

Challenges of synthesizing clinical trials: a systematic reviewer's perspective

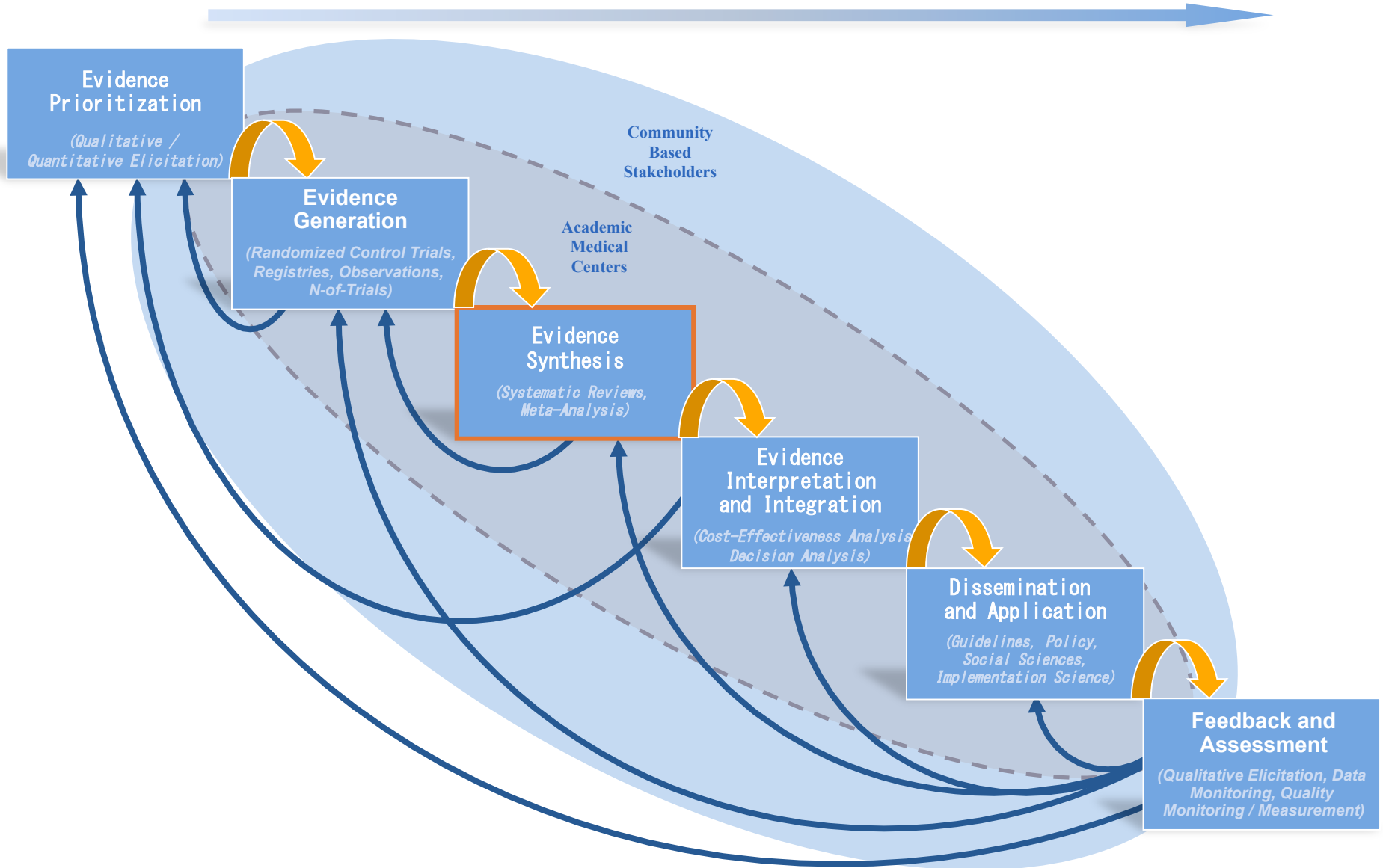
Joseph Lau, MD
Tufts Medical Center

NLM 175th Anniversary
June 7, 2011

Disclosures

- I direct the Tufts Evidence-based Practice Center
- All of my research funding comes from AHRQ and NIH
- I own no stocks in any company

Translational Spectrum of Comparative Effectiveness Research



Uses of clinical trials publications by systematic reviewers

- Systematic reviews/meta-analyses (journals pubs)
- AHRQ evidence reports
 - NIH Consensus Development Conferences
 - ODS request for IOM DRI panel on vitamin D
 - Technology assessments for CMS
 - Comparative effectiveness reviews (CERs)
- Evidence-based clinical practice guidelines
- Topic identification for future CERs
- Future research needs documents
- Methods research

Some issues to address

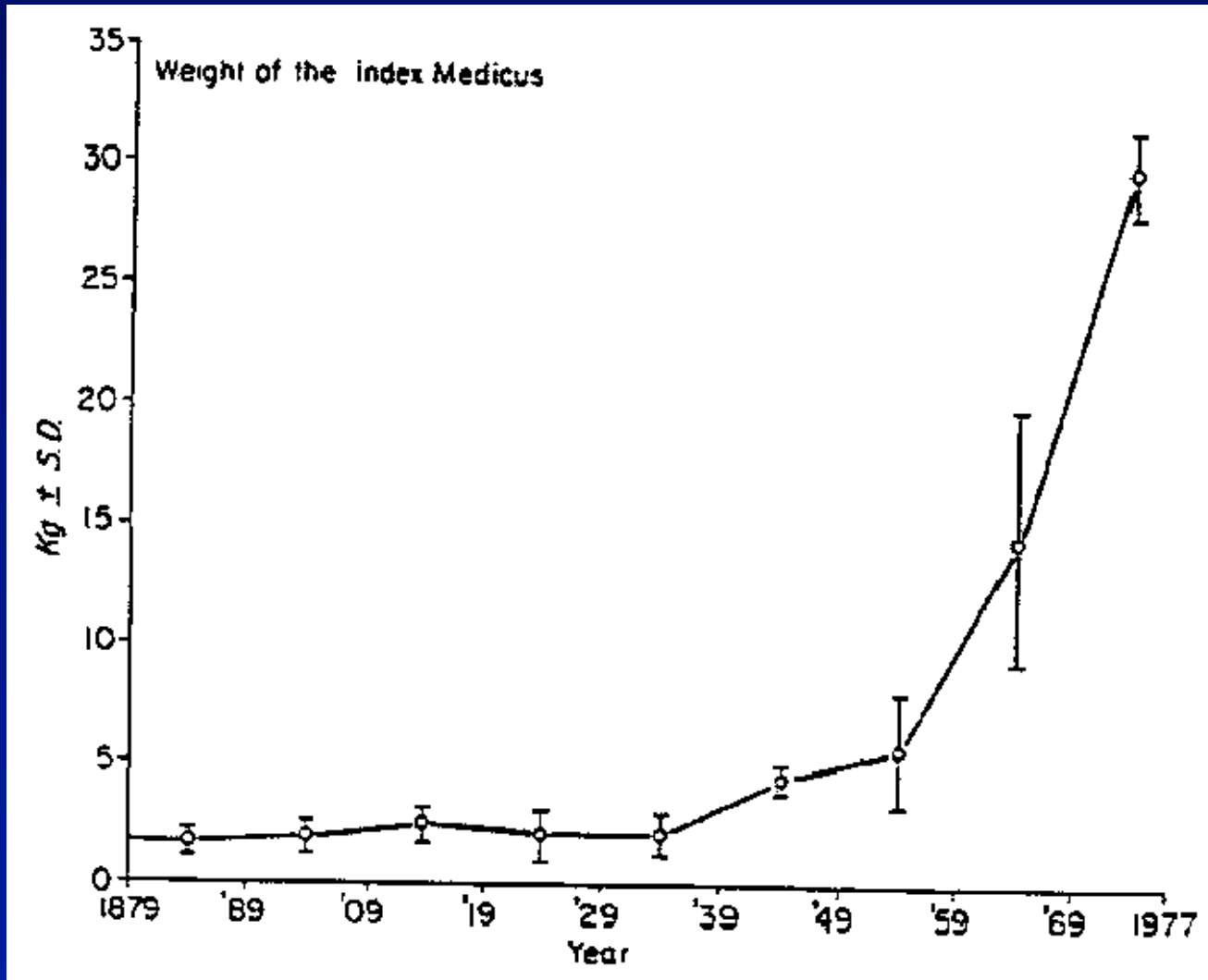
- How many trials are there? Do they address our needs?
- How do we select trials?
- How do we interpret them?
 - Trials are heterogeneous
 - Quality of trials vary
- The need for synthesis

What do clinical trials and potato chips have in common?

- You can't have just one!

The weight of medical knowledge

David T. Durack, M.B., D. Phil.; NEJM 1978



Weight of the Index Medicus According to 10-Year Periods from 1879 to 1977

Randomized trials in perinatology: Major achievements and future potential. Grant A. Ann NY Academy Sciences 1993;703:107-117.

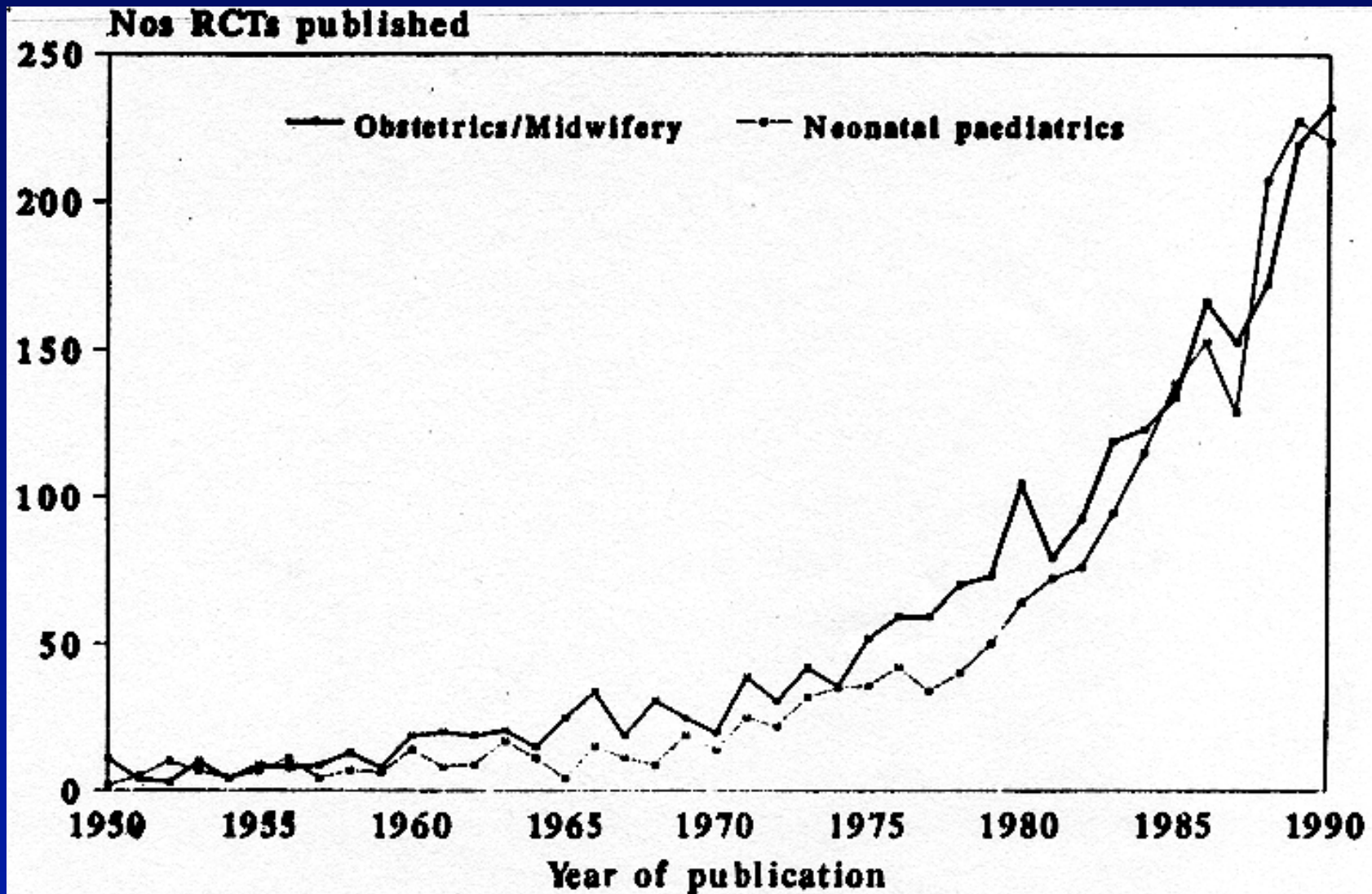


FIGURE 1. Annual numbers of published reports of perinatal trials.

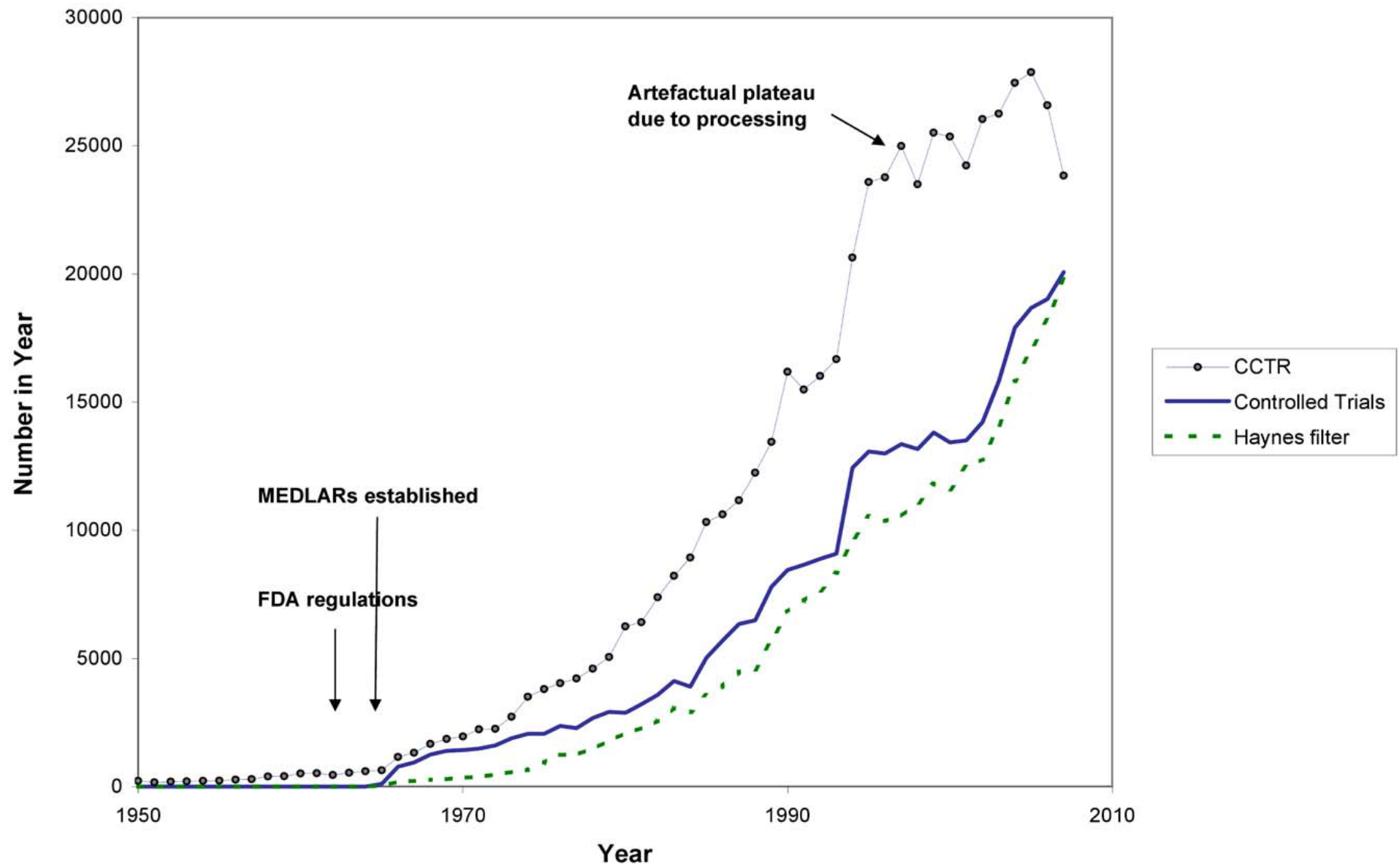
Policy Forum

Seventy-Five Trials and Eleven Systematic Reviews a Day: How Will We Ever Keep Up?

Hilda Bastian^{1*}, Paul Glasziou², Iain Chalmers³

1 German Institute for Quality and Efficiency in Health Care (IQWiG), Cologne, Germany, **2** Centre for Research in Evidence-Based Practice, Faculty of Health Sciences, Bond University, Gold Coast, Australia, **3** James Lind Library, James Lind Initiative, Oxford, United Kingdom

Figure 2. The number of published trials, 1950 to 2007. CCTR is the Cochrane Controlled Trials Registry; Haynes filter uses the “narrow” version of the Therapy filter in PubMed:ClinicalQueries. Bastian et al. PLOS Med 2010.



What does the medical literature offer?

- Lots of articles and trials
- Pubmed
 - Indexes ~5,000 biomedical journals from around the world
 - over 20 million articles indexed
- Cochrane Central Register of Controlled Trials
 - Indexed ~500,000 records

What do clinical trials and politicians have in common?

- There may be too many of them
- Some are not useful
- Some are good and some are bad
- You can't accept them on face value, you have to critically appraise what they say and place it in the right context

Lots of studies does not necessarily translate to lots of clinically useful evidence

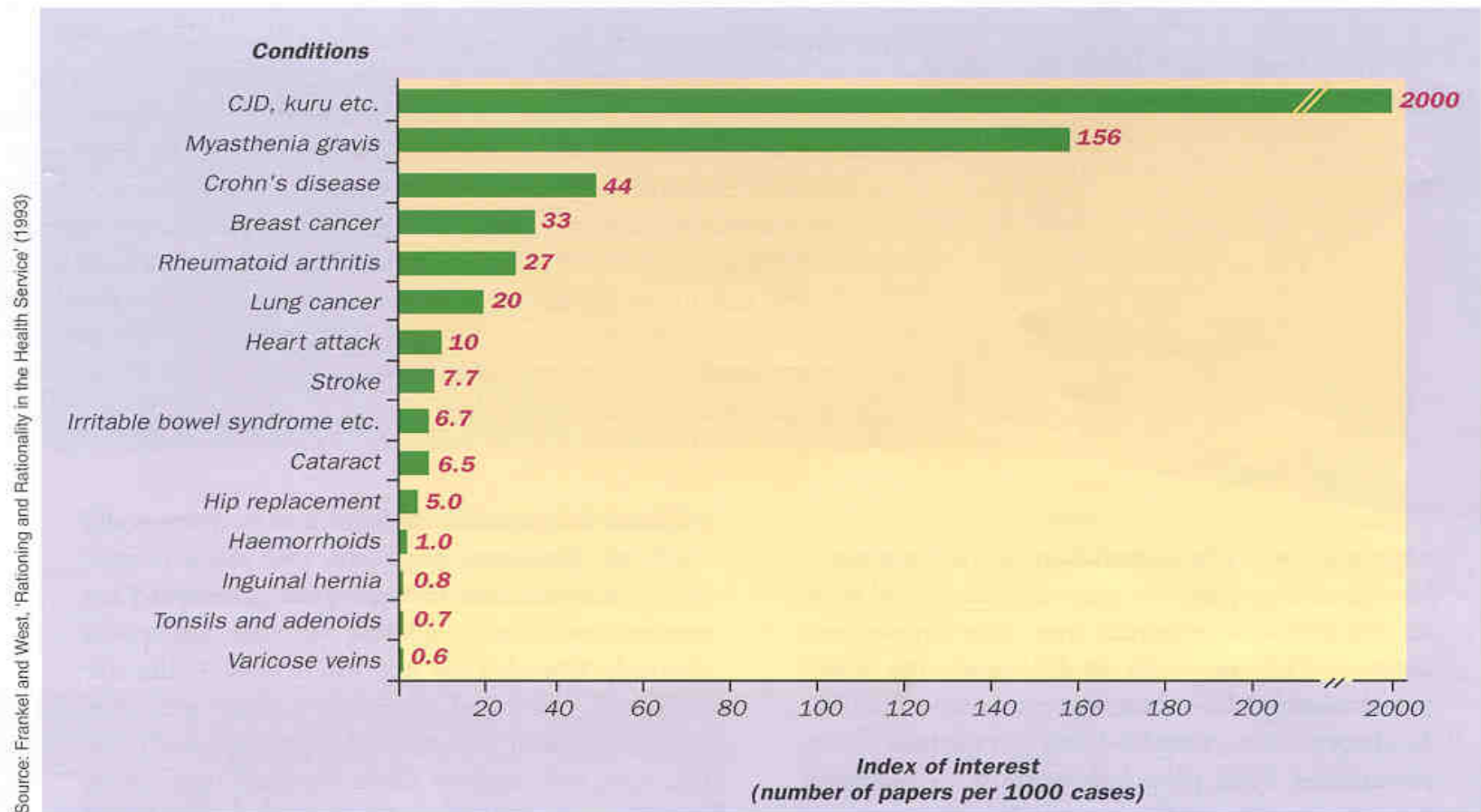


Figure 1 An interesting condition: this graph shows the widely different levels of interest that medical research appears to have in different diseases. The figures were arrived at by finding the number of papers relating to each condition published during 1986 and listed in Indexus Medicus, and dividing this by the number of thousands of patients treated for each disease in the same year. The resulting "index of interest" varies from 2000 for CJD-type human diseases to 0.6 for varicose veins.

Essay

Why Most Published Research Findings Are False

John P. A. Ioannidis

Summary

There is increasing concern that most current published research findings are false. The probability that a research claim is true may depend on study power and bias, the number of other studies on the same question, and, importantly, the ratio of true to no relationships among the relationships probed in each scientific field. In this framework, a research finding is less likely to be true when the studies conducted in a field are smaller; when effect sizes are smaller; when there is a greater number and lesser preselection of tested relationships; where there is greater flexibility in designs, definitions, outcomes, and analytical modes; when there is greater financial and other interest and prejudice; and when more teams are involved in a scientific field in chase of statistical significance. Simulations show that for most study designs and settings, it is more likely for a research claim to be false than true

factors that influence this problem and some corollaries thereof.

Modeling the Framework for False Positive Findings

Several methodologists have pointed out [9–11] that the high rate of nonreplication (lack of confirmation) of research discoveries is a consequence of the convenient, yet ill-founded strategy of claiming conclusive research findings solely on the basis of a single study assessed by formal statistical significance, typically for a p -value less than 0.05. Research is not most appropriately represented and summarized by p -values, but, unfortunately, there is a widespread notion that medical research articles

It can be proven that most claimed research findings are false.

is characteristic of the field and can vary a lot depending on whether the field targets highly likely relationships or searches for only one or a few true relationships among thousands and millions of hypotheses that may be postulated. Let us also consider, for computational simplicity, circumscribed fields where either there is only one true relationship (among many that can be hypothesized) or the power is similar to find any of the several existing true relationships. The pre-study probability of a relationship being true is $R/(R + 1)$. The probability of a study finding a true relationship reflects the power $1 - \beta$ (one minus the Type II error rate). The probability of claiming a relationship when none truly exists reflects the Type I error rate, α . Assuming that c relationships are being probed in the field, the expected values of the 2×2 table are given in Table 1. After a research finding has been claimed based on

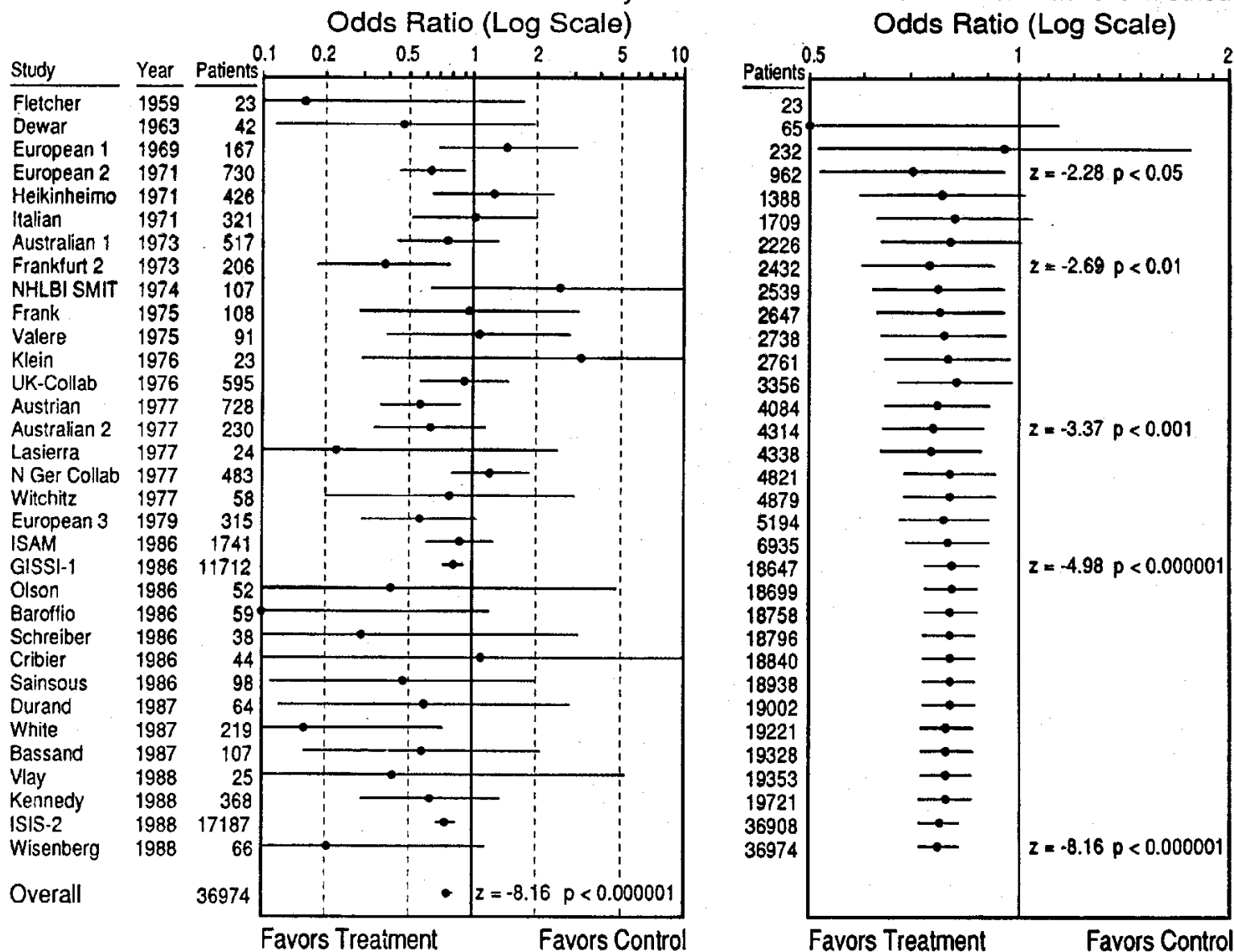
Problems of having many articles

- Too many?
- Many may be useless information for clinical decision making (i.e. basic science research)
- Some clinical studies may be flawed and therefore the results misleading; selective use may lead to biased conclusions
- Most clinicians don't know how to access this large volume of literature (literature search)
- No clinician (in this world) is able to follow this much literature
- Most clinicians don't know how to evaluate the literature and synthesize it

Intravenous Streptokinase Therapy in Acute Myocardial Infarction

Individual RCT and Overall Meta-Analysis Results

Cumulative Mantel-Haenszel method

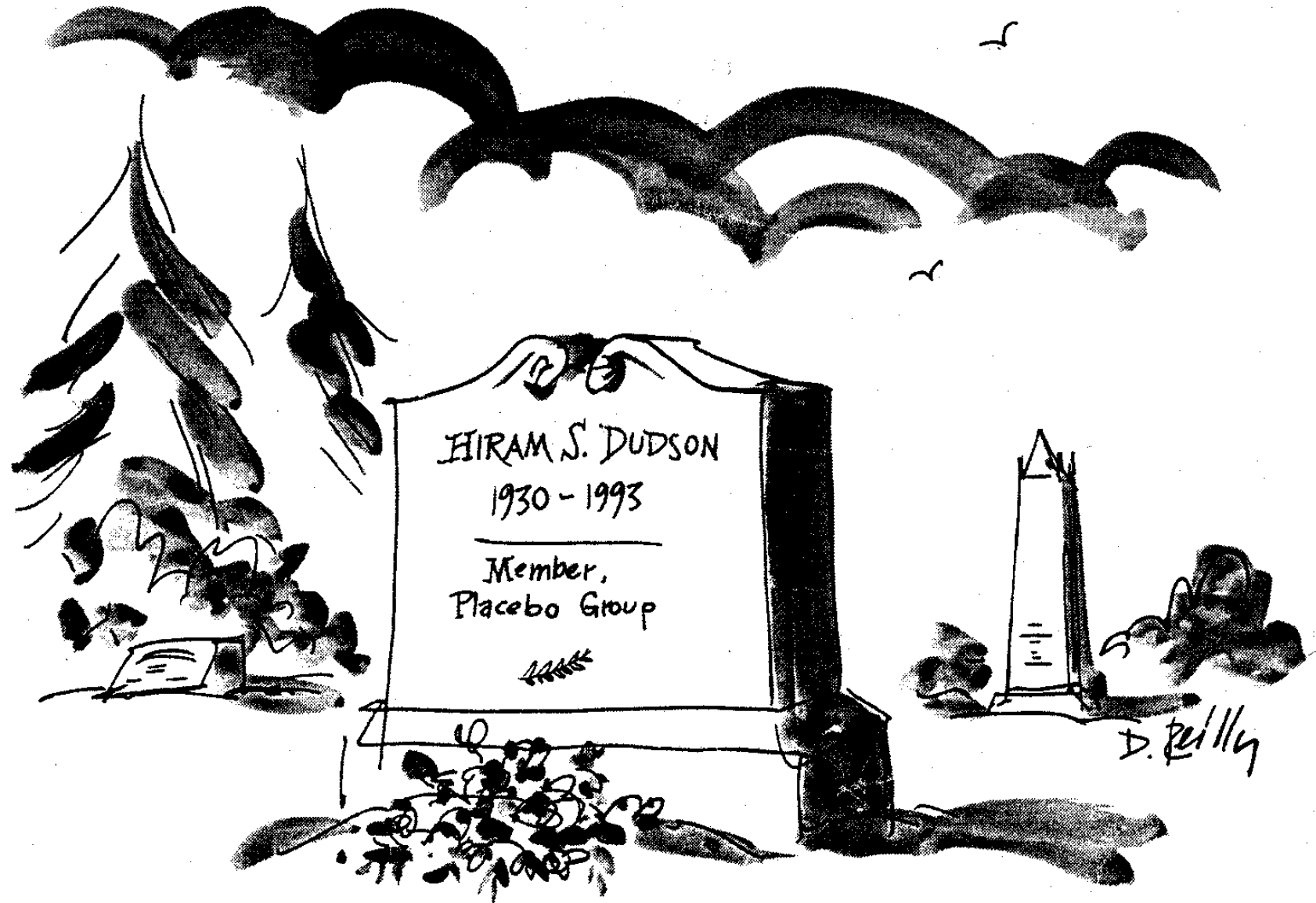


Lau J, Antman EM, et al. N Engl J Med. 1992; 327:248-54.

The research of many commentators have already thrown much darkness on this subject, and it is probable that, if they continue, we shall soon know nothing at all about it.

Mark Twain

An ethical issue of clinical trials



Use of cumulative meta-analysis in the design, monitoring, and final analysis of a clinical trial: a case study.

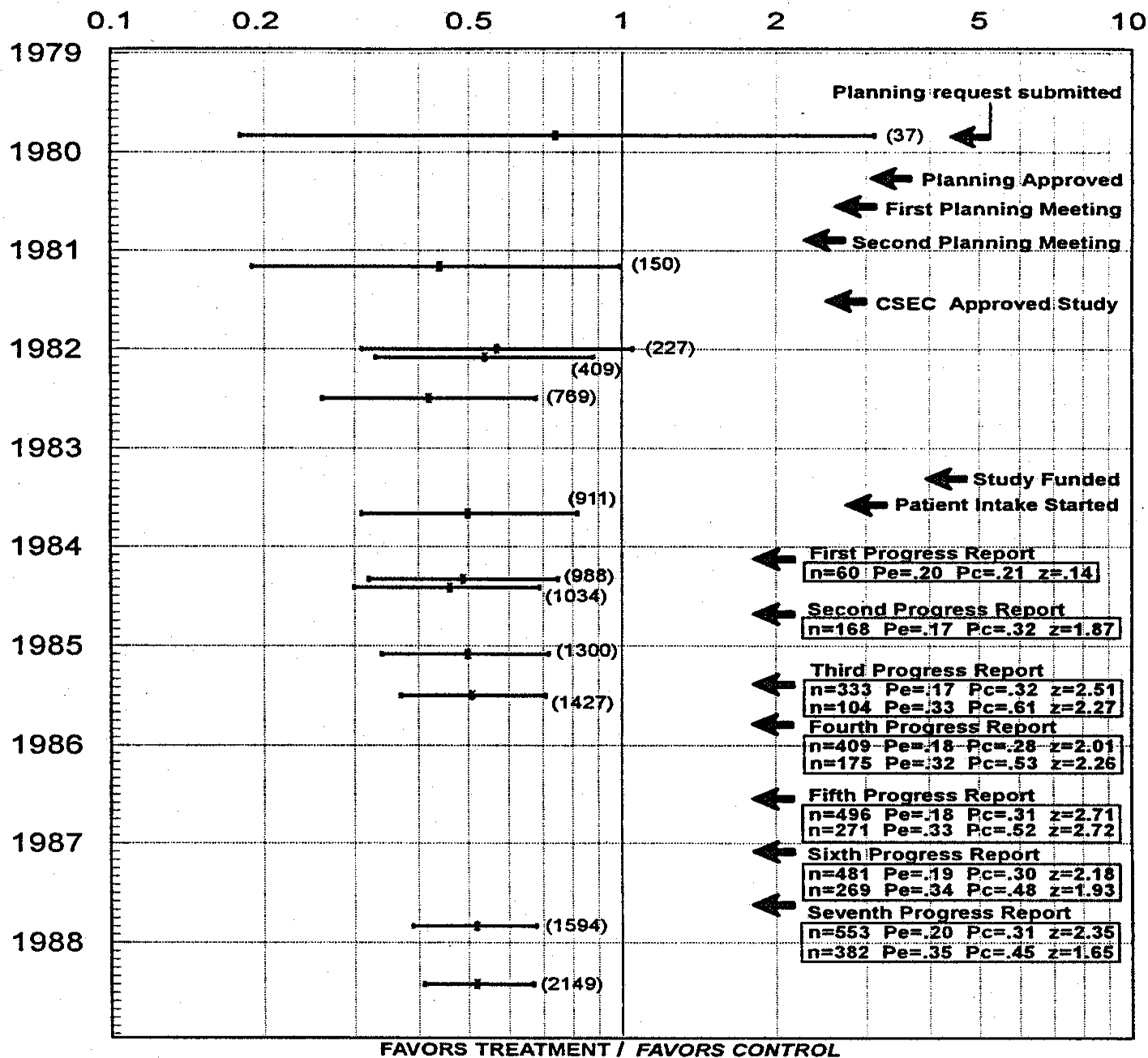
Henderson WG, Moritz T, Goldman S, Copeland J, Sethi G.
Control Clin Trials 1995 Oct;16(5):331-41.

From 1983 to 1987, the Department of Veterans Affairs (DVA) Cooperative Studies Program (CSP) conducted a multicenter clinical trial (CSP #207) to determine whether four different antiplatelet regimens compared to placebo could prevent the occlusion of grafts following coronary artery bypass surgery.

RESULTS

The study showed that all the active regimens tended to be better than placebo and that the three regimens containing aspirin were statistically significantly better.

A cumulative meta-analysis of 12 trials performed shortly before the end of the trial raised the issue as to whether the meta-analysis, if done earlier, would have changed the conduct of the trial.



Conclusion by the authors

Cumulative meta-analysis could be useful as an adjunct in the planning, conduct, and final analysis of a clinical trial. It could also be used as one piece of evidence in the monitoring of the ongoing phase of a trial.

Henderson WG, Moritz T, Goldman S, Copeland J, Sethi G.
Controlled Clin Trials 1995;16:331-41.

Heterogeneity in clinical trials and challenges of synthesis



Evidence Report/Technology Assessment

Number 9



Agency for Health Care Policy and Research

**Diagnosis and Treatment
of Acute Bacterial
Rhinosinusitis**

Characteristics of acute sinusitis medical literature on interventions

- 1999 AHRQ Evidence Report on diagnosis and management of acute sinusitis
- Evaluated 1,857 Medline indexed citations between 1966 to March 1998
- 68 antibiotics RCT (placebo control or another antibiotic)

The PICO(TS) method to formulate research question on interventions

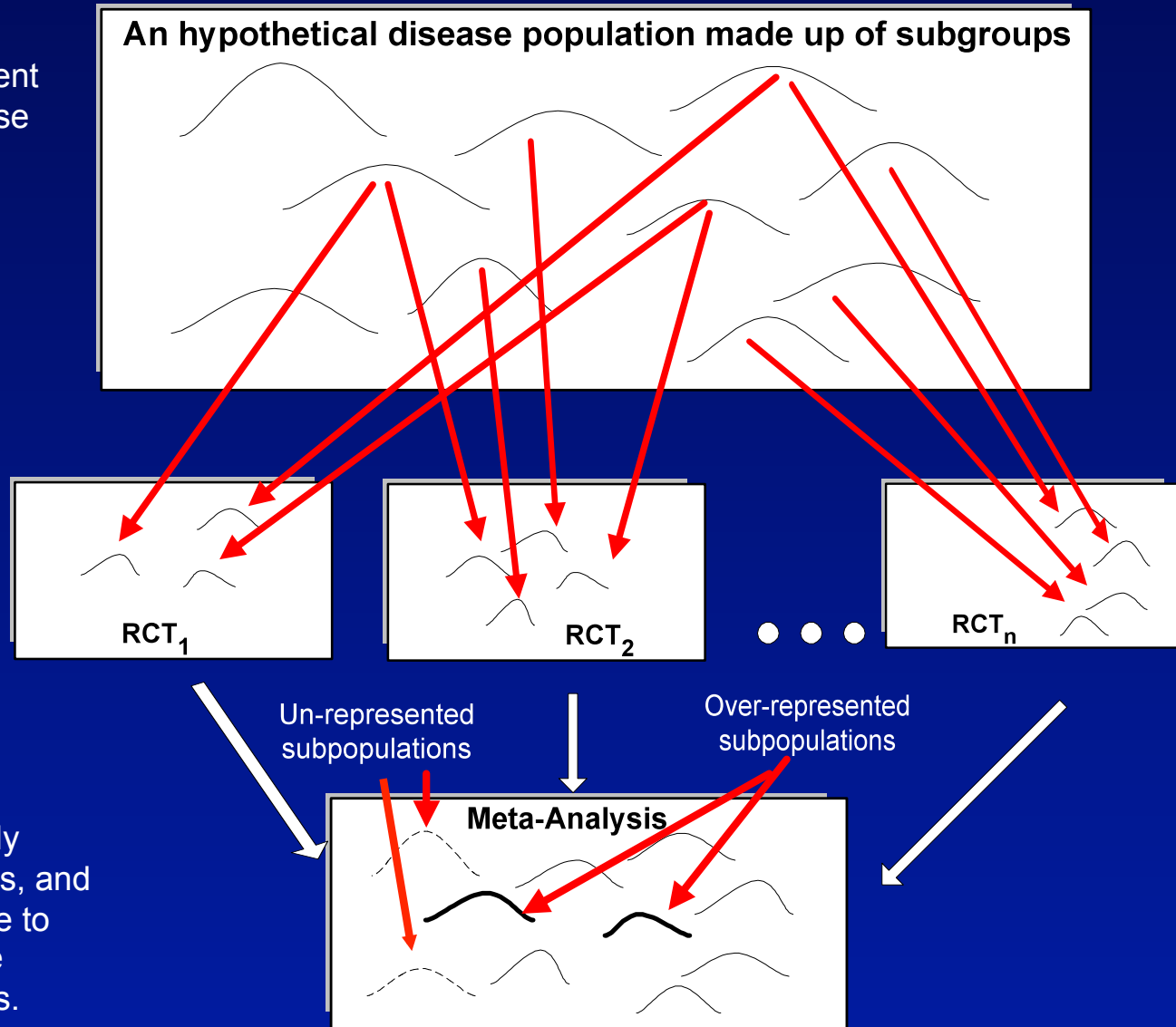
<u>Participants</u>	<u>Interventions</u>	<u>Comparator</u>	<u>Outcomes</u>
<i>Adults</i>	<i>Amoxicillin</i>	<i>Placebo</i>	<i>Clinical failure</i>
<i>Children</i>	<i>TMP-SMX</i>	<i>No control</i>	<i>Radiologic resolution</i>
<i>Inclusion criteria (strict, loose)</i>	<i>Erythromycin</i>	<i>Active comparator</i>	<i>Recurrence</i>
	<i>Quinolones</i>	<i>Alternative antibiotics</i>	<i>Adverse effects</i>
	<i>Many others</i> <i>...</i>		

Heterogeneity in a disease population, RCTs, and meta-analysis of the trials

Different subgroups representing various patient characteristics and disease manifestations may have different responses to a treatment.

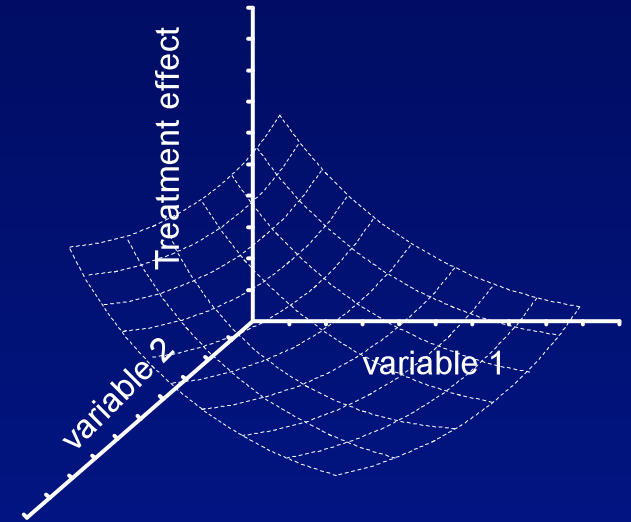
Different inclusion criteria, patient recruitment, and random variations may result in study cohorts consisting of different distributions and combinations of subgroups in RCTs.

Protocol differences, study design and reporting flaws, and publication bias contribute to bias or exclusion of some studies in a meta-analysis.

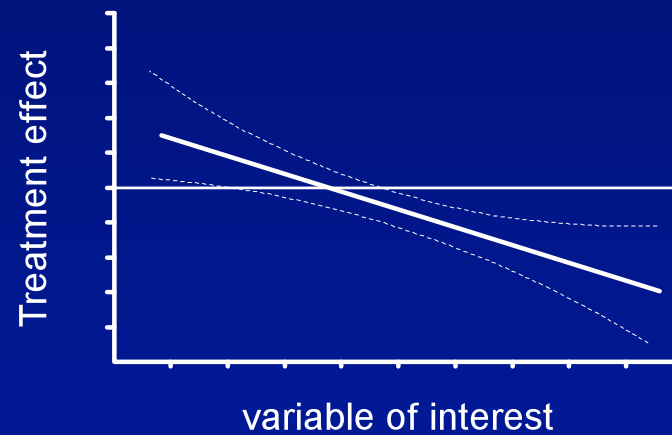


Interpreting the results of meta-analysis of RCTs depends on how the data are synthesized: weighted average, regression, or individual patient data modeling.

RESPONSE SURFACE
modeling individual patient data

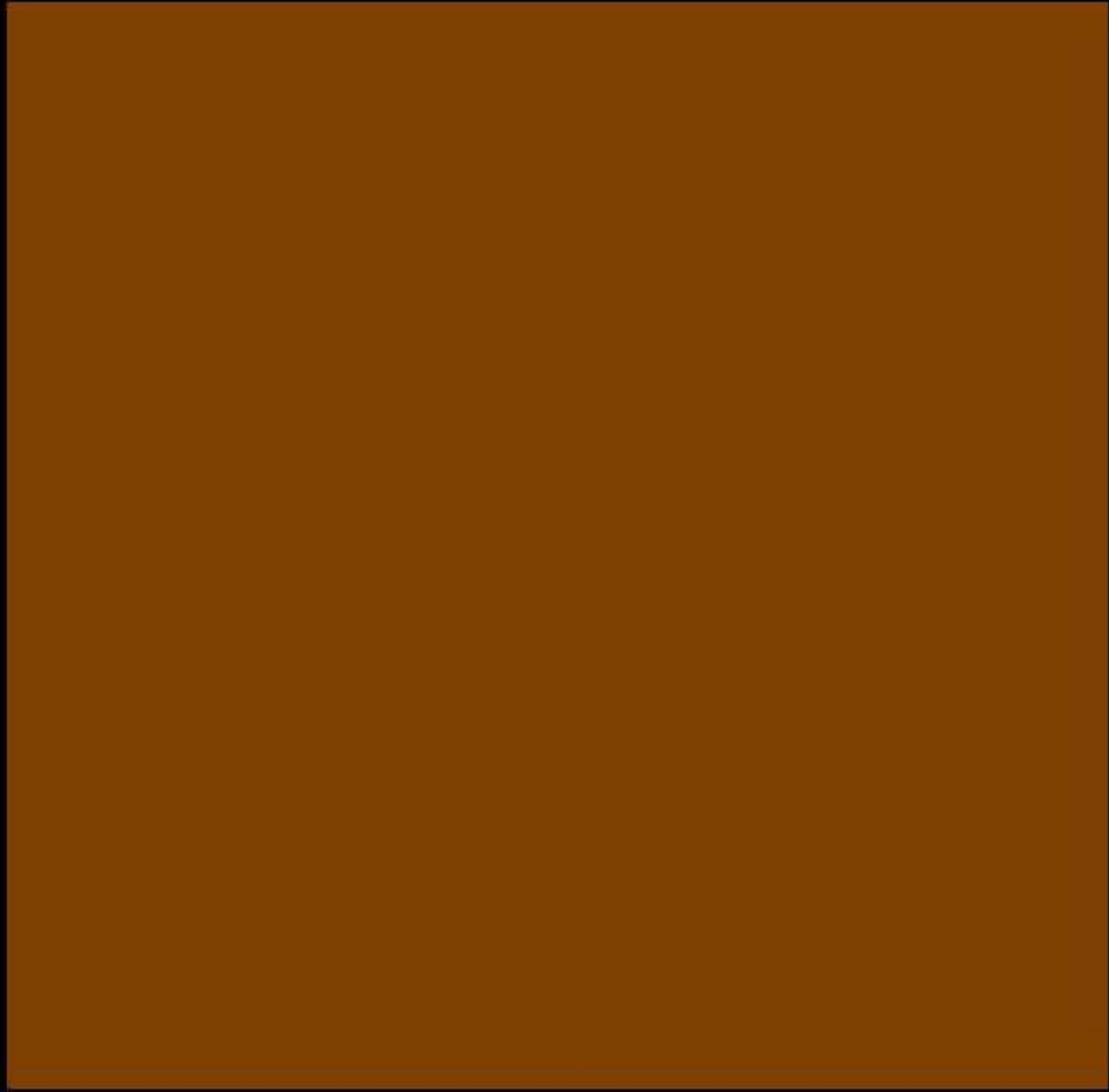


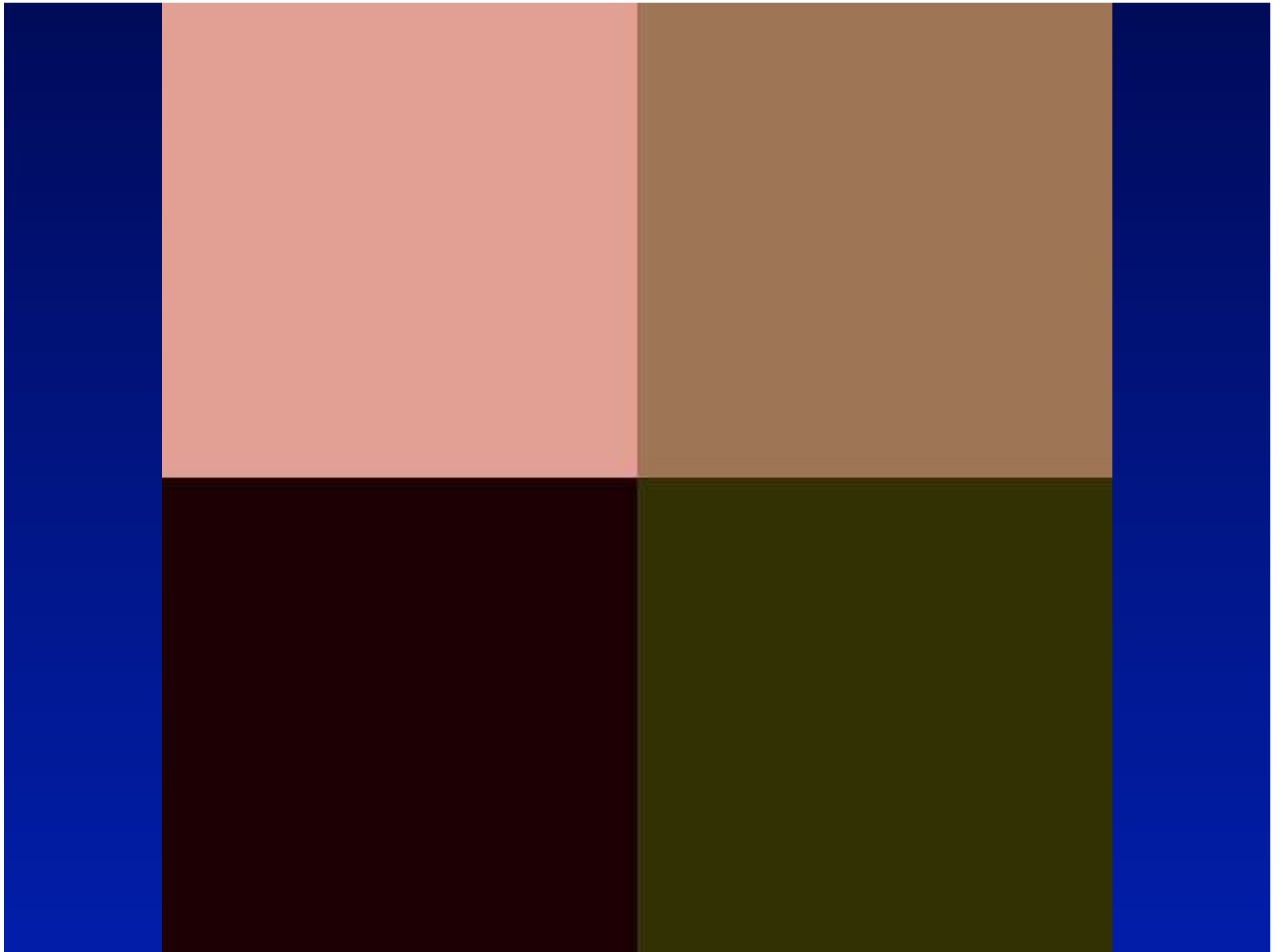
META-REGRESSION
modeling summary data

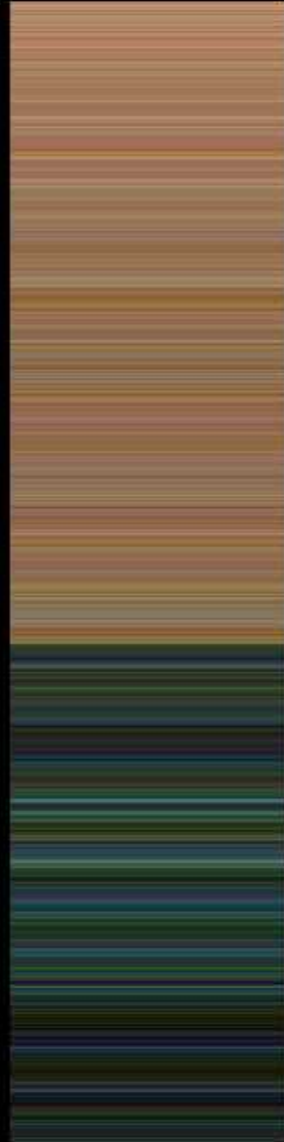


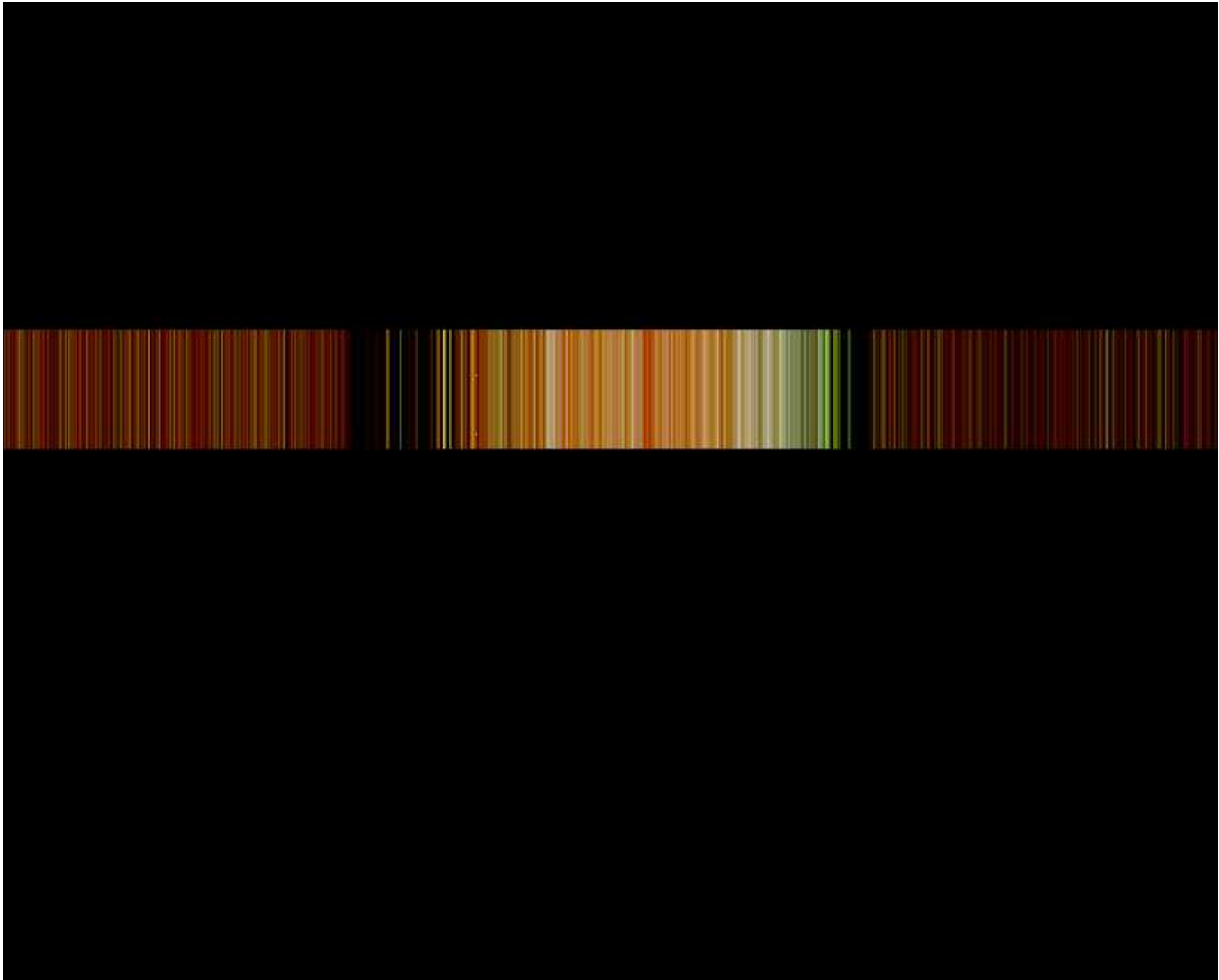
OVERALL ESTIMATE
combining summary data

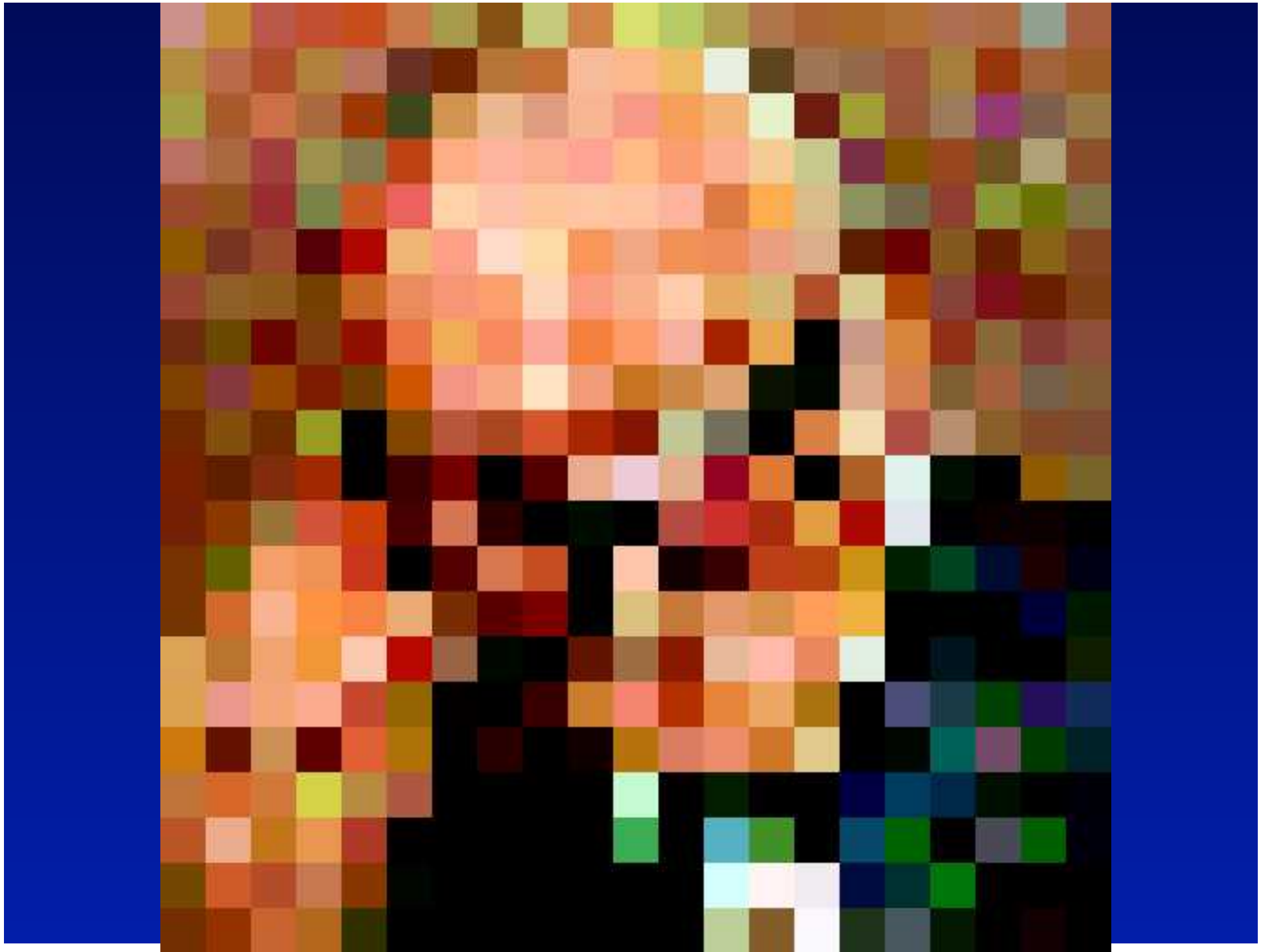


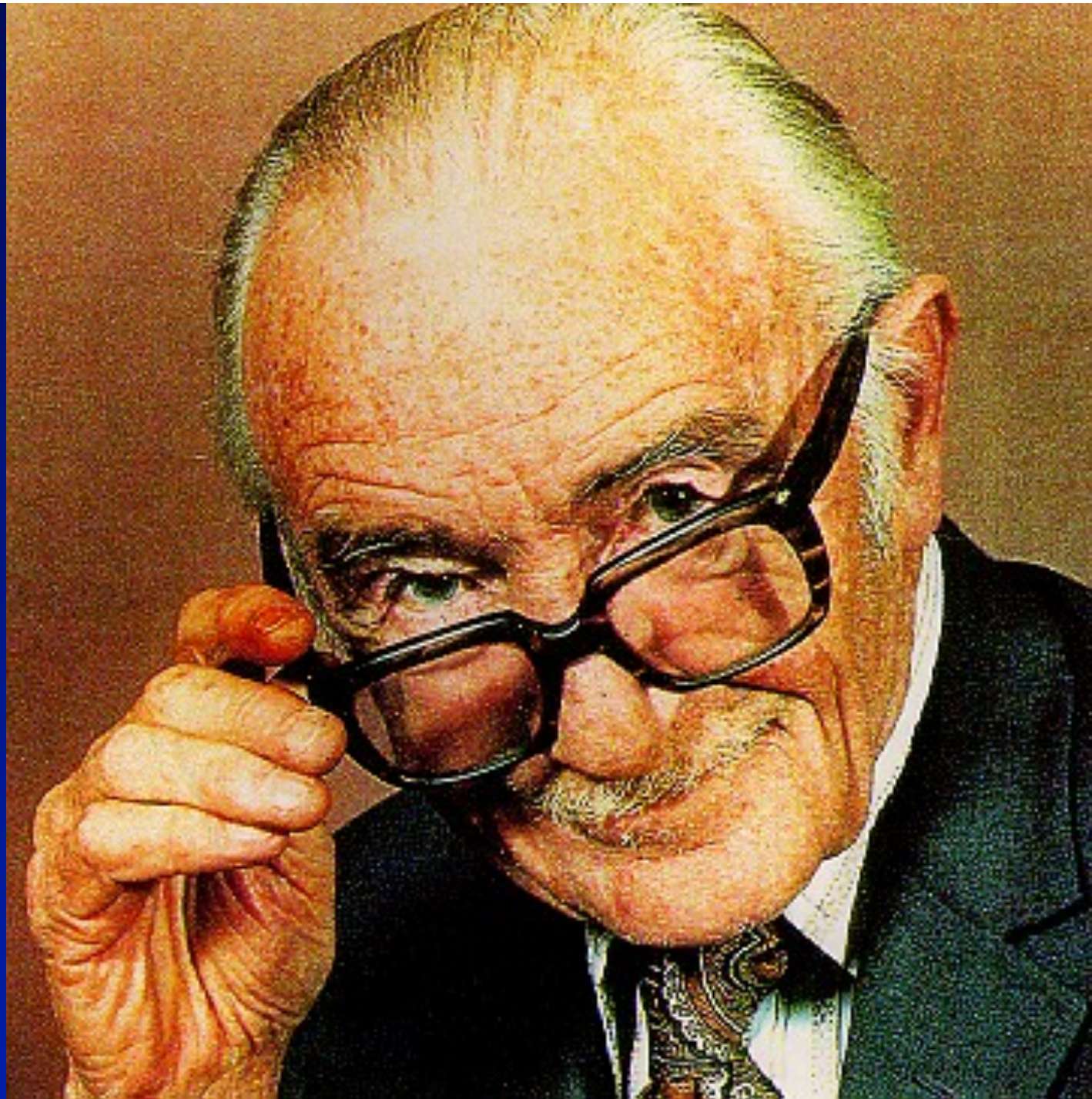












Conclusions

- We need more clinical trials ... that are well designed, conducted, and reported to answer clinically important questions
- Trials should be designed considering prior evidence and with future synthesis in mind
- Make patient-level data available

Bastian et al. PLOS Med 2010

- To meet the needs of patients, clinicians, and policymakers, **unnecessary trials need to be reduced**, and systematic reviews need to be prioritized.
- Streamlining and innovation in methods of systematic reviewing are necessary to enable valid answers to be found for most patient questions.
- Finally, clinicians and patients require open access to these important resources.