

TESTING TREATMENTS

Chapter 9

9 Regulating tests of treatments: help or hindrance?

By now you will have realized that, all too often, careful evaluations of treatments do not happen and uncertainties about treatment effects persist unnecessarily. Perversely, as we commented in Chapter 5, some prevailing attitudes actively deter health professionals from working with patients to learn more about the effects of treatments. And, strange as it may seem, systems for regulating medical research in most countries contribute to this problem by forcing an artificial split between research and treatment. Research is assumed to be a highly risky activity requiring stringent oversight, whereas routine treatment

WHO SAYS MEDICAL RESEARCH IS BAD FOR YOUR HEALTH

‘Most discussion about the ethics of medical research addresses the question of how research should be regulated. Indeed, medical research is in many ways much more strictly regulated than medical practice. From a perusal of the innumerable guidelines on medical research you could be forgiven for thinking that medical research, like smoking, must be bad for your health.’

Hope T. *Medical ethics: a very short introduction*.
Oxford: Oxford University Press, 2004, p99.

is regarded as much less problematic – even though, as we have described, patients can be put at risk by being given unevaluated or poorly evaluated treatments outside a research context.

Why is research seen as so risky and requiring special regulation, but routine treatment (which affects many more patients) is not? There is no ignoring a history of abuse by researchers, including experiments in which patients were exploited and used as a means to an end. And things do go wrong in research from time to time, so there is an available fund of horror stories. There is always the worry, too, that once people become research participants, their individual interests may become less important to health professionals than the overall interests of research.

The situation is further complicated by the highly variable motives of researchers: while some researchers conduct studies primarily to benefit the public, others are clearly motivated by money, or by enhanced career prospects. And sometimes it may be difficult to judge what the researchers' motives are. Research may therefore appear to be a scary prospect for patients and members of the public. It is partly because of this that there is a high level of regulation of research in healthcare.

Independent committees generally known as Research Ethics Committees (RECs, eg, in Europe) or Institutional Review Boards (IRBs, eg, in the USA) have helped to protect people from abuses perpetrated in the name of research. They review each research project and advise whether it can proceed or not, and play an important part in providing oversight of research and reassuring the public that approved studies have been designed with their interests at heart.

These committees are often made up of unpaid volunteers, including lay people. They review many different kinds of study protocols (the researchers' plans for what they intend to do) and also all the information that will be given to those who might take part in the study. The committees can require researchers to make changes to their protocols or to the information for participants. Without approval of the committees, studies will not go ahead. The committees therefore help to ensure that research participants are not put at unnecessary risk, and reassure participants and the

public that researchers cannot simply do as they like.

Research is subject to many other forms of regulation. Laws specific to research exist in most countries. All countries in the European Union, for example, must comply with the Clinical Trials Directive, which lays out the requirements in relation to so-called 'clinical trials of medicinal products' – essentially this means drug trials. Several countries also operate regulatory systems that affect all or most types of research in healthcare. Many other laws can potentially affect research, even though they were not designed with research as their primary purpose. For example, data protection laws, intended to protect the confidentiality of people's personal data, apply, in many countries, to medical research. A range of different agencies is also usually involved in regulating research in most countries.

The conduct of research is also governed by professional codes of practice and by international statements. Doctors and nurses, for example, are bound by the codes of practice of their professional bodies, and can risk losing their registration or having other sanctions applied if they violate these codes. And international statements, such as the World Medical Association Declaration of Helsinki, are often highly influential in setting standards even when they have no legal force.

DO REGULATORY SYSTEMS FOR TESTING TREATMENTS GET IT RIGHT?

Although the level of regulation can be reassuring, current regulatory systems impose very onerous burdens on anyone wishing to study a poorly evaluated treatment rather than offer it to patients in normal clinical practice. In many countries, the sheer complexity of the system – involving laws, agencies, codes of practice, and so on – is overwhelming and time-consuming. Researchers may need to get multiple approvals from different places, and sometimes have to face resultant contradictory requirements.

Moreover, taken as a whole, the system can seriously discourage and delay the collection of information that would

IN AN IDEAL WORLD

'In an ideal world, wherever possible, we could be gathering anonymised outcome data and comparing this against medication history, making exceptions only for those who put their anxieties about privacy above the lives of others . . . In an ideal world, wherever a patient is given any treatment, and there is genuine uncertainty about which treatment is best, they would be simply and efficiently randomised to one treatment, and their progress monitored. In an ideal world, these notions would be so routinely embedded in our notion of what healthcare looks like that no patient would be bothered by it.'

Goldacre B. Pharmaco-epidemiology would be fascinating enough even if society didn't manage it really really badly. *The Guardian*, 17 July 2010. Available online: www.badsience.net/2010/07/pharmaco-epidemiology-would-be-fascinating-enough-even-if-society-didnt-manage-it-really-really-badly

make healthcare safer for everyone. For example, data protection laws and codes of practice on confidentiality, although introduced with the best of intentions, have made it extremely difficult for researchers to collect routine data from medical records that may help to pinpoint treatment side-effects. And for researchers planning clinical trials, it can take several years to get from a trial idea to recruiting the first patient, and even then recruitment to trials can be slowed by regulatory requirements. But while researchers try to get studies through the system, people suffer unnecessarily and lives are being lost.

In practice, what this means is that clinicians can give unproven treatments to patients, as long as patients consent, if therapies are given within the context of 'routine' clinical practice. By contrast, conducting any study of the same treatments to evaluate them properly would involve going through the protracted regulatory process. So clinicians are discouraged from assessing treatments fairly, and instead can continue to prescribe treatments without committing to

BIASED ETHICS

'If a clinician tries a new therapy with the idea of studying it carefully, evaluating outcomes, and publishing the results, he or she is doing research. The subjects [sic] of such research are thought to be in need of special protection. The protocol must be reviewed by an Institutional Review Board (IRB) [equivalent to a research ethics committee in Europe]. The informed consent form will be carefully scrutinised and the research may be forbidden. On the other hand, a clinician may try this new therapy without any intention of studying it, merely because he believes it will benefit his patients. In that situation, trying the new therapy is not research, the trial does not need IRB approval, and consent may be obtained in a manner governed only by the risk of malpractice litigation.

It would seem that the patients in the second situation (non research) are at much higher risk than are the patients in the first situation (being part of formal clinical research). Furthermore, the physician in the first situation seems more ethically admirable. The physician in the first situation is evaluating the therapy, whereas the physician in the second situation is using the therapy based on his or her imperfect hunches. Nevertheless, because ethical codes that seek to protect patients focus on the goal of creating generalizable knowledge, they regulate the responsible investigator but not the irresponsible adventurer.'

Lantos J. Ethical issues – how can we distinguish clinical research from innovative therapy? *American Journal of Pediatric Hematology/Oncology* 1994;16:72-75.

addressing any uncertainty about them (see Chapter 5).

The regulatory system for research, in its preoccupation with risk and protecting potential research participants, has become over-protective and overlooks the fact that patients and the public are increasingly involved as partners in the research process (see Chapter 11). However, there is one encouraging note. Research regulators are beginning to acknowledge that

the ‘one-size-fits-all’ approach to research ethics review may be unnecessarily burdensome.¹ In the UK, for example, procedures for ‘proportionate review’ are now being evaluated to see whether a simplified and swifter review process can be safely used for research studies that do not raise any material ethical issues.

INFORMATION AND CONSENT

Requirements relating to provision of information and consent for studies are one of the ways in which the regulatory system acts to discourage rather than encourage research to address uncertainties about treatments. It is important – and ethical – to consider the interests of *everyone* currently receiving treatment, not just the few who participate in controlled trials.² The standard for informed consent to treatment should therefore be the same whether people are being offered treatment within or outside the context of formal treatment assessments. To come to a decision that accords with their values and preferences, patients should have as much information as they want, and at a time that they want it.

When treatment is being offered or prescribed in day-to-day practice, it is accepted that people may have different individual preferences and requirements, which may change over time. It is also recognized that people may vary not only in the amount or type of information they want, but also in their ability to understand all the information in the time available, and in their degree of anxiety

RETHINKING INFORMED CONSENT

‘[Some] have come to suspect that informed consent is not fundamental to good biomedical practice, and . . . attempts to make it so are neither necessary nor achievable. We hope that the juggernaut of informed consent requirements that has been constructed across the last fifty years will be reformed and reduced within a far shorter period.’

Manson NC, O’Neill O. *Rethinking informed consent in bioethics*. Cambridge: Cambridge University Press, 2007, p200.

and fear. Health professionals are encouraged to help patients make choices about treatment in ways that are responsive and sensitive to what each individual wants at a particular time.

In research, however, provision of information to potential participants is overseen by regulatory agencies which often insist on the fullest possible disclosure of all potentially relevant information at the time that people are being invited to take part in studies. This may needlessly upset, frustrate, or frighten those who prefer to 'leave it to the doctor', or may raise needless concerns.³

The clinical trial of caffeine in premature babies that we mentioned in Chapter 5 (p57-58) provides a vivid illustration of how harm can be done by insisting that the fullest possible information be given to people who are candidates for research studies. The caffeine study recruited over 2,000 premature infants worldwide, but it took a year longer than expected because recruitment to the trial was slow. Recruitment was particularly

A COMMONSENSE APPROACH TO INFORMED CONSENT IN GOOD MEDICAL PRACTICE

'What is missing in the debate surrounding informed consent is the true nature of patient understanding, what information patients want to know, and how to deal with patients who wish to know only the minimum. There is little work in the area of assessing the understanding of the information given to patients. Clinicians often find it difficult to be certain how much patients or their relatives have correctly understood the information given to them. Understanding is affected by who is giving them the information, how it is explained, and the time or environment required to assimilate information. A paternalistic approach is unacceptable in medical practice; a common sense approach – explaining things clearly, tailoring what is said to what the patient seems to want, and checking understanding – is required for good medical practice.'

Gill R. How to seek consent and gain understanding. *BMJ* 2010;341:c4000.

slow in the UK, where several centres pulled out of the trial owing to regulatory delays in the approval process. On top of that, the research ethics committee insisted on parents being told that caffeine could cause fits in babies – when this complication had only been seen after a ten-fold overdose. So parents were being confronted by apparently frightening information that they probably did not need, and probably would not have been given if caffeine were to be used as part of routine treatment.

There is little evidence that widely promoted forms of research regulation do more good than harm.⁴ Indeed, what evidence there is, is very disturbing. For example, in studies assessing the effects of treatments that have to be given without delay, requiring that the ‘ritual’ of written informed consent be observed can result in avoidable deaths as well as underestimates of the effects of treatments.⁵

Obtaining consent is a public health intervention which can do more harm than good. Like other well-intentioned interventions, its effects should be evaluated rigorously. The lethal consequences we have described might have been identified decades ago had the research ethics community accepted a responsibility to provide robust evidence showing that its ‘prescriptions’ are likely to do more good than harm.

A flexible approach to providing information for potential research participants, recognizing that trust between clinician and patient is the bedrock of any satisfactory consultation, is better than a rigid, standardized approach. But because of the way that regulatory systems intervene in research, clinicians are not currently free to choose how to explain research studies to patients. Moreover, they often find it difficult to talk about the uncertainties inherent in research. For example, as we mentioned in Chapter 5, clinicians recruiting patients to clinical trials often feel uncomfortable saying ‘I don’t know which treatment is best’ and patients often do not want to hear it. Both doctors and patients therefore need a better appreciation of uncertainties and a better understanding of why research is needed (see Chapter 11).

ACADEMIC NICETY – OR SENSIBLE CHOICE?

‘Twelve years ago I crossed the line between clinician and patient when, at the age of 33 years, I found out that I had breast cancer. At the time, I was doing a PhD about the problems of using randomised controlled trials (RCTs) to assess the effectiveness of treatments in my own discipline (orthodontics). During my research, I had become aware of the benefits of taking part in clinical trials and, ironically, the uncertainties about treating younger women with early breast cancer. So at the time of my diagnosis I asked my consultant if there were any RCTs that I could take part in. His response shocked me. He said that I “must not let academic niceties get in the way of the best treatment for me”. But what was the best treatment? I certainly didn’t know and also recognised that the profession was questioning what the optimum treatment was for early breast cancer in women younger than 50 years. So what was I to do?’

Harrison J. Testing times for clinical research. *Lancet* 2006;368:909-10.

WHAT REGULATORY SYSTEMS DO NOT DO

Although regulatory systems for research impose onerous requirements on researchers before studies start, there are many things they conspicuously fail to do, or do not do well. Many systems do not do enough to ensure that proposed studies are actually needed – for example, they do not require researchers to demonstrate that they have undertaken a thorough review of the existing evidence before embarking on new studies (see Chapter 8 for why systematic reviews are so important).

Moreover, most of the effort in regulating research is at the start-up stage, with the emphasis on controlling the entry of participants to studies. But there is surprisingly little effort devoted to monitoring studies once they are running, and to ensuring that researchers publish reports promptly at the end of their work (or even at all), stating how their findings have reduced uncertainty.

WHAT RESEARCH REGULATION SHOULD DO

'If ethicists and others want something to criticise in clinical trials, they should look at scientifically inadequate work, reinvention of wheels, and above all, unjustifiable exclusions and unjust and irrational uses of resources. The present debate is flawed by a failure to take note of what trials are for – to make sure that the treatments we use are safe, and do what they do better than the alternatives. There are no short cuts in ethics – no more than in trials.'

Ashcroft R. Giving medicine a fair trial. *BMJ* 2000;320:1686.

People who are invited to participate in research on the effects of treatments need to have confidence that the studies are worthwhile, and that their contributions will be useful. Regulatory systems need to do more to reassure them on both counts and dismantle needless barriers to good research directed towards research questions that matter to patients. There is a growing realization that testing treatments is everybody's business. As patients and the public take up the opportunities now being offered to become involved in planning and conducting research (see Chapter 11), they are likely to have an increasing voice in ensuring that regulatory obstacles are addressed.

KEY POINTS

- Regulation of research is unnecessarily complex
- Current systems of research regulation discourage fair tests of treatments that would make for better healthcare
- Despite the onerous regulatory requirements placed on researchers, regulatory systems do little to ensure that proposed studies are genuinely needed
- Research regulation does little to monitor and follow-up approved research