Corruption of the Evidence as Threat and Opportunity for Evidence-Based Medicine

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It was seventeen years ago that a set of ideas that had been evolving over the previous three decades became embodied in a unifying term: evidence-based medicine. It is impossible to think of medicine today without reference to evidence-based medicine: as of April 2007, there were 25,000 entries in MEDLINE, 1.24 million Google-identified hits on the Internet, and over 300 books on the topic in the Library of Congress catalog.

The impact of evidence-based medicine extends beyond medical practice into medical education, translational research, and public health policy. For instance, the Accreditation Council for Graduate Medical Education mandates the teaching of evidence-based medicine competencies for postgraduate medical training[1]. Both the National Institutes of Health Roadmap Initiative[2], through its translational research programs, and the U.S. Agency for Healthcare Research and Quality, through its funding of Evidence Practice Centers and other programs to promote and enhance evidence-based practice[3], are examples of the influence of evidence-based medicine on the national research agenda. The World Health Organization is moving vigorously to a more evidence-based approach to its health policy guidelines, epitomized by a recent guideline concerning avian influenza[4]. Recently, health care opinion leaders concluded that evidence-

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based medicine, this paradigm shift in the practice and teaching of medicine, represents a medical milestone in the same league as antibiotics and anesthesia[5].

Defined as the conscientious, judicious, and explicit use of the best available evidence from clinical care research in making health care decisions[6], evidence-based medicine is perhaps better understood as the practice of medicine that adheres to the following two fundamental principles[7].

The first principle is that the higher the quality of the evidence the more confident the decision-maker. This suggests a hierarchy of research evidence (we use the word "evidence" to mean any observation in nature, e.g., the apparent association between treatment and outcomes) with some research being higher quality than other research. When establishing optimal therapy for a patient or group of patients, evidence-based medicine suggests that decision-makers judge the quality of the best evidence about therapy[8]. For such patient management decisions, the pertinent hierarchy of evidence will prioritize high quality randomized trials with multiple features that protect from bias.

Clinicians would be most confident in applying this evidence to their patients if many high quality randomized trials measuring patient-important outcomes in disparate populations and settings yield similar answers. When trials are of poor quality, use observational designs and are thus open to bias, are small in size, inconsistent in results, or fail to measure the outcomes of importance to patients, inferences become weaker.

Guyatt et al[9] have summarized the key factors that decrease the quality of the evidence:

- Poor quality of planning and implementation of the available randomized controlled trials suggesting high likelihood of bias
- Inconsistency of results
- Indirectness of evidence
- Sparse evidence
- Reporting bias (including publication bias)

The second principle of evidence-based medicine is that the evidence alone never tells one what to do. Making sound decisions requires the clinician to expertly assess the patient's personal, social, and clinical context and integrate this information with the values and preferences of the informed patient and the best available evidence.

In this review, we will consider the ongoing challenges to the practice of evidence-based medicine. In particular, we will note how trends in research conduct have corrupted the evidence chain. One paradox will become obvious: the explicit nature of the evidence-based medicine process both facilitates the detection and description of these challenges and offers effective approaches to decrease their adverse impact on evidence-based practice.

The Corruption of the Evidence: Bias

Before evidence-based practice became fully established, pioneers including Alvan Feinstein, David Sackett and Archie Cochrane sought to bring the methods of the scientist to the practice of medicine[10]. These methods included both those of basic science that attend to careful measurement in the laboratory and those of

the epidemiologist that provide strategies for studying large groups to identify difficult-to-measure associations. The field of clinical epidemiology that emerged in the late 1960s borrowed the core principles of these sciences and applied them to the investigation of clinical questions of therapy, diagnosis, prognosis and establishing harm. The new discipline produced a number of insights which, distilled and packaged for the practitioner, described how to "critically appraise" the medical literature. Through critical appraisal, the practitioner could discriminate between clinical research flawed by serious methodological limitations indicating systematic (also known as bias) or random error from those relatively free of such problems.

Over time, the leaders of evidence-based medicine refined the methods of critical appraisal, and a second generation of methodologists, clinicians, and educators formed the Evidence-based Medicine Working Group and began publishing the series "Users' Guides to the Medical Literature" in the Journal of the American Medical Association[11]. Some of these were collated into a handbook to promote the practicing and teaching of evidence-based medicine[12]. A revised, updated, and expanded collection of the Users' Guides articles appeared in 2002 as a book by the same name[13].

As an example of their approach to validity, the Users' Guides suggest that practitioners seeking to critically appraise a randomized trial consider whether (1) participants started up with the same prognosis thanks to unadulterated random allocation of participants to alternative interventions; and (2) investigators ensured that participants retained balance in prognosis throughout the trial by avoiding co-intervention and bias in outcome assessment (most effectively by blinding patients, caregivers, and those involved in assessment of outcome), achieving complete follow-up, and analyzing patients in the groups to which they were randomized. Adherence to these criteria leads to clinical research that provides clinicians with confidence that the study results provide an unbiased estimate of the underlying treatment effect.

We recently reviewed 199 diabetes trials published in prestigious journals[18]. In this review we found that 89% failed to report information about allocation concealment, between 4 and 50% failed to report blinding of participants, clinicians, and researchers including data collectors, outcome adjudicators, and data analysts, and 29% failed to report on the extent of loss to follow-up. Key to understanding this survey of the extant literature is to reflect on the fact that these deficiencies were determined from the published report – it is likely that in fact these trials had better safeguards against bias that the authors fail to reported or removed from the manuscript[19]. This behavior of authors and editors may reflect the persistent failure of many scientists to understand the importance of the safeguards against bias in randomized trials. One has to wonder whether, even though they had designed the study properly, this disregard for methodological rigor in the publication phase of the research was manifested during the study conduct itself.

More recently, we have identified an additional potential source of bias: stopping a clinical trial early for benefit. In a systematic review of the literature, we identified 143 randomized trials stopped early because of apparent and unexpected benefit[14]. Such trials are increasing in preva-

lence, particularly in high impact journals – most notably, the New England Journal of Medicine and the Lancet. Investigators are at risk of introducing bias when they stop a randomized trial early at a "random high" in the apparent magnitude of the treatment effect. Because random fluctuations in the magnitude of effect tend to be more extreme early on when few events have accrued, trials stopped early for benefit are at greatest risk of overestimating the treatment effect.

In the systematic review of randomized trials stopped early, the median relative risk reduction (RRR) was 47% with a quarter of the trials reporting RRRs of greater than 70%[14]. The magnitude of these effects is – unfortunately – not consistent with the modest effects we expect from most treatments. Furthermore, trials that stopped on the basis of less than the median number of events (66) were far more likely to generate RRRs greater than 47% (odds ratio 31, 95% confidence interval 12 to 82).

A randomized trial of perioperative beta-blockers in patients undergoing vascular surgery provides a striking example of how trials stopped early for benefit may distort the evidence base for clinical decision making[15]. On the basis of this trial, published in the New England Journal of Medicine, clinical practice guidelines and quality improvement activities have led to widespread adoption of this intervention. This trial was stopped early after 112 patients had been randomized; only nine myocardial infarctions and eleven deaths had occurred when the authors reviewed the data and decided to terminate the trial. At this point, they found a 100% reduction in the risk of nonfatal myocardial infarctions and an equally implausible 80% reduction in the relative risk of cardiac death.

A systematic review published in 2005 summarized all the randomized trials of perioperative beta blockers conducted in the last ten years[16] and revealed that this trial was an outlier in a sea of trials that offered little evidence of efficacy for perioperative beta blockers. Furthermore, three other trials that enrolled almost 2000 additional patients have since been published. These trials found no evidence of a significant mortality benefit (using the data from these trials to update the previous meta-analysis yields a pooled relative risk of 1.02, 95% confidence interval 0.8, 1.3). The ongoing Perioperative Ischemic Evaluation (POISE) trial, a 10000 patient trial, will likely provide the definitive answer to this question with the publication of its results in 2008[17].

The Corruption of the Evidence: Spin

While scientists' personal and career aspirations and ambitions (i.e., obtaining funding, jobs, satisfaction) may support representing research as more rigorous and important than it really is, profit may be an even stronger motive for introducing "spin" in otherwise well-conducted research. By "spin" we mean the conscious presentation of evidence in a manner geared to produce a particular effect; spin is ubiquitous, but it becomes problematic when those presenting the evidence have little compunction against frankly misleading characterizations, or have a particularly well developed capacity for self-deception.

Take, for example, a study of the rheto-

ric of the conclusions of randomized trials. Als-Nielsen and colleagues measured the enthusiasm for the experimental intervention in 370 RCTs from twenty-five high quality reviews[20]. They found that authors were more likely to show extreme enthusiasm for the experimental intervention, in the form of calling this intervention the treatment of choice in patients with the condition of interest, when for-profit agencies supported the trials than when they did not. Furthermore, they adjusted for the size of the effect (excluding the explanation that for-profit agencies may be picking winners – that is, drugs with bigger effect – and still found an odds ratio for extreme enthusiasm of 5.3 (95% confidence interval 2.0, 14.4).

If it is true that profit is a strong motive for misleadingly sanguine presentations of intervention benefits, then the problem is likely to worsen over time: there are clear trends favoring the rapid expansion of for-profit funding (2.4-fold increase in last 20 years) and of authors with affiliations to for-profit interests (8-fold increase in last 20 years)[21].

We have recently published an approach to help practitioners avoid being misled by spin[22]. According to this approach, clinicians and users of the literature should:

- Read only methods section and results
- Read abstract reported in evidence-based secondary publications
- Beware of inadequate patients and faulty comparators
- Beware of composite endpoints
- Beware of small treatment effects
- Beware of subgroup analyses

In the article in which we presented these approaches, we provided examples from otherwise high quality RCTs published in prestigious medical journals[22]. In this review, we will restrict our illustrations of spin corrupting the evidence to examples of the use and abuse of composite endpoints.

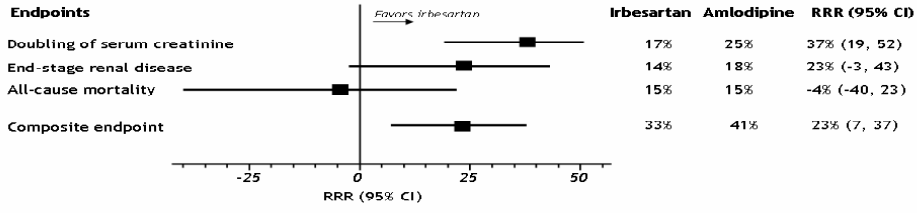
In an RCT of amlodipine and irbesartan for the treatment of hypertension in 1715 diabetic patients with nephropathy followed for 2.6 years,[23] the authors concluded that "treatment with irbesartan was associated with a risk of the primary composite end point that was 23% lower than that in the amlodipine group (P=0.006).[23]" The components of the primary composite endpoint to which the authors refer included doubling of creatinine, onset of end-stage renal disease, or death from any cause. There are three possible interpretations of this result. First, the intervention reduces the risk of each of the three components of the composite outcome by 23%. Second, the intervention reduces the frequency of the composite by 23%, but we cannot comment on its impact on any of the individual components. Third, we could ignore the composite and focus exclusively on results for each component.

A review of the results of the trial (Figure 1) offers insights into what should be the appropriate interpretation. Clearly, the composite endpoint has been dominated by the impact of treatment on the markers of kidney function. The result is misleading in relation to the impact of irbesartan in the risk of death – the best estimate of its effect is a small increase in death rates, the confidence interval tells us the results are consistent with an increase in the risk of dying of up to 40%.

This difference in results between the components of the composite would be

Figure 1– Results of a trial or irbesartan vs. amlodipine in patients with diabetic hypertensive nephropathy

The figure shows the results distributed across each component and the composite endpoint. The squares represent the point estimates of the relative risk reduction (RRR) and the horizontal lines across each box are their 95% confidence intervals (CI). Point estimates to the right of the vertical line favor irbesartan over amlodipine. Confidence intervals crossing the vertical line are considered not statistically significant. Adapted from Lewis et al.[23]



less troubling were there a smaller gradient in the relative importance of the three components: people are far more concerned about the risk of dying than the risk of having their creatinine level increase by a factor of two. Similarly, this large gradient in importance would not be as problematic if the relative risk reduction were similar, and similarly precise, across the components. The likelihood of the result of the composite misleading clinicians and patients becomes a particular concern with the combination of a large gradient in both importance and effect across components[24].

In another study, the Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) trial published in 2006,[25] the authors summarized the trial results this way: "This large, prospective, blinded international clinical trial shows that 8 mg of rosiglitazone daily, together with lifestyle recommendations, substantially reduces the risk of diabetes or death by 60% in individuals at high risk for diabetes". While technically correct given the use of the composite endpoint, the large gradient in patient importance between these two components and the large gradient in events (1.1% vs. 1.3% of patients died; 10.6% vs. 25% of patients developed diabetes) makes this presentation of the trial results very misleading.

We recently completed a systematic review of RCTs in cardiology and found that 112 of 242 trials used composite endpoints to assess the effect of treatments.[26] Of these, 86% had either a large or moderate gradient in patient importance or a large or moderate gradient in treatment effects; 54% had a large or moderate gradient in both. These results suggest a high frequency of potentially misleading composite endpoints within cardiology trials.

The Corruption of the Evidence: Biased Reporting

Practitioners may feel justifiably daunt-

ed by the need to acquire critical appraisal skills to detect the potential for bias and the need to exercise approaches to avoid being misled by spin. Only highly sophisticated and dedicated methodologists may be ready and able to address a recently characterized mechanism of evidence corruption: reporting bias. By reporting bias, we mean the selective or differential reporting of outcomes, or trials, according to their results.[27]

Chan and collaborators studied 102 RCT protocols submitted for ethical review and followed up on their published results (122 reports) up to ten years later.[28] They found that 50% of the outcomes were incompletely reported and that the odds of full reporting were 2:1 if the outcome result was statistically significant. Thus, the consequence of reporting bias is often to give readers an overly enthusiastic impression of an intervention's efficacy and safety.

We recently documented the extent to which reporting bias can introduce a misleadingly sanguine perception of the efficacy of interventions.[29] On average, only half of the eligible trials included in 156 meta-analyses contributed results to these pooled estimates, a proportion consistent with the Chan et al findings. We found an inverse relationship between the proportion of eligible trials that contributed data to the meta-analysis and the magnitude of the pooled treatment effect: for each 10% decrease in the proportion of trials contributing data to a meta-analyses the pooled odds ratio increased by 1.05 (95% confidence interval 1.004, 1.09). The investigators who conducted the systematic reviews failed to highlight the potential impact of selective reporting on their results. These findings illustrate the insidious and deleterious impact of reporting bias.

Another form of reporting bias is publication bias. Publication bias refers to the selective publication of trials according to their results.[30] The consequence of publication bias is that reviewers assessing a body of literature bearing on a clinical question will overestimate the magnitude of treatment effect. The bias may be introduced by not publishing trials that show small, negligible, or unconvincing results, by publishing them in obscure journals or non-English language publications exclusively in abstract form, or delaying their publication.[27] Table 1 describes two cases of apparent publication bias.

The Corruption of the Evidence: Fraud

Extreme examples of biased reporting including suppression of data and partial reporting of trial results have recently emerged and led to allegations of fraud, litigation, and loss of public trust in the scientific and regulatory processes.[31, 32] Scientific misconduct and fraud are inaccessible to the sophisticated evidence-based practitioner who must rely on the same mechanisms (e.g., whistleblowers) as everyone else to discover these corruptions of the evidence base.

Consequences of the corruption of evidence on evidence-based medicine

The corruption of the evidence base includes the lack of protection against bias in the conduct of clinical trials, the use of

Table 1 – Cases of apparent publication bias

Intervention	Publication (impact factor)	Results
Perioperative betablockers		
Poldermans et al[15]	A 112-patient trial published in the New England Journal of Medicine (44.02)	Significant effect (80% reduction) on mortality. This trial was stopped early for benefit.
Subsequent trials published in lower impact journals		
DIPOM trial[40]	A 921-patient trial published in the British Medical Journal (9.05)	Nonsignificant effect (3% reduction) on mortality
POBBLE trial[41]	A 103-patient trial published in the Journal of Vascular Surgery (3.17)	Nonsignificant effect (6% increase) on mortality
MAVS trial[42]	A 496-patient trial published in the American Heart Journal (3.55)	Nonsignificant effect (15% decrease) on mortality
Statins for patients with diabetes		
CARDS trial[43]	A 2838-patient trial completed in 2002 and published in The Lancet (23.87) in 2004	Significant effect (35% reduction) on acute coronary events. This trial was stopped early for benefit.
Subsequent trial completed at about the same time but published much later in a lower impact journal		
ASPEN trial[44]	A 2410-patient trial completed in 2002 and published In Diabetes Care (7.84) in 2006	Nonsignificant effect (27% decrease) on myocardial infarction

spin to mislead the evidence user, biased reporting, and overt fraud. If clinicians and those who guide them in their practice are unable to detect these problems and alert the clinical community to their existence, the result will be the dissemination of inaccurate (and usually inflated) estimates of treatment effect. Apparent evidence-based practice will in fact be based on inaccurate information.

The proliferation of "evidence-based" guidelines and quality improvement programs may further increase the likelihood of the naïve user falling prey to the effects of corrupted evidence. There are recent revelations of orchestrated campaigns that have combined corruptions in the evidence with efforts to directly impact guidelines and programs.[33, 34] Once these programs are in place, the objections di-

rected at questioning the quality of the evidence are often considered academic and irrelevant and are caricatured as symptoms of resistance to change.

To the extent – and this is increasingly the case – that patients access evidence directly, they too may suffer the adverse consequences of corrupted evidence. Newspapers, magazines, and the electronic media all include health stories that often focus on apparent breakthroughs. Use of corrupted evidence in marketing campaigns including direct-to-consumer advertising will influence the patient-consumer. Indeed, one could argue that unless these advertising campaigns include a strong element of spin, those initiating the campaigns are not doing their job.

For some, the extent of the ongoing corruption of the evidence base may mean the end of evidence-based medicine. Many academics may want to seek refuge in a deeper understanding of pathophysiology and pharmacology; practicing clinicians would want to rely heavily on their formal education, their experience, and their intuition. Loss of trust in the research enterprise and lack of skills to appropriately appraise its products could lead many to stop perusing the literature. The paradox is that, aside from fraud, it is the approaches and tools of evidence-based medicine that have uncovered the problems we have described here.

The promise is that advances in evidence-based medicine may ameliorate the negative impact of corruption of evidence on practice. In fact, some specific solutions – currently at different stages of implementation – offer even short term solutions. As mentioned previously, in another publication and in Table 3 of this article, we have offered specific strategies for clinicians to avoid being misled by spin. Clinical trial registration has enjoyed early success thanks to the policies of the medical journals,[35-37] but there is a need for consolidating the existing many trial registries into a few. Major policy changes in the way we generate new knowledge and evaluate new interventions may be necessary to decrease the unfavorable effects of for-profit interests on the design and conduct of clinical trials and on the dissemination of research results. The following represents a list of these initiatives and policy changes:

- Change funding models for clinical trials to create a firewall between for profit interests and the researchers.
- Expand the evidence synthesis enterprise, to search for the available evidence (even in obscure sources), appraise it for bias and spin, remediate to the extent possible reporting and publication bias, and identify new knowledge gaps.
- Promote the measurement of patient important outcomes in clinical trials[38] placing a high value on validity, ease of interpretation, and relevance to patients and a lower value on saving research resources by using surrogate markers of uncertain validity.
- Promote methodological research to generate empirical evidence of bias associated with different research approaches (e.g., stopping trials early for apparent benefit), identify best strategies to detect potential for bias and spin, and to ameliorate the effect of spin on trial conclusions.
- Enforce the prospective registration of clinical trials and clinical trial protocols to detect and minimize reporting

and publication biases.

- Promote the training of new scientists in the conduct of rigorous research with a focus on producing results that will make a difference in practice.
- Promote rigorous, complete, and open reporting of trial results according to state-of-the-art standards (e.g., CONSORT[39]).
- Production of evidence summaries and guidelines free of commercial and personal conflict of interest.

Conclusion

Evidence-based medicine offers guides to use the scientific literature to help achieve optimal clinical practice. Biased research results and misleading presentations of accurate research results may severely undermine the usefulness of evidence-based approaches to practice. Ironically, evidence-based approaches also provide the tools to detect these problems and can make important contributions to their amelioration and, in some cases, resolution.

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