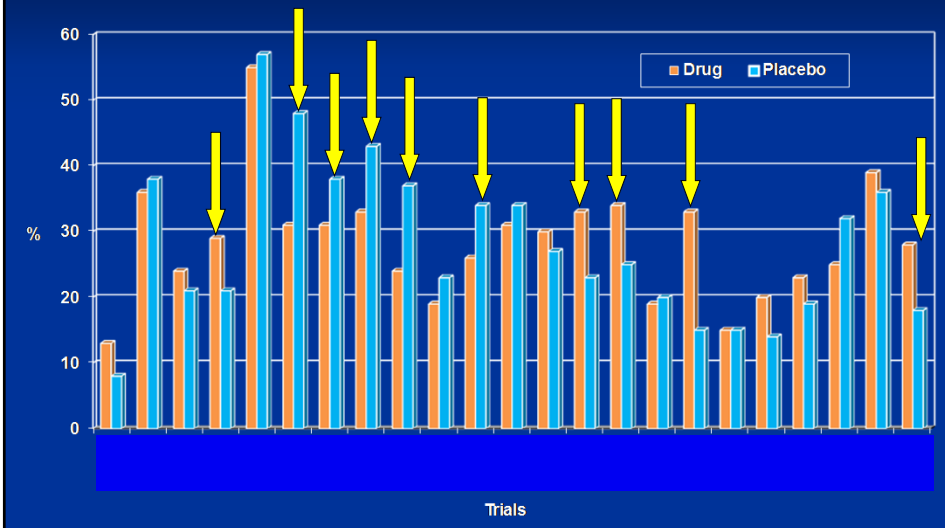
Hammad TA, Laughren T, Racoosin J. *Archives of General Psychiatry*. 2006; 63:332-339

Frequency of Discontinuation by Trial



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Randomization Creates Equal Distribution of Known and Unknown Factors That Might Affect the Comparison (continued)

Practice

- Dropout rate can be significant in some trials, more than 50% sometimes
  - The longer the follow up period, the higher the dropout rate
  - Confounding Effect: due to imbalance between comparison groups, eg, in follow up time, age, gender, co-morbidity, etc
    - May adjust for known confounders, but not for unknown ones
    - Relying on person-time assumes constant risk

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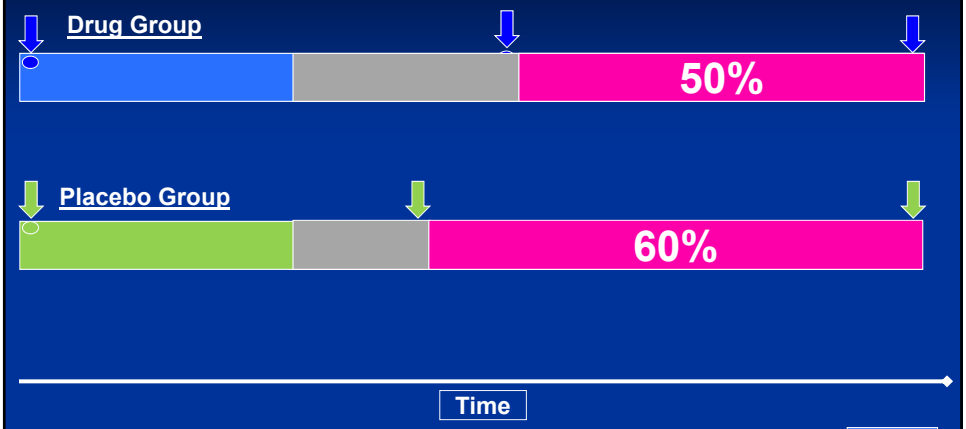
Differential Premature Discontinuation



Imbalance:

1. Person-years
2. Distribution of risk factors (known and unknown)
3. Capture of morbidity and mortality
4. Attribution of cause-specific mortality

Drug
Placebo
Discontinued
Risk factors

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Randomization Creates Equal Distribution of Known and Unknown Factors That Might Affect the Comparison (continued)

Practice

- **Dropout rate** can be significant in some trials (continued)
  - **Informative censoring effect**: If patients with chest pain, for example, tend to drop out, then capturing myocardial infarction might be a challenge
    - **Reason** for dropping out is not readily available
    - **Follow-up** after drop out is not always done

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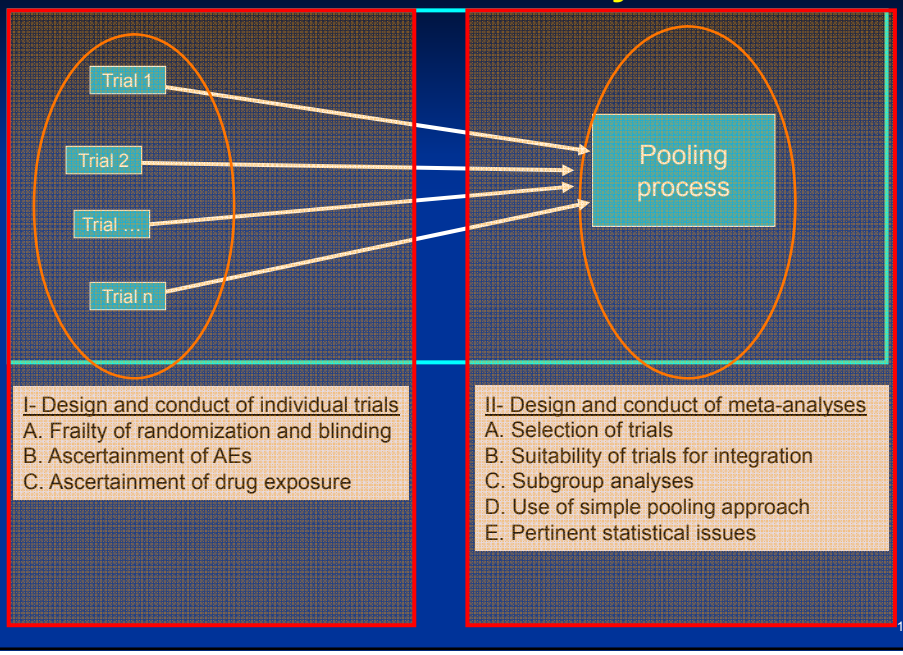
Sources of Bias in Meta-analysis of RCTs



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II- Design and Conduct of Meta-analyses

A. Selection of Trials

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Are We Seeing the Full Picture When it Comes to RCTs?

- In 2007 the US government began requiring that researchers register trials conducted in the US and abroad and report the results on ClinicalTrials.gov
- Michael R. Law, Yuko Kawasumi, and Steven G. Morgan. doi: 10.1377/hlthaff.2011.0172 *HEALTH AFFAIRS* 30, NO. 12 (2011): 2338–2345

Good news
- Trials funded by industry, three times as likely to report results than trials funded by NIH

Bad news
- 39% of trials registered late after the mandate's deadline (21 days of 1st patient enrollment)

Worse news
- Only 12% of completed studies reported results within a year, as required by the mandate

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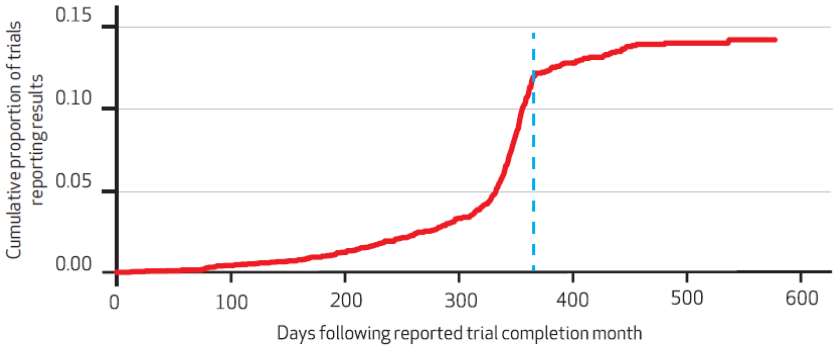
EXHIBIT 4

Cumulative Proportion Of Drug And Biologic Trials Having Reported Results In ClinicalTrials.gov



SOURCE Authors' analyses of data from ClinicalTrials.gov. **NOTES** Includes only Phase II and higher trials that reported being completed after September 2008. The dashed line represents one year after completion, the mandated date for reporting results unless researchers receive an exemption. Cumulative proportions are based on Kaplan-Meier survival estimates and account for censoring at the end of the study follow-up period.

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II- Design and Conduct of Meta-analyses

D. Use of Simple (Crude) Pooling Approach

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Simple (Crude) Data Pooling

- All data are pooled together, not respecting randomization boundaries:
  - Publications based on FOI sources
  - Integrated Summary of Safety (ISS) in NDA
    - Sometimes controlled and uncontrolled phases of trials, and also data from earlier phases, which would include healthy volunteers

- This approach fails to preserve the randomization effect and might introduce bias through "confounding by study"

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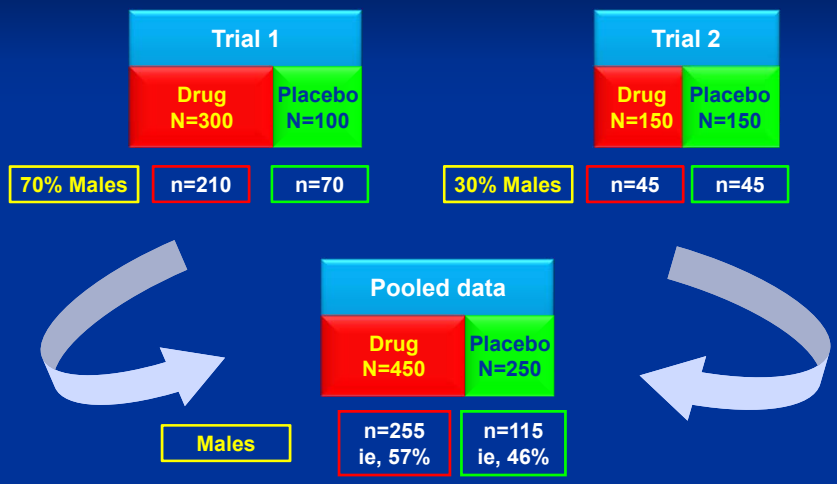
Example of a Scenario That Might Lead to *Confounding by Study* With Simple Pooling of Randomized Clinical Trials



Hammad TA, Pinheiro SP, Neyarapally GA. Secondary Use of Randomized Controlled Trials to Evaluate Drug Safety: a Review of Methodological Considerations. *Clinical Trials*. 2011;8(5):559-570.

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The Emerging Question…

How Many Published Meta-analyses of Drug Safety Actually Address the Issues Raised in This Lecture?

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CLINICAL TRIALS ARTICLE

Clinical Trials 2013; 0: 1–9

Reporting of meta-analyses of randomized controlled trials with a focus on drug safety: An empirical assessment

Tarek A Hammad, George A Neyarapally, Simone P Pinheiro, Solomon Iyasu, George Rochester and Gerald Dal Pan

27 MA

Background Due to the sparse nature of serious drug-related adverse events (...) meta-analyses combining data from several randomized controlled trials (RCTs) to evaluate drug safety issues are increasingly being conducted and published, influencing clinical and regulatory decision making. Evaluation of meta-analyses involves the assessment of both the individual constituent trials and the approaches used to combine them. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting framework is designed to enhance the reporting of systematic reviews and meta-analyses. However, PRISMA may not cover all critical elements useful in the evaluation of meta-analyses with a focus on drug safety particularly in the regulatory-public health setting.

Purpose This work was conducted to (1) evaluate the adherence of a sample of published drug safety–focused meta-analyses to the PRISMA reporting framework, (2) identify gaps in this framework based on key aspects pertinent to drug safety, and (3) stimulate the development and validation of a more comprehensive reporting tool that incorporates elements unique to drug safety evaluation.

Methods We selected a sample of meta-analyses of RCTs based on review of abstracts from high-impact journals as well as top medical specialty journals between 2009 and 2011. We developed a preliminary reporting framework based on PRISMA with specific additional reporting elements critical for the evaluation of drug safety meta-analyses of RCTs. The reporting of pertinent elements in each meta-analysis was reviewed independently by two authors; discrepancies in the independent evaluations were resolved through discussions between the two authors.

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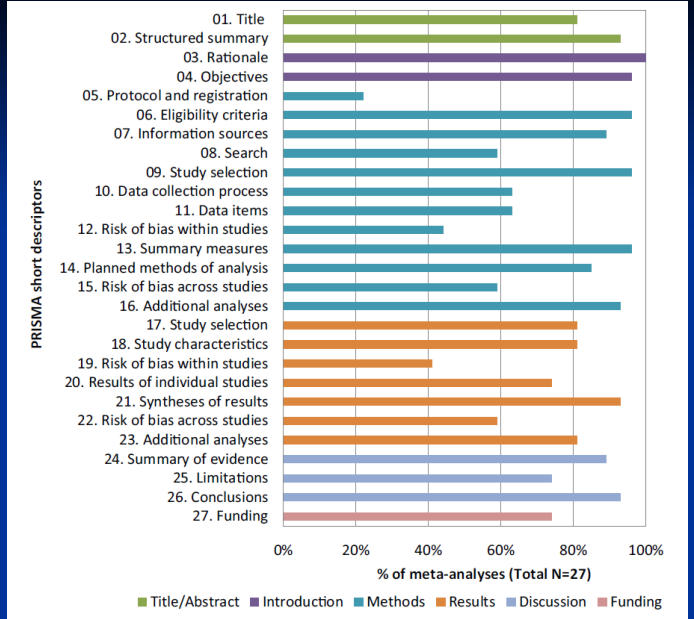

Figure 1. Percentage of meta-analyses addressing each PRISMA element.
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

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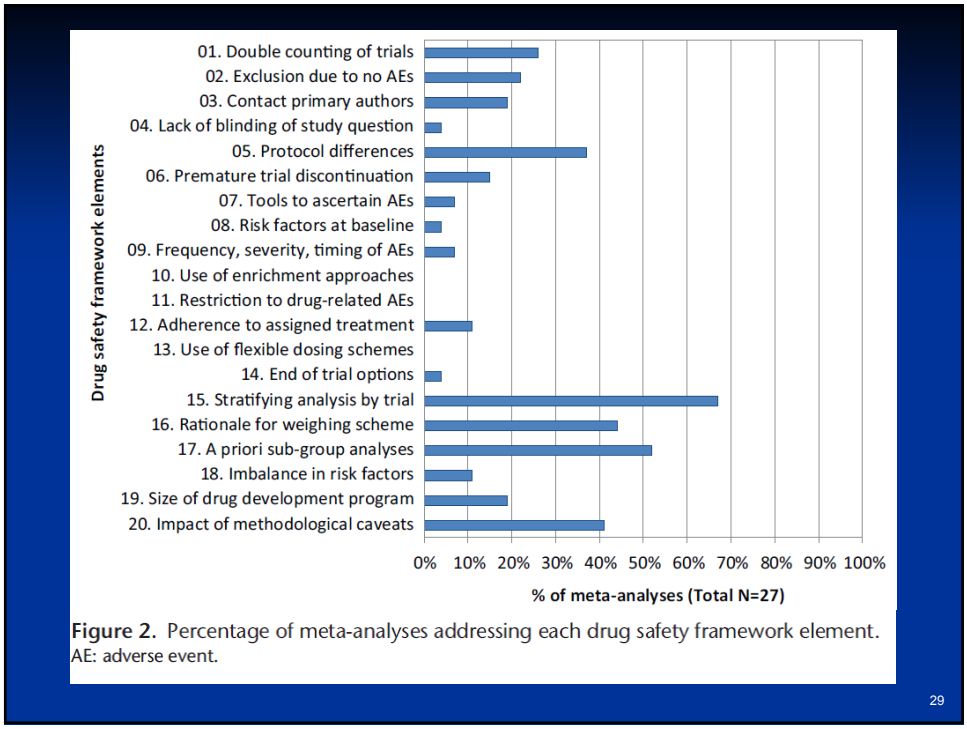

Figure 2. Percentage of meta-analyses addressing each drug safety framework element.
AE: adverse event.

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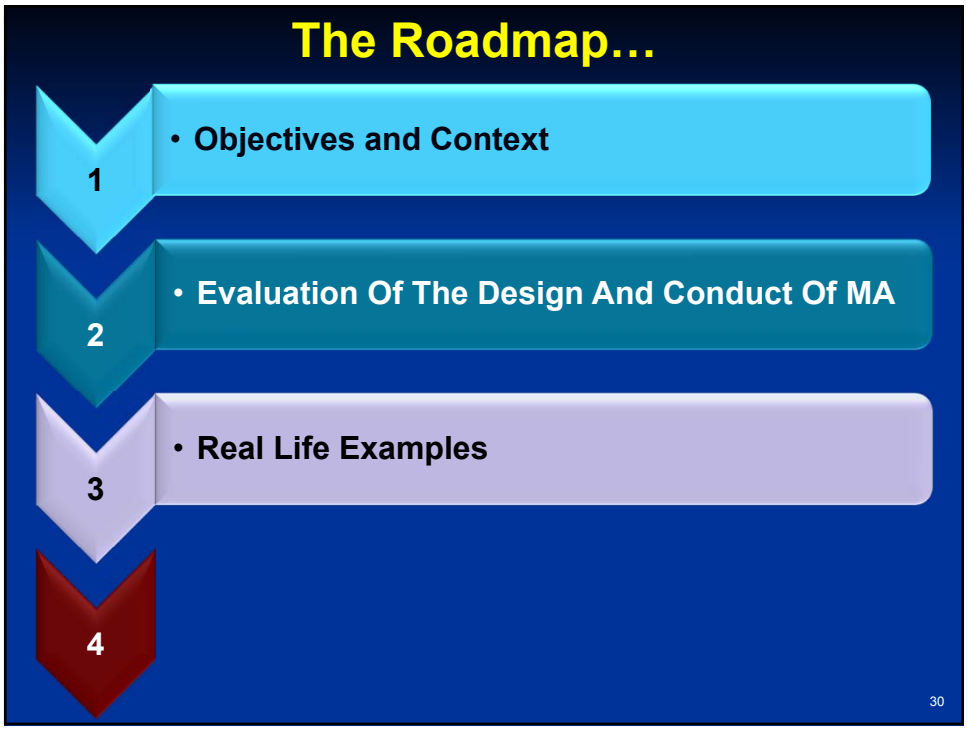

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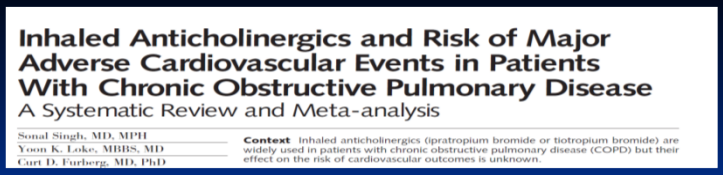
Need Empirical Evidence…?

Examples of Discrepancies



Inhaled Anticholinergics and Risk of Major Adverse Cardiovascular Events in Patients With Chronic Obstructive Pulmonary Disease

A Systematic Review and Meta-analysis

Sonal Singh, MD, MPH
Yoon K. Loke, MBBS, MD
Curt D. Furberg, MD, PhD

Context Inhaled anticholinergics (ipratropium bromide or tiotropium bromide) are widely used in patients with chronic obstructive pulmonary disease (COPD) but their effect on the risk of cardiovascular outcomes is unknown.

Tiotropium (*Spiriva*®)

- Singh et al meta-analysis of 15 trials (*JAMA* Sept 24, 2008) raised questions about the safety of the inhaled anticholinergic agents regarding:
  - Increased risk of all-cause and cardiovascular mortality
  - Increased risk of cardiovascular events

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"Fail-Safe" Number

- To reverse the significantly increased risk seen in the long-term trials, using Rosenthal's method, 16 non-significant long-term trials, each with a sample size of 1450 participants, would be required
- What does this mean?

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What Do You Think the FDA Should Do and in What Order? (Remember it Is a *JAMA* Paper!)

1. Early communication? (1-2 months)
2. Re-do the meta-analysis? (1-2 years)
3. Conduct another clinical trial? (4-5 years)
4. Conduct an epidemiological study? (2-3 years)
5. Lots of prayers (few minutes)

Votes?

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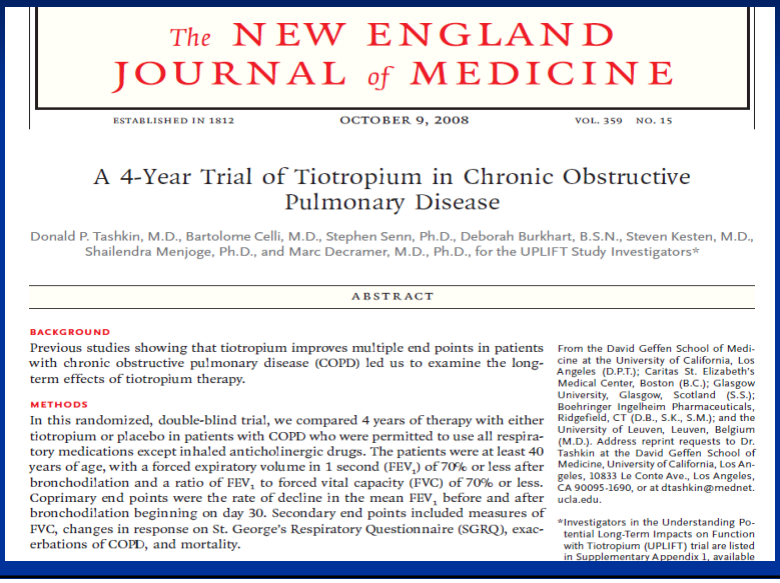
Look at The Power of Prayers: Two Weeks Later



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 9, 2008 VOL. 359 NO. 15

A 4-Year Trial of Tiotropium in Chronic Obstructive Pulmonary Disease

Donald P. Tashkin, M.D., Bartolome Celli, M.D., Stephen Senn, Ph.D., Deborah Burkhart, B.S.N., Steven Kesten, M.D., Shailendra Menjoge, Ph.D., and Marc Decramer, M.D., Ph.D., for the UPLIFT Study Investigators*

ABSTRACT

BACKGROUND

Previous studies showing that tiotropium improves multiple end points in patients with chronic obstructive pulmonary disease (COPD) led us to examine the long-term effects of tiotropium therapy.

METHODS

In this randomized, double-blind trial, we compared 4 years of therapy with either tiotropium or placebo in patients with COPD who were permitted to use all respiratory medications except inhaled anticholinergic drugs. The patients were at least 40 years of age, with a forced expiratory volume in 1 second (FEV_1) of 70% or less after bronchodilation and a ratio of FEV_1 to forced vital capacity (FVC) of 70% or less. Coprimary end points were the rate of decline in the mean FEV_1 before and after bronchodilation beginning on day 30. Secondary end points included measures of FVC, changes in response on St. George's Respiratory Questionnaire (SGRQ), exacerbations of COPD, and mortality.

From the David Geffen School of Medicine at the University of California, Los Angeles (D.P.T.); Caritas St. Elizabeth's Medical Center, Boston (B.C.); Glasgow University, Glasgow, Scotland (S.S.); Boehringer Ingelheim Pharmaceuticals, Ridgefield, CT (D.B., S.K., S.M.); and the University of Leuven, Leuven, Belgium (M.D.). Address reprint requests to Dr. Tashkin at the David Geffen School of Medicine, University of California, Los Angeles, 10833 Le Conte Ave., Los Angeles, CA 90095-1690, or at dtashkin@mednet.ucla.edu.

*Investigators in the Understanding Potential Long-Term Impacts on Function with Tiotropium (UPLIFT) trial are listed in Supplementary Appendix 1, available

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UPLIFT Trial (1/2)

- One large randomized (as large as ALL the trials in the meta-analysis combined), double-blind trial was published (UPLIFT, NEJM, Oct 9, 2008)
- The study suggested that long-term use of tiotropium was associated with decreased risk of cardiovascular events and all-cause mortality

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UPLIFT Trial (2/2)

- Multicenter, multinational RCT comparing 4 years of tiotropium/placebo therapy in COPD patients (N=2,986 tiotropium, N=3,006 placebo)
- Vital status: collected on all patients who prematurely discontinued
  - Known for 97% of placebo 98% of tiotropium groups
  - The primary cause of death was adjudicated by an independent committee
- Safety endpoints collected: all adverse events, including serious adverse events, and all-cause mortality (during study plus 30 days)

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The Roadmap…

1. Objectives and Context
2. Evaluation Of The Design And Conduct Of MA
3. Real Life Examples
4. Challenges and Final Thoughts

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Challenges and Final Thoughts…

Challenges…

- What if:
  - Some trials "fail" in efficacy for a particular indication; how should we deal with the safety information?
  - The specific caveats are not evaluable? e.g. reason for discontinuation,…
  - The impact of the caveat can not be quantified and controlled? e.g. informative censoring,…
  - These caveats are non-consequential?
- In short: considering that time crunch is a leading challenge: when trying hard is NOT good enough?

Final thoughts…

- Meta-"analysis", a misnomer ? most of the challenges in MA are not statistical in nature.
  - "Statistics serve as fallible pattern-recognition devices. Explanation of the origin of observed patterns is beyond the scope of these devices (Greenland, 1998)"

- Meta-analysis is mostly , by definition, a post-hoc endeavor and should be evaluated with caution
  - Newly published meta-analyses should be viewed as "preliminary/inconclusive evidence" until thoroughly reviewed/investigated