SYNTHESIZING INFORMATION FROM RESEARCH

More than a century ago, the president of the British Association for the Advancement of Science, Lord Rayleigh, commented on the need to set the results of new research in the context of other relevant evidence:

'If, as is sometimes supposed, science consisted in nothing but the laborious accumulation of facts, it would soon come to a standstill, crushed, as it were, under its own weight . . . Two processes are thus at work side by side, the reception of new material and the digestion and assimilation of the old; and as both are essential we may spare ourselves the discussion of their relative importance . . . The work which deserves, but I am afraid does not always receive, the most credit is that in which discovery and explanation go hand in hand, in which not only are new facts presented, but their relation to old ones is pointed out.'

Rayleigh, Lord. In: *Report of the fifty-fourth meeting of the British Association for the Advancement of Science; held at Montreal in August and September 1884*. London: John Murray, 1884: pp3-23.

alongside evidence from the other, similar fair comparisons. Reporting new test results without interpreting them in the light of other relevant evidence, reviewed systematically, can delay identification of both useful and harmful treatments, and lead to unnecessary research.

SYSTEMATIC REVIEWS OF ALL THE RELEVANT, RELIABLE EVIDENCE

Whilst it is easy to state that we should review the results of a particular study alongside other relevant, reliable evidence, this is a challenge in many ways. Reviews are important because people should be able to depend on them, and that means that they must be done systematically, otherwise they will be misleading.

THE IMPORTANCE OF SYSTEMATIC REVIEWS

'Systematic reviews and meta-analyses have become increasingly important in health care. Clinicians read them to keep up to date with their field, and they are often used as a starting point for developing clinical practice guidelines. Granting [funding] agencies may require a systematic review to ensure there is justification for further research, and some health care journals are moving in this direction. As with all research, the value of a systematic review depends on what was done, what was found, and the clarity of reporting. As with other publications, the reporting quality of systematic reviews varies, limiting readers' ability to assess the strengths and weaknesses of those reviews.'

Moher D, Liberati A, Tetzlaff, Altman DG. The PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement (www.equator-network.org), 2009.

Systematic reviews addressing what appears to be the same question about treatments may reach different conclusions. Sometimes this is because the questions addressed are subtly different, or because the methods used by the researchers differed; and sometimes it is because the researchers have introduced 'spin' in their conclusions. So, it is important to identify reviews that address the treatment questions that match those we are interested in; which are most likely to have been prepared in ways that reduce the effects of biases and the play of chance successfully; and which reach honest conclusions, in ways that reflect the evidence presented.

Reducing biases in systematic reviews

Just as biases can distort individual tests of treatments and lead to false conclusions, so they can also distort reviews of evidence. For example, researchers can simply 'cherry pick' those studies which they know will support the treatment claims they wish to make.

To avoid these problems, plans for systematic reviews, as for

individual research studies, should be set out in research protocols. Protocols need to make clear what measures researchers will take to reduce biases and the effects of the play of chance during the process of preparing the reviews. These will include specifying which questions about treatments the review will address; the criteria that make studies eligible for inclusion in the review; the ways in which potentially eligible studies will be identified; and the steps that will be taken to minimize biases in selecting studies for inclusion in the review, and for analysing the data.

Identifying all the relevant evidence for systematic reviews

Identifying all the relevant evidence for systematic reviews – irrespective of the language or format of the relevant reports – always presents a substantial challenge, not least because some relevant evidence has not been reported in public. Under-reporting stems principally from researchers not writing up or submitting reports of their research for publication because they were disappointed with the results. And pharmaceutical companies suppress studies that do not favour their products. Journals, too, have tended to show bias when they reject submitted reports because they deem their results insufficiently 'exciting'.[3]

Biased under-reporting of research is unscientific and unethical, and there is now widespread acceptance that this is a serious problem. In particular, people trying to decide which treatments to use can be misled because studies that have yielded 'disappointing' or 'negative' results are less likely to be reported than others, whereas studies with exciting results are more likely than others to be 'over-reported'.

The extent of under-reporting is astonishing: at least half of all clinical trials are never fully reported. This under-reporting of research is biased and applies to large as well as small clinical trials. One of the measures that has been taken to tackle this problem has been to establish arrangements for registering trials at inception, and encouraging researchers to publish the protocols for their studies.[3]

Biased under-reporting of research can even be lethal. To their great credit, some British researchers decided to report in 1993 the results of a clinical trial that had been done thirteen

MARKETING-BASED MEDICINE

'Internal documents from the pharmaceutical industry suggest that the publicly available evidence base may not accurately represent the underlying data regarding its products. The industry and its associated medical communication firms state that publications in the medical literature primarily serve marketing interests. Suppression and spinning of negative data and ghostwriting [see Chapter 10, p124-5] have emerged as tools to help manage medical journal publications to best suit product sales, while disease mongering and market segmentation of physicians are also used to efficiently maximize profits. We propose that while evidence-based medicine is a noble ideal, marketing-based medicine is the current reality.'

Spielmans GI, Parry PI. *From Evidence-based Medicine to Marketing-based Medicine: Evidence from Internal Industry Documents. Journal of Bioethical Inquiry* 2010;7(1):13-29. Available online: http://tinyurl.com/Spielmans.

years earlier. It concerned a new drug for reducing heart rhythm abnormalities in patients experiencing heart attacks. Nine patients had died after taking the drug, whereas only one had died in the comparison group. 'When we carried out our study in 1980,' they wrote, 'we thought that the increased death rate in the drug group was an effect of chance… The development of the drug [lorcainide] was abandoned for commercial reasons, and this study was therefore never published; it is now a good example of "publication bias". The results described here…might have provided an early warning of trouble ahead'.[4] The 'trouble ahead' to which they were referring was that, at the peak of their use, drugs similar to the one they had tested were causing tens of thousands of premature deaths every year in the USA alone (see Chapter 2, p14-15).[5]

Reducing the play of chance in systematic reviews

In Chapter 7 (p91), we explained how the play of chance can be reduced by combining data from similar but separate studies – a process known as 'meta-analysis'. We used the example of five studies in five different countries organized and funded separately to address a 60-year-old quandary about what blood level of oxygen in prematurely born infants is needed to maximize the likelihood that they will survive with no major disabilities. That example illustrated how this process could be planned *before* the results of the studies were available, but the same process can be used *after* a group of similar studies have been completed.

For example, in 1974 a Swedish doctor conducted a systematic review of studies comparing the results of surgery for breast cancer with or without radiotherapy.[6] He found that, in all of the studies, women were more likely to die in the groups receiving radiotherapy. When all of this evidence was synthesized statistically using meta-analysis, it became clear that this excess mortality was unlikely to reflect the play of chance. Subsequent, more detailed analyses, based on evidence from individual patients, confirmed that the radiotherapy being used during that era did indeed increase mortality.[7] Recognizing this led to the development of safer practices.

Recognizing vested interests and spin in systematic reviews

What if the reviewers have other interests that might affect the conduct or interpretation of their review? Perhaps the reviewers have received money from the company that made the new treatment being tested. When assessing the evidence for an effect of evening primrose oil on eczema, reviewers who were associated with the manufacturer reached far more enthusiastic conclusions about the treatment than those with no such commercial interest (see Chapter 2, p18-20). However, commercial interests are not alone in leading to biased reviews. We all have prejudices that can do this – researchers, health professionals, and patients alike.

Disappointingly, people with vested interests sometimes exploit biases to make treatments look as if they are better than they really are (see also Chapter 10).[8] This happens when some researchers – usually but not always for commercial reasons –

deliberately ignore existing evidence. They design, analyze, and report research to paint their own results for a particular treatment in a favourable light. This is what happened in the 1990s when the manufacturer of the anti-depressant drug Seroxat (paroxetine) withheld important evidence suggesting that, in adolescents, the drug actually increased symptoms that prompted some of these young patients to contemplate suicide as a way of dealing with their depression.[9]

Over-reporting is a problem as well. In a phenomenon known as 'salami slicing', researchers take the results from a single trial (the salami) and slice the results into several reports without making clear that the individual reports are not independent studies. In this way, a single 'positive' trial can appear in several journals in different articles, thereby introducing a bias.[10] Here again, registering trials at inception with unique identifiers for every study will help to reduce the confusion that can result from this practice.

WHAT CAN HAPPEN IF ALL THE RELEVANT, RELIABLE EVIDENCE IS NOT ASSESSED?

Fair tests of treatments involve reviewing systematically all the relevant, reliable evidence, to see what is already known, whether from animal or other laboratory research, from the healthy volunteers on whom new treatments are sometimes tested, or from previous research involving patients. If this step is overlooked, or done badly, the consequences can be serious – patients in general, as well as participants in research, may suffer and sometimes die unnecessarily, and precious resources both for healthcare and for research will be squandered.

Avoidable harm to patients

Recommended treatments for heart attacks that had appeared in textbooks published over a period of 30 years were compared with evidence that could have been taken into account had the authors systematically reviewed the results of fair tests of treatment reported during that time.[11] This comparison showed that the textbook recommendations were often wrong because the authors