

13 Research for the right reasons: blueprint for a better future

Medical research has undoubtedly contributed to better quality of life and increased longevity. Nevertheless, we have illustrated in this book how the existing ‘drivers’ for research – commercial and academic – have not done enough to identify and address patients’ priorities.

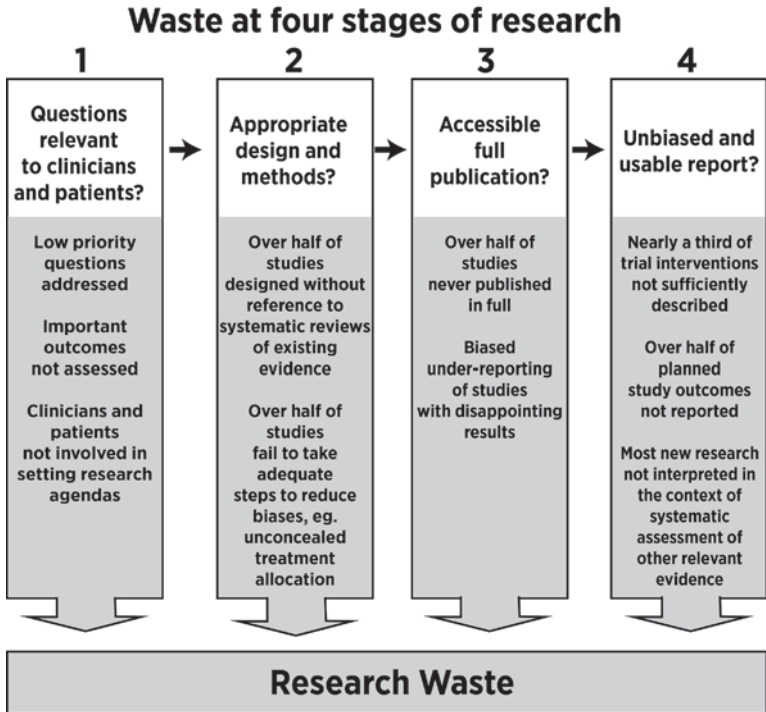
Huge sums of money – over \$100 billion every year worldwide – are spent on funding medical research.¹ However, most of this funding is invested in laboratory and animal studies, rather than in studies that are likely to produce evidence more immediately relevant to patients.

Even when it comes to deciding which questions about the effects of treatments will be studied, patients’ priorities are widely ignored. The drug industry’s financial power means it is very influential in decisions about what gets researched. Because industry can pay handsomely (thousands of pounds/dollars) for each patient recruited to its clinical trials, academics – and the institutions they work in – too often take part in clinical trials that address questions of interest to industry rather than to patients.

Regrettably, much of the money spent on medical research is wasted at successive stages – by asking the wrong research questions; by doing studies that are unnecessary or poorly designed; by failing to publish and make accessible the research results in full; and by producing biased and unhelpful research reports. This should matter to everyone – researchers, research funders, clinicians, tax payers, and above all patients.

Before setting out our blueprint for a better future, we briefly outline why, if research is to be better, it is vitally important to:

1. Ask the right research questions
2. Design and conduct research properly
3. Publish all the results and make them accessible
4. Produce unbiased and useful research reports



How the money spent on medical research is wasted at successive stages.¹

1. Ask the right research questions

Sometimes doctors do not know which treatment is likely to be best for their patients because the available options have not been properly studied. Such studies, which can have important implications for patient care, may be of little or no interest to industry or academia so important questions remain unanswered. And not answering these questions can lead to immense harm. Take one example – whether steroid drugs given to people with brain damage as a result of physical injury increase or decrease their chances of survival. Steroids were used for decades before a well-designed study showed that this established treatment had probably been killing thousands of patients with brain injury.² Proposals for this study were initially opposed by industry

and some university researchers. Why? They were engaged in commercial trials assessing the effects of expensive new drugs (so-called neuroprotective agents) on outcome measures of questionable importance to patients, and they did not wish to face competition for participants.

Another reason for tackling these unanswered questions is to help ensure that the precious resources available for healthcare are not being wasted. When human albumin solution, given as an intravenous drip, was introduced during the 1940s to resuscitate burned and other critically ill patients, theory suggested that it should reduce their chances of dying. Amazingly, this theory was not subjected to fair tests until the 1990s. At that point, a systematic review of the relevant randomized trials could find no evidence that human albumin solution reduced the risk of death compared with simple salt solutions. What the systematic review showed, in fact, was that if albumin had any effect on death risk it was to increase it.³ The findings in this review prompted doctors in Australia and New Zealand to get together to do the first sufficiently large fair comparison of human albumin solution with saline (salt water), an alternative resuscitation fluid.⁴ This study – which should have been done half a century earlier – could find no evidence that albumin was better than salt water. Since albumin is about 20 times more expensive than saline, huge sums of money from healthcare budgets worldwide must have been wasted over the past 50 years or so.

2. Design and conduct research properly

Stimulated by surveys revealing the poor quality of many reports of clinical trials, reporting standards have been developed and applied. Such standards make clear how many patients have been asked to participate in a study and how many declined the invitation. Results are presented according to the various treatment groups selected at the outset. But there is still a long way to go to improve: (a) the choice of questions being addressed in research; (b) the way that these questions are formulated to ensure that the outcomes of treatments chosen for assessment are those that patients regard as important; and (c) the information made available to patients. (See Chapters 11 and 12.)

To see whether a proposed trial might be feasible and acceptable, exploratory work involving groups of patients can be useful. This may highlight shortcomings in the design plans; or help to define outcomes that are more relevant; or even suggest that the concept is a non-starter.^{5, 6}

This can save a lot of time, money, and frustration. The clinical trial in men with localized prostate cancer that we described in Chapter 11 (p140-141) showed how the research design was improved by careful consideration of the terms used by clinicians to describe the trial's purpose and the treatment options. Exploration of patients' views led to an acceptable study because the concerns and information needs of the men being invited to participate had been identified, and the information provided to potential participants took account of these findings.⁷

3. Publish all the results and make them accessible

Selective reporting of the results of research can lead to serious biases. Some 'negative' studies are never published when the results do not match the expectations of the investigators or funders. Without a published report to tell the tale, these trials disappear without trace.⁸ Furthermore, results within published trials may be selectively reported – that is, some of the results are excluded because they are not so 'positive' for the treatment being tested.⁹ Patients have suffered and died because of biased reporting of research on the effects of treatments. This practice is unethical as well as unscientific.

4. Produce unbiased and useful research reports

Even when studies are published, they often omit important elements that enable readers to assess and apply the findings. One review of 519 randomized trials published in reputable journals during December 2000 found that 82% did not describe the process of allocation concealment and 52% did not provide details of measures to reduce observer biases – both features that we suggested in Chapter 6 were crucial to good studies.¹⁰ This poor reporting of details extends even to the description of the treatments used. A trial showing that giving a specific booklet (compared with no booklet) helped patients with irritable bowel

syndrome, omitted to describe the contents of the booklet or how to obtain it; the ‘treatment’ could therefore not be used by any other patients or doctors. This was just one example in an analysis of trials in major journals that found about a third omit such crucial details.¹¹

Finally, most published trials do not set their results in the context of previous similar trials. Without this key step, as we explained in Chapter 8, it is impossible to know what the results actually mean. Four-yearly checks of randomized trials reported in five major medical journals over a period of 12 years – 1997-2009 – illustrate the extent of the problem. Overall, only 25 of 94 (27%) reports made any reference at all to systematic reviews of similar trials. Only 3 of 94 reports actually contained updated reviews integrating the new results, and so showing what difference the new results had made to the totality of evidence. Sadly, there was no evidence of improvement in reporting practice with the passage of time.¹² This failure can lead to clinicians using different treatments depending on which journals they happen to read.

BLUEPRINT FOR A BETTER FUTURE

Medical research *could* be done for the right reasons and could be done and reported well. Taken individually, none of the suggestions that follows is novel. Taken together and promoted jointly by patients and clinicians, our eight action points constitute a blueprint for a better future in the testing and use of treatments.

1. Increase general knowledge about how to judge whether claims about treatment effects are trustworthy

A condition for change is greater public awareness of the ways in which bias and the play of chance can seriously distort evidence about the effects of treatments. One of the most important features of scientific investigation – recognizing and minimizing bias – can hardly be regarded as ‘general knowledge’ at present. We need more determined efforts to reduce these important gaps in understanding, and to make these concepts a routine part of education, from school age onwards.

2. Increase the capacity for preparing, maintaining, and disseminating systematic reviews of research evidence about the effects of treatments

Many of the answers to questions about the effects of treatments can be readily addressed by systematically reviewing evidence that already exists, by keeping such reviews up to date, and by disseminating the results efficiently to professionals and patients. There is a long way to go before the messages from existing evidence are readily available in systematic reviews. Addressing this deficiency should be one of the prime goals of health systems, so that reliable information about the effects of treatments is synthesized and made readily accessible.

3. Encourage honesty when there are uncertainties about the effects of treatments

Admitting uncertainty is often hard for health professionals, and it is sometimes not welcomed by patients. As a result, patients are sometimes given a false sense of security and are not informed about the uncertainties in the evidence. If clinicians and patients are to work together successfully for more efficient assessment of treatment effects, both must be more ready to acknowledge that inadequately evaluated treatments can do substantial harm; they must become more familiar with the methods needed to obtain reliable evidence. We need to find the best ways of making this happen.

4. Identify and prioritize research addressing questions deemed important by patients and clinicians

The portfolios of research funders and academic institutions are dominated by basic research that is unlikely to benefit patients in the foreseeable future, and by research directed at maximizing profits for industry. Applied research into questions that offer no potential to make money, yet matter to patients, has to fight for resources, even when it is publicly supported. We should see to it that more is done to identify what questions patients and clinicians are asking about the effects of treatments, and that research funders take account of them in prioritizing research to reduce these uncertainties.

5. Confront double standards on consent to treatment

Clinicians who are prepared to admit uncertainties about the effects of treatments and address them in formal treatment comparisons are subject to more stringent rules for interacting with patients than are their colleagues who are not. This perverse double standard is illogical and indefensible. When there are uncertainties about treatment effects, participation in randomized trials or other methods of unbiased evaluation should be the norm. We should ensure that participation in research on treatment effects is not presented as a necessarily risky endeavour, implying that 'standard' practice is always effective and safe.

6. Tackle inefficiencies within the research community

Many people are astonished to find that researchers are not required to assess systematically what is known already when they seek funding and ethical approval for new research. The consequence is inevitable – poorly designed and frankly unnecessary research continues on a scale that is unacceptable on ethical as well as scientific grounds. We should press research funders and research ethics committees to ensure that researchers do not embark on new research of any kind without referring to systematic reviews of existing relevant evidence. Reports of new research should begin by referring to systematic reviews showing why the additional research is needed, and end by showing what difference the new results have made to the totality of evidence.

7. Outlaw biased publication practices

To help stamp out biased publication practices steps are needed both when trials begin and when they end. When trials begin they should be registered and the protocols made publicly available for scrutiny. On completion, the results of all trials should be published and the raw data made accessible for scrutiny and further analysis.

8. Demand transparency of information about commercial and other conflicts of interests

There is now substantial evidence that vested financial and other interests sometimes take precedence over the interests of

patients in the design, conduct, analysis, interpretation and use of research. This jeopardizes the mutual trust required to ensure that research serves the interests of patients more effectively. Everyone involved, from commercial companies to patient pressure groups, should be required to be transparent about any vested interests other than the well-being of patients.

Action is needed now

A revolution in testing treatments is long overdue. If professionals and patients act together, the steps that we advocate are eminently practicable. You, the readers, should demand change – now.

AN ACTION PLAN – THINGS YOU CAN DO

Identify questions about the effects of treatment that are important to you.

Learn to recognize uncertainty; speak up; ask questions; seek honest answers.

Don't be afraid to ask your doctor what treatments are available; what may happen if you choose a particular treatment; AND what might happen if you don't.

When thinking about possible treatments, you may find the information on decision aids at www.ohri.ca/DecisionAid helpful. See also: Additional Resources (Do you want to know more about shared decision-making?)

Use reliable websites such as NHS Choices (www.nhs.uk). See: Chapter 12 and the *Additional Resources* section in this book.

Be a healthy sceptic about unfounded claims and media reports of treatment 'breakthroughs'; about the way that 'numbers' are reported in the media – especially large numbers in headline claims!

Challenge treatments offered to you or your family on the basis of beliefs and dogmas, but unsubstantiated by reliable evidence.

Be wary of unnecessary disease 'labelling' and over-investigation (see Chapters 2 and 4) – find out if the disease in question is considered high risk or low risk for you. Ask what would happen if nothing immediate is done.

Agree to participate in a clinical trial only on condition (i) that the study protocol has been registered and made publicly available (ii) that the protocol refers to systematic reviews of existing evidence showing that the trial is justified; and (iii) that you receive a written assurance that the full study results will be published, and sent to all participants who indicate that they wish to receive them.

Encourage and work with health professionals, researchers, research funders, and others who are trying to promote research addressing inadequately answered questions about the effects of treatment which you regard as important.

Encourage wider education about the effects of biases and the play of chance, and lobby your elected political representative and others about doing more to emphasize this in school curricula, beginning in primary schools.