10 Research – good, bad and unnecessary

In earlier chapters we emphasized why tests of treatments must be designed properly and addressed questions that matter to patients and the public. When they are, everyone can take pride and satisfaction in the results, even when hoped-for benefits do not materialize, because important insights will have been gained and uncertainty lessened.

Although much health research is good – and it is steadily improving as it conforms with design and reporting standards[1] – bad and unnecessary research continues to be done, and published, for various reasons. And as for the perpetual demand 'more research is needed', a better strategy would be to do less, but to focus the research on the needs of patients, and so help to ensure that it is done for the right reasons. We explore these issues in this chapter.

GOOD RESEARCH

Stroke

Stroke is a leading cause of death and long-term disability. The death rate is between one in six and two in six during a first stroke, rising to four in six for subsequent strokes. One of the underlying causes of stroke is narrowing (stenosis) of the carotid artery, which provides blood to the brain. The fatty material that coats the inside of the carotid artery sometimes breaks away, blocking smaller arterial tributaries, and thus causing a stroke. In the 1950s surgeons began to use an operation known as carotid endarterectomy to remove these fatty deposits. The hope was that

surgery would reduce the risk of stroke. As with any operation, however, there is a risk of complications from the surgical procedure itself.

Although carotid endarterectomy became increasingly popular, it was not until the 1980s that randomized trials were set up to assess the risks and benefits of surgery. Clearly this knowledge would be vitally important for patients and their doctors. Two well-designed trials – one in Europe and the other in North America – were carried out in patients who already had symptoms of carotid artery narrowing (minor stroke or fleeting, stroke-like symptoms) to compare surgery with the best available non-surgical treatment. Several thousand patients took part in these long-term studies. The results, published in the 1990s, showed that surgery can reduce the risk of stroke or death but that benefit depends on the degree of narrowing of the carotid artery. Patients with relatively minor narrowing were, on balance, harmed by surgery, which can itself cause stroke. These important findings had direct implications for clinical practice.[2, 3]

Pre-eclampsia in pregnant women

Another outstanding example of good research concerns pregnant women. Worldwide, about 600,000 women die each year of pregnancy-related complications. Most of these deaths occur in developing countries and many are linked to pregnancy-associated convulsions (fits), a condition known as eclampsia. Eclampsia is a devastating condition that can kill both mother and baby. Women with the predisposing condition – pre-eclampsia (also known as toxaemia) – have high blood pressure and protein in their urine.

In 1995, research showed that injections of magnesium sulphate, a simple and inexpensive drug, could prevent fits *recurring* in women with eclampsia. The same study also showed that magnesium sulphate was better than other anticonvulsant drugs, including a much more expensive one, in stopping convulsions. So, the researchers knew it was important to find out whether magnesium sulphate could prevent convulsions *occurring* in women with pre-eclampsia.

The Magpie trial, designed to answer this question, was a

MY EXPERIENCE OF MAGPIE

'I was really pleased to be part of such an important trial. I developed swelling at 32 weeks which grew progressively more severe until I was finally diagnosed with pre-eclampsia and admitted to hospital at 38 weeks. My baby was delivered by caesarean section and thankfully we both made a complete recovery. Pre-eclampsia is a frightening condition and I really hope the results of the trial will benefit women like me.' Clair Giles, Magpie participant.

MRC News Release. Magnesium sulphate halves risk of eclampsia and can save lives of pregnant women. London: MRC, 31 May 2002.

major achievement, involving more than 10,000 pregnant women with pre-eclampsia in 33 countries around the globe. In addition to normal medical care, half the women received an injection of magnesium sulphate and half a placebo (sham preparation). Magpie gave clear and convincing results. It showed that magnesium sulphate more than halved the chance of convulsions occurring. In addition, although the treatment did not apparently reduce the baby's risk of death, there was evidence that it could reduce the risk of the mother dying. And apart from minor side-effects, magnesium sulphate did not appear to harm the mother or the baby.[4, 5]

HIV infection in children

The results of good research are also making a real difference to children infected with HIV (human immunodeficiency virus), the cause of AIDS. At the end of 2009, figures from UNAIDS (the joint United Nations Programme on HIV/AIDS) show that an estimated 2.5 million children were living with HIV around the world, 2.3 million of them in sub-Saharan Africa. Every hour, around 30 children were dying as a result of AIDS.[6] Bacterial infections, such as pneumonia, which are associated with the children's weakened immune system, are a common cause of death. Co-trimoxazole is a widely available, low-cost antibiotic

that has been used for many years to treat children and adults with chest infections unrelated to AIDS. Studies in adults with HIV additionally showed that the drug reduces other complications from bacterial infections.[7]

When preliminary evidence showed that the infections in children with HIV might also be reduced, a group of British researchers got together with colleagues in Zambia to assess the effects of co-trimoxazole as a possible preventive medicine in a large study. The trial, which started in 2001 and lasted about two years, compared the antibiotic with a placebo in over 500 children. The results became clear sooner than anticipated when it was shown that the drug cut AIDS-related deaths by 43% (74 deaths in the co-trimoxazole group compared with 112 in the placebo group) and also reduced the need for hospital admissions. At this point the independent committee scrutinizing the results recommended that the trial be stopped.

One immediate outcome was that all children in the trial were given co-trimoxazole as part of a Zambian government initiative. A wider consequence was that the World Health Organization and UNICEF promptly altered their advice on medicines for children with HIV.[8, 9]

These organizations continue to recommend co-trimoxazole as an inexpensive, life-saving and safe treatment for such children.[10]

BAD RESEARCH

Psychiatric disorders

Regrettably, research is not always well done or relevant. Take the example of a distressing condition known as tardive dyskinesia. This is a serious side-effect associated with long-term use of drugs called neuroleptics (antipsychotics), which are prescribed for psychiatric disorders, especially schizophrenia. The most prominent features of tardive dyskinesia are repetitive, involuntary movements of the mouth and face – grimacing, lip-smacking, frequent poking out of the tongue, and puckering or blowing out of the cheeks. Sometimes these are accompanied by twitching of the hands and feet. One in five patients taking a neuroleptic for more than three months experiences these side-effects.

In the 1990s a group of researchers began exploring, systematically, what treatments had been used for tardive dyskinesia over the preceding 30 years. Writing in 1996, they were rather surprised to have identified about 500 randomized trials involving 90 different drug treatments. Yet none of these trials had produced any useful data. Some of the trials had included too few patients to give any reliable results; in others the treatments had been given so briefly as to be meaningless.[11]

Members of the same research group went on to publish a comprehensive survey of the content and quality of randomized trials relevant to the treatment of schizophrenia in general. They looked at 2,000 trials and were disappointed in what they found. Over the years, drugs have certainly improved the prospects for people with schizophrenia in some respects. For example, most patients can now live at home or in the community. Yet, even in the 1990s (and still today), most drugs were tested on patients in hospital, so their relevance to outpatient treatment is uncertain. On top of that, the inconsistent way in which outcomes of treatment were assessed was astonishing. The researchers discovered that over 600 treatments – mainly drugs but also psychotherapy, for example – were tested in the trials, yet 640 different scales were used to rate the results and 369 of these were used only once. Comparing outcomes of different trials was therefore severely hampered and the results were virtually uninterpretable by doctors or patients. Among a catalogue of other problems, the researchers identified many studies that were too small or short term to give useful results. And new drug treatments were often compared with inappropriately large doses of a drug that was well known for its side-effects, even when better tolerated treatments were available – an obviously unfair test. The authors of this review concluded that half a century of studies of limited quality, duration, and clinical utility left much scope for well-planned, properly conducted, and competently reported trials.[12]

Epidural analgesia for women in labour

The importance of assessing outcomes that matter to patients is clearly illustrated – in a very negative fashion – by early trials of epidural analgesia given to women for pain relief during labour.

In the 1990s researchers reviewed the experience with controlled trials of epidural versus non-epidural analgesia. They estimated that, despite millions of women having been offered an epidural block over the preceding 20 years, fewer than 600 appeared to have participated in reasonably unbiased comparisons with other forms of pain relief. They identified nine comparison trials that could be confidently analyzed. The comparisons were commonly measured in terms of levels of hormones and other substances believed to reflect stress during labour. Outcomes for the baby were also the focus of some attention. Yet any comparison of the pain reported by the women themselves was absent in all but two of the trials. In other words, those conducting the trials had largely overlooked an outcome that was surely of supreme importance – how effectively a woman's pain had been relieved.[13]

UNNECESSARY RESEARCH

Respiratory distress in premature babies

Some research falls in between good and bad – it is plainly unnecessary. An example of such research concerns premature babies. When babies are born prematurely their lungs may be underdeveloped, with the risk of life-threatening complications such as respiratory distress syndrome. By the early 1980s there was overwhelming evidence that giving a steroid drug to pregnant women at risk of giving birth prematurely reduced the frequency of respiratory distress syndrome and death in newborn babies. Yet over the ensuing decade trials continued to be done in which steroids were compared with a placebo or no treatment. If the results of earlier trials had been reviewed systematically and combined using meta-analysis (see Chapters 7 and 8), it is unlikely that many of the later trials would have been started – the collective evidence would have shown that there was simply no need. These unnecessary studies therefore denied effective treatment to half the participants in these trials.

Stroke

Another example of unnecessary research, yet again because the results of preceding studies had not been gathered together and

analyzed, concerns the treatment of stroke with a drug called nimodipine (one of a group of drugs called calcium antagonists). If it were possible to limit the amount of brain damage in patients who suffer a stroke, their chances of disability should be lessened. Beginning in the 1980s, nimodipine was tested for this purpose in stroke patients after some animal experiments had given encouraging results. Although a clinical trial in stroke patients published in 1988 suggested a beneficial effect, the results of several more clinical trials of nimodipine and other calcium antagonist drugs proved conflicting. When the accumulated evidence of clinical trials involving nearly 8,000 patients was reviewed, systematically, in 1999, no beneficial effect of the drugs was found (see Chapter 8, p102).[14] Since the use of nimodipine was apparently based on sound scientific evidence, how had this come about?

In the light of the results of research in patients, the findings from the animal experiments were scrutinized properly for the first time. Only when the animal studies were reviewed systematically did it become clear that the design of the animal experiments was generally poor and the results were beset by biases and therefore unreliable. In other words, there had been no convincing justification for carrying out trials in stroke patients in the first place.[15]

Aprotinin: effect on bleeding during and after surgery

Research funders, academic institutions, researchers, research ethics committees, and scientific journals are all complicit in unnecessary research (see Chapter 9). As we explained in Chapter 8, and as the first two examples of unnecessary research indicate, new research should not be designed or implemented without first assessing systematically what is known from existing research.

A shocking analysis published in 2005 focused on controlled trials of a drug called aprotinin to reduce bleeding during and after surgery. Aprotinin works. The shocking bit is that, long after strong evidence had accumulated showing that the drug substantially reduces the use of blood transfusion, controlled trials continued to be done.[16] At the time of the analysis, the reports of 64 trials

had been published. Between 1987 and 2002, the proportion of relevant previous reports cited in successive reports of aprotinin trials fell from a high of 33% to only 10% among the most recent reports. Only 7 of 44 subsequent reports referenced the report of the largest trial (which was 28 times larger than the median trial size); and none of the reports referenced systematic reviews of these trials published in 1994 and 1997.

As the authors of the analysis emphasized, science is meant to be cumulative, but many scientists are not accumulating evidence scientifically. Not only are most new studies not designed in the light of systematic reviews of existing evidence but also new evidence is only very rarely reported in the context of updates of those reviews (see Chapter 8).

DISTORTED RESEARCH PRIORITIES

For most of the organizations supporting biomedical research and most of the researchers doing it, their stated aim is straightforward: to contribute information to improve people's health. But how many of the millions of biomedical research reports published every year really do make a useful contribution to this worthy cause?

Questions that are important for patients

Researchers in Bristol decided to pose a fundamental question: 'To what extent are questions of importance to patients with osteoarthritis of the knee and the clinicians looking after them reflected in the research on this condition?'[17] They began by convening four focus groups – of patients, rheumatologists, physiotherapists, and general practitioners, respectively. These groups were unanimous in making clear that they did not want any more trials sponsored by pharmaceutical companies comparing yet another non-steroidal anti-inflammatory drug (the group of drugs that includes, for example, ibuprofen) against a placebo. Instead of drug trials, patients wanted rigorous evaluation of physiotherapy and surgery, and assessment of the educational and coping strategies that might help patients to manage this chronic, disabling, and often painful condition more successfully.

Of course, these forms of treatment and management offer much less scope than drugs for commercial exploitation, and so are often ignored.

How many other fields of therapeutic research would, if evaluated in this way, reveal similar mismatches between the questions about treatment effects that matter to patients and clinicians, and those that researchers are addressing? Regrettably, mismatch appears to be the rule rather than the exception.[18, 19,20, 21]

Minor changes in drug formulation rarely lead to the drugs having substantially new, more useful effects, yet these types of studies dominate research into treatments not only for arthritis but also for other chronic disorders. What a waste of resources!

Who decides what gets studied?

Clearly this situation is unsatisfactory, so how has it come about? One reason is that what gets studied by researchers is distorted by external factors.[22] The pharmaceutical industry, for example, does research for its primary need – to fulfil its overriding responsibility to shareholders to make a profit. Its responsibility to patients and clinicians comes second. Businesses are driven by large markets – such as women wondering whether to use hormone replacement therapy, or people who are depressed, anxious, unhappy, or in pain. Yet only rarely in recent decades has this commercially targeted approach led to important new treatments, even for 'mass market' disorders. Rather, within groups of drugs, industry has usually produced many very similar compounds – so-called 'me-too' drugs. This is reminiscent of the days when the only bread available in supermarkets was endless variations on the white sliced loaf. Hardly surprising, then, that the pharmaceutical industry spends more on marketing than on research.

But how does industry persuade prescribers to use these new products rather than existing, less expensive alternatives? A common strategy is to commission numerous small research projects showing that the new drugs are better than giving nothing at all, while not doing any research to find out whether the new drugs are better than the existing ones. Regrettably, industry has little difficulty in finding doctors who are willing to enrol their patients in this fruitless enterprise. And the same doctors often

IMPACT OF 'ME-TOO' DRUGS IN CANADA

'In British Columbia most (80%) of the increase in drug expenditure between 1996 and 2003 was explained by the use of new, patented drug products that did not offer substantial improvements on less expensive alternatives available before 1990. The rising cost of using these me-too drugs at prices far exceeding those of time tested competitors deserves careful scrutiny. Approaches to drug pricing such as those used in New Zealand may enable savings that could be diverted towards other healthcare needs. For example, $350m (26% of total expenditure on prescription drugs) would have been saved in British Columbia if half of the me-too drugs consumed in 2003 were priced to compete with older alternatives. This saving could pay the fees of more than a thousand new doctors.

Given that the list of top 20 drugs in global sales includes newly patented versions of drugs in long established categories . . . me-too drugs probably dominate spending trends in most developed countries.'

Morgan SG, Bassett KL, Wright JM, *et al*. 'Breakthrough' drugs and growth in expenditure on prescription drugs in Canada. *BMJ* 2005;331:815-6.

end up prescribing the products studied in this way.[23] Moreover, drug licensing authorities often make the problem worse by insisting that new drugs should be compared with placebos, rather than with existing effective treatments.

Another strategy is ghostwriting. This is what happens when a professional writer writes text that is officially credited to someone else. Most people will have come across 'celebrity autobiographies' that have clearly been 'ghosted' in this way. However, ghostwritten material appears in academic publications too – and with potentially worrying consequences. Sometimes the pharmaceutical industry employs communication companies to prepare articles which, unsurprisingly, cast the industry's product in a favourable light. Once the article is ready, an academic is

DOCTORS AND DRUG COMPANIES

'No one knows the total amount provided by drug companies to physicians, but I estimate from the annual reports of the top nine US drug companies that it comes to tens of billions of dollars a year. By such means, the pharmaceutical industry has gained enormous control over how doctors evaluate and use its own products. Its extensive ties to physicians, particularly senior faculty at prestigious medical schools, affect the results of research, the way medicine is practiced, and even the definition of what constitutes a disease.'

Angell M. *Drug companies & doctors: a story of corruption*. New York Review of Books, January 15, 2009.

signed up, for an 'honorarium', to 'author' it. Then the article is submitted for publication. Commentaries are especially popular for this purpose. Industry also targets journal supplements – separately bound publications that, while carrying the name of the parent journal, are often sponsored by industry and tend not to be as rigorously peer-reviewed as the parent journal.[24] Marketing messages created and promoted in ways such as these have led to the benefits of products being oversold and harms being downplayed (see also Chapter 8, p97).

Drug companies also place adverts in medical journals to promote their products. Typically these adverts include references to sources of evidence to back the claims being made. These may be convincing at first glance, but a different picture emerges when the evidence is scrutinized independently. Even when the evidence comes from randomized trials – which those reading the adverts might well assume to be a reliable assessment – all is not as it seems. When researchers analyzed adverts in leading medical journals to see whether the randomized trial evidence stacked up, they found that only 17% of the trials referenced were of good quality, supported the claim being made for the drug in question, and were not sponsored by the drug company itself. And it is known that research sponsored in this way is more likely

DODGY, DEVIOUS, AND DUPED?

Writing a light-hearted article for a Christmas edition of the *British Medical Journal*, two researchers created a spoof company called HARLOT plc to provide a series of services for trial sponsors. For example:

'We can guarantee positive results for the manufacturers of dodgy drugs and devices who are seeking to increase their market shares, for health professional guilds who want to increase the demand for their unnecessary diagnostic and therapeutic services, and for local and national health departments who are seeking to implement irrational and self serving health policies . . . for dodgy "me too" drugs [our E-Zee-Me-Too Protocol team] can guarantee you a positive trial.'

To their astonishment, the authors received some apparently serious inquiries about the amazing HARLOT plc portfolio.

Sackett DL, Oxman AD. HARLOT plc: an amalgamation of the world's two oldest professions. *BMJ* 2003;327:1442-5.

to find a favourable outcome for the company's product.[25, 26]

Commentaries in prestigious medical journals such as *The Lancet*[27] have drawn attention to the perverse incentives now driving some of those involved in clinical research, and the increasingly dubious relationships between universities and industry. A former editor of the *New England Journal of Medicine* asked bluntly 'Is academic medicine for sale?'[28]

Commercial priorities are not the only perverse influences on patterns of biomedical research which ignore the interests of patients. Many people within universities and research funding organizations believe that improvements in health are most likely to stem from attempts to unravel basic mechanisms of disease. So, they do research in laboratories and with animals. Although such basic research is unquestionably needed, there is precious little evidence to support its substantially greater share of funding

ALL IT TAKES IS TO FIND THE GENE

'It's . . . hoped that the genetic revolution will cure every problem known to man. We will be able to locate and replicate the genes that predispose us towards building better housing, eliminating pollution, enduring cancer more bravely, implementing funds for universally available child-care facilities, and agreeing on the location and design of a national sports stadium. Soon, every newborn will be delivered on to a genetically level playing field. The gene that, say, makes girls do better at GCSEs [high school exams] than boys will be identified and removed. The genetic possibilities are endless. . . . So, yes we're entering an uncertain world, but one that holds out certain hope. For whatever the grave moral quandaries the genetic issue throws up, it will one day be possible to isolate the gene that solves them.'

Iannucci A. *The Audacity of Hype*. London: Little, Brown, 2009, pp270-1

than research involving patients.[29, 30] Yet the consequence has been a massive outpouring of laboratory research that has not been properly evaluated to see how relevant it is to patients.

One reason for this distortion is the hype surrounding the hoped-for clinical advances that basic research, especially genetics, might offer (see Chapter 4, p43-44 for genetic tests). Yet, as Sir David Weatherall, a distinguished clinician and genetics researcher, observed in 2011, 'Many of our major killers reflect the action of a large number of genes with small effects, combined with a major input from the physical and social environment. This work is producing valuable information about some disease processes, but it also emphasises the individuality and variability of the underlying mechanisms of diseases. Clearly, the era of personalised medicine based on our genetic makeup is a long way in the future.'[31]

Now, over fifty years after the structure of DNA was discovered, the cacophony of claims about early healthcare benefits of the 'genetic revolution' seems to be diminishing. Reality is starting to set in. One scientist, talking about the potential for genetics to

PSORIASIS PATIENTS POORLY SERVED BY RESEARCH

'Few trials involved comparison of different options or looked at long-term management. The duration of studies is unconvincingly brief in the context of a disease of potentially near life-long chronicity. We seem to know reliably only that our treatments are better than nothing at all. Tellingly, researchers have completely ignored patient experience, views, preferences, or satisfactions.'

R Jobling, Chairman, Psoriasis Association

Jobling R. Therapeutic research into psoriasis: patients' perspectives, priorities and interests. In: Rawlins M, Littlejohns P, eds. *Delivering quality in the NHS 2005.* Abingdon: Radcliffe Publishing Ltd, pp53-56.

result in development of new drugs, commented 'We have moved into an era of realism. . . . genetic aspects have to be looked at in association with other factors including environment and the clinical use of drugs. Just because a drug doesn't work in a patient doesn't indicate genetic variation in response is the cause.'[32] And an editorial in the science journal *Nature*, in an issue celebrating the tenth anniversary of the sequencing of the human genome, noted '. . . there has been some progress, in the form of drugs targeted against specific genetic defects identified in a few types of cancer, for example, and in some rare inherited disorders. But the complexity of post-genome biology has dashed early hopes that this trickle of therapies would become a flood.'[33]

There is simply no way of bypassing responsibly the need for well-designed research in patients to test the therapeutic theories derived from basic research. And, all too often, such theories are never followed through to see if they do have any relevance for patients. More than two decades after researchers identified the genetic defect leading to cystic fibrosis, people with the condition are still asking a fundamental question. When will they see dividends to their health resulting from the discovery?

Even when research may seem relevant to patients, researchers

often appear to overlook patients' concerns when they design their studies. In a telling illustration, lung cancer doctors were asked to put themselves in the position of patients and to consider whether they would consent to participate in each of six lung cancer trials for which they might, as patients, be eligible. Between 36 and 89 per cent of them said that they would *not* participate.[34]

Similarly, in clinical trials in psoriasis – a chronic and disabling skin condition that affects about 125 million people worldwide – patients' interests have been poorly represented.[35, 36] For example, the Psoriasis Association in the UK found that researchers persisted in using a largely discredited scoring system in many studies to assess the effects of various treatments. Among its deficiencies, the scoring system concentrates on measures such as total area of skin affected and thickness of the lesions, whereas patients, not surprisingly, are more troubled by lesions on the face, palms and soles, and genitals.[37]

KEY POINTS

- Unnecessary research is a waste of time, effort, money, and other resources; it is also unethical and potentially harmful to patients
- New research should only proceed if an up-to-date review of earlier research shows that it is necessary, and after it has been registered
- Evidence from new research should be used to update the previous review of all the relevant evidence
- Much research is of poor quality and done for questionable reasons
- There are perverse influences on the research agenda, from both industry and academia
- Questions that matter to patients are often not addressed