11 Getting the right research done is everybody's business

In the preceding chapters we have shown how much time, money, and effort can be wasted in doing bad or unnecessary research into the effects of treatments – research that does not, and never will, answer questions that matter to patients. We hope we have convinced you that better testing of treatments in the future should come from productive partnerships between patients, clinicians, the public, and researchers.

HOW CAN PATIENTS AND THE PUBLIC HELP TO IMPROVE RESEARCH?

The formerly closed world of medicine is increasingly opening its doors to admit fresh ideas and former 'outsiders', and paternalism is steadily diminishing. As a result, patients and the public are contributing more and more to the conduct of healthcare research – both what is researched and how studies are undertaken.[1] Worldwide, there is growing support for collaborating with patients as partners in the research process, and useful guidance is now available for professionals who wish to involve patients and the public.[2,3,4]

Patients have experience that can enhance deliberations and provide insights. Their first-hand knowledge can shed valuable light on the way in which people react to illness and how this affects choice of treatments. Accumulating evidence from questionnaire surveys;[5] systematic reviews of research reports;[1]

PATIENTS' CHOICE: DAVID AND GOLIATH

'Who has the power to see that research questions actually address the greatest needs of patients in all their misery and diversity? Why aren't the most relevant questions being asked? Who is currently setting the questions? Who should be? Who shall direct this prioritisation? Patients are best able to identify the health topics most relevant to them and to inform their comfort, care, and quality of life, as well as its quantity. The patients are the David, who must load their slings against the Goliaths of the pharmaceutical companies who need evidence to market goods and make profits, and trialists who are driven by curiosity, the need to secure research money, professional acclaim, and career development. Profit, scientific inquiry, grant money, and research papers are acceptable only if the central motivation is the good of patients. Independent patients and organisations that advocate good quality research should ready their sling, carefully choose their stone, take aim, and conquer.'

Refractor. Patients' choice: David and Goliath. *Lancet* 2001;358:768.

reports of individual trials;[6] and impact assessments[7] shows that involvement of patients and the public can contribute to improving tests of treatments.

Among many initiatives, the Cochrane Collaboration (www.cochrane.org), an international network of people who review, systematically, the best available evidence about treatments, has embraced the input of patients from its inception in 1993. The James Lind Alliance (www.lindalliance.org), established in 2004, brings together patients, carers, and clinicians to identify and prioritize those unanswered questions about the effects of treatments that they agree are most important. This information about treatment uncertainties helps to ensure that those who fund healthcare research know what matters most to patients and clinicians.[8] Beginning in 2008, the European Commission

A KEY PARTNERSHIP

'People-focused research in the NHS simply cannot be delivered without the involvement of patients and the public.

No matter how complicated the research, or how brilliant the researcher, patients and the public always offer unique, invaluable insights. Their advice when designing, implementing and evaluating research invariably makes studies more effective, more credible and often more cost effective as well.'

Professor Dame Sally Davies. Foreword to Staley K. *Exploring impact: public involvement in NHS, public health and social care research*. Eastleigh: INVOLVE, 2009. Available from: www.invo.org.uk.

funded a project to promote the role of patient organizations in clinical trials with the aim of pooling experience among European countries through workshops, reports, and other exchanges.[9] In other countries, too, there is active public representation in research activities generally.

Roles are continually evolving[10] in various ways, enabling patients and the public to work together with health professionals, and new methods of doing so are being developed (see below *Bridging the gap between patients and researchers*, and Chapter 13, point 2, *Design and conduct research properly*).[11] This is happening across the whole spectrum of research activities:

- formulation of questions to be addressed
- design of projects, including selecting which outcomes are important
- project management
- development of patient information leaflets
- analysis and interpretation of results, and
- dissemination and implementation of findings to inform treatment choices.

INVOLVING PATIENTS IN RESEARCH

How has this involvement of patients in research come about? In Chapter 3 we showed, for example, how the treatment excesses formerly imposed on women with breast cancer led to challenges and changes, both from a new breed of clinician-researchers and then from patients. Clinicians and patients collaborated to secure the research evidence that met both rigorous scientific standards and the needs of women. When women challenged the practice of radical mastectomy they signalled that they were concerned about more than eradication of cancer: they demanded a say in the tactics employed to identify effective ways of dealing with the disease.

For those patients and members of the public who want to become fully involved as co-researchers, there are several possible avenues. For example, they can be involved individually or as a member of a health/disease support group, or they may participate in a facilitated group activity such as a focus group. Irrespective of the mechanism of their involvement, it will certainly help if they become familiar with the nuts and bolts of research methodologies so that they can contribute confidently and effectively in partnership with health professionals. And for this they will require good-quality information and training relevant to their role. We go on to explain in Chapter 12 why the way in which this information is presented, especially in terms of statistics, is critically important to proper understanding. There are also many less prominent ways in which patients and the public can contribute to research efforts, particularly if we can develop a culture of collaboration which accepts insights and observations from a patient's viewpoint.

Today's active patient-researchers can look back thankfully to the pioneering activity of early 'patient pioneers' who realized that they should speak up and challenge the status quo – and that to do so they needed accurate information. For example, in the USA in the early 1970s, a small group of breast cancer patients, led by Rose Kushner, set about educating themselves so that they could become effective. Then they started to educate others. Kushner was a breast cancer patient and freelance writer who, in the

LAY PEOPLE HELP TO RETHINK AIDS

'Credibility struggles in the AIDS arena have been multilateral: they have involved an unusually wide range of players. And the interventions of lay people in the proclamation and evaluation of scientific claims have helped shape what is believed to be known about AIDS – just as they have made problematic our understanding of who is a "layperson" and who is an "expert". At stake at every moment has been whether specific knowledge claims or spokespersons are credible. But at a deeper level, the stakes have involved the very mechanisms for the assessment of credibility: how are scientific claims adjudicated, and who gets to decide? [As this study shows,] debates *within* science are simultaneously debates *about* science and how it should be done – or who should be doing it.'

Epstein S. *Impure science: AIDS, activism and the politics of knowledge*. London: University of California Press, 1996.

early 1970s, challenged the traditional authoritarian physician-patient relationship and the need for radical surgery.[12] She wrote a book based on her thorough review of evidence of the effects of radical mastectomy. By the end of the decade, her influence and acceptability were such that she worked with the US National Cancer Institute reviewing proposals for new research.[13] Similarly, in the UK, lack of information prompted women to take action. For example, Betty Westgate set up the Mastectomy Association in the 1970s, and in the 1980s Vicky Clement-Jones founded the charity CancerBACUP (now part of Macmillan Cancer Support).

People with HIV/AIDS in the USA in the late 1980s were exceptionally knowledgeable about their disease. They were politically geared to defend their interests against the establishment, paving the way for patients to participate in the design of studies. This involvement ultimately led to a choice of treatment options being offered to patients in the studies and flexible designs to encourage participation. This example was

followed in the early 1990s in the UK when an AIDS patient group was involved in studies at the Chelsea and Westminster Hospital, London: the patients helped to design studies.[14]

These AIDS activists made researchers sit up: what some researchers had viewed as havoc caused by organized patient groups was in fact a legitimate challenge to the researchers' interpretation of uncertainty. Until then, the researchers' approach had overlooked the patients' preferred outcomes. On the other hand, patients came to appreciate the dangers of making hasty judgements about the effects of new drugs and of demanding release of a 'promising' new AIDS drug before it had been evaluated rigorously. The researchers may have remonstrated that 'compassionate release' of new drugs in this way had merely prolonged the agony of uncertainty for current and future patients. However, the patients countered that it ultimately hastened the understanding of both patients and researchers about the need for unhurried, controlled evaluations of treatments, designed jointly, and taking account of the needs of both parties.[15]

In the 1990s, one AIDS trial provided a particularly clear illustration of the importance of patient involvement in research. This was at a time when the drug zidovudine had recently been introduced for the treatment of AIDS. In patients with advanced disease there was good evidence of a beneficial effect. The obvious next question was whether use of zidovudine earlier in the course of infection might delay disease progression and further improve survival. So, trials were begun in both the USA and Europe to test this possibility. The US trial was stopped early when a possible but still uncertain beneficial effect was found. With active participation and the agreement of patient representatives, and despite the US results, the European trial continued to a clear endpoint. The conclusions were very different: zidovudine used early in the course of infection did not appear to confer any benefit. The only clear effects of the drug in these circumstances were its unwanted side-effects.[16]

HOW PATIENTS CAN JEOPARDIZE FAIR TESTS OF TREATMENTS

Involving patients in research is not always helpful in promoting fair tests of treatments. A survey of researchers in 2001 revealed some very positive experiences resulting from involving patients in clinical trials but it also laid bare some very real problems. These mostly resulted from everyone's lack of experience of this type of collaboration. First, there were often substantial delays in initiating research. There were also concerns about conflicting interests and 'representativeness' of some patients who had not yet appreciated the need to avoid bringing only their own interests to trial management meetings.[5]

Many of these problems seemed to arise from patients' understandable lack of knowledge about how research is done and funded. Desperate circumstances sometimes provoke desperate efforts to access treatments that have not been adequately evaluated and may do more harm than good, even to patients who are dying. We have already referred to the way that lobbying by patients and their advocates for 'compassionate' release of 'promising' new drug treatments for AIDS had its downside: it delayed the identification of treatments directed at outcomes that mattered to patients. More recently, counterproductive and misinformed advocacy, by both individuals and patient groups, has affected the prescribing of drugs for multiple sclerosis and breast cancer.

In the mid-1990s, interferons were introduced to treat patients with the relapsing-remitting form of multiple sclerosis on the basis of scant evidence of benefit. Very quickly, patients with all forms of multiple sclerosis clamoured for these costly drugs, and healthcare services agreed to fund their use. Interferons became an accepted standard treatment for this debilitating disease. As a result, we will never know how to give interferons appropriately in multiple sclerosis – the research was never done and it is now too late to turn the clock back. However, with the passage of time one thing has become abundantly clear – interferons have nasty side-effects, such as 'flu-like' symptoms.

Herceptin (trastuzumab), as we explained in Chapter 1, p9-12, is not a wonder drug for all women with breast cancer. Firstly,

PESTER POWER AND NEW DRUGS

'New drugs by their very nature are incomplete products, as full information about their safety, effectiveness and impact on costs are [sic] not yet available.

It is worth noting that enthusiastic support for what is "new" is not the sole preserve of newspapers and can often easily be seen in other media outlets and among the medical and scientific communities.

"Pester power" is a concept normally associated with advertising aimed at children. The question to be asked in this context is, are we witnessing patient pester power or quasi direct-to-consumer advertising, where awareness is raised about new products and patients, charities and indeed clinicians then demand that these products be made available? If this is the case, we need to know more about who is driving this type of marketing, its actual impact on clinician and consumer behaviours and whether it is permitted within the existing regulatory code of practice.'

Wilson PM, Booth AM, Eastwood A et al. Deconstructing media coverage of trastuzumab (Herceptin): an analysis of national newspaper coverage. *Journal of the Royal Society of Medicine* 2008:101:125-32

its effectiveness depends on a particular genetic make-up of the tumour, which is present in only 1 in 5 women with breast cancer. On top of that, the drug has potentially serious side-effects on the heart. Yet patient advocacy, fuelling a media frenzy, led politicians to go with the flow of public opinion: use of Herceptin was officially endorsed with scant regard for the existing evidence or acknowledgement that further evidence concerning the balance of benefits and harms was still awaited.

Patients' organizations: independent voices or not?

Another less well known conflict of interest exists in the relationship between patients' organizations and the

INVOLVING CITIZENS TO IMPROVE HEALTHCARE

'The confluence of interest between advocacy groups, those who sell treatments, and those who prescribe them makes for a potent cocktail of influence, almost always pushing policy makers in one direction: more tests, more procedures, more beds, more pills. . .

As someone reporting in this field for more than a decade, I sense that what's often missing from the debate is a voice genuinely representing the public interest. Sponsored advocacy groups are quick to celebrate a new treatment or technology but slow to publicly criticise its limited effectiveness, excessive cost, or downright danger. And, like many journalists, politicians tend to be unnecessarily intimidated by senior health professionals and passionate advocates, who too often lend their credibility to marketing campaigns that widen disease definitions and promote the most expensive solutions.

The emergence of new citizens' lobbies within healthcare, well versed in the way scientific evidence can be used and misused, may produce a more informed debate about spending priorities. Such citizens' groups could routinely expose misleading marketing in the media and offer the public and policy makers realistic and sophisticated assessments of the risks, benefits, and costs of a much broader range of health strategies.'

Moynihan R. Power to the people. *BMJ* 2011;342:d2002.

pharmaceutical industry. Most patients' organizations have very little money, rely on volunteers, and get little independent funding. Grants from and joint projects with pharmaceutical companies can help them grow and be more influential, but can also distort and misrepresent patients' agendas, including their

research agendas. The scale of this problem is difficult to gauge but a fascinating insight comes from a survey done to assess the level of corporate sponsorship of patient and consumer organizations working with the European Medicines Agency. This Agency coordinates the evaluation and monitoring of new drugs throughout Europe and, to its credit, has actively involved patient and consumer groups in its regulatory activities. However, when 23 such groups were surveyed between 2006 and 2008, 15 were shown to receive partial or significant funding from medicines manufacturers or pharmaceutical industry associations. Moreover, fewer than half of the groups accurately identified to the Agency the source or amount of funding that they received.[17]

In some cases patient organizations have been set up by drug companies to lobby on behalf of their products. For instance, one of the companies that makes interferon formed a new patient group 'Action for Access' in an attempt to get the UK National Health Service to provide interferons for multiple sclerosis (see above).[18,19] The message heard by patient groups from all of this publicity was that interferons were effective but too expensive, when the real issue was whether the drugs had any useful effects.

Bridging the gap between patients and researchers

We drew attention above to problems that can result from patients becoming involved in testing treatments, and ways in which they may unintentionally jeopardize fair tests. As with most things, good intentions do not guarantee that more good than harm will be done. Nevertheless, there are clear examples of the benefits of researchers and patients working together to improve the relevance and design of research. As a result, many researchers actively seek patients with whom they can collaborate.

In an example of the value of collaborative preparatory work, researchers explored with patients and potential patients some of the difficult issues involved in testing treatments given in an emergency. If therapies for acute stroke are to succeed, they need to be started as soon as possible after the stroke occurs. Because they were unsure of the best way to proceed, the researchers asked patients and carers to help them. They convened an exploratory meeting with a group of patients and health professionals, and

conducted focus groups involving older people. As a result, plans for the trial were clarified and patients helped the researchers to draft and revise trial information leaflets.[20]

This thorough preliminary research led to plans for a randomized trial which were endorsed promptly by the research ethics committee. The focus group participants had recognized the ethical dilemmas of trying to obtain informed consent from someone with an acute illness which may well have left them confused, or unable to communicate, even if not unconscious. They were able to suggest solutions that led to an acceptable trial design for all parties, and substantial improvements in the information leaflets.

Social scientists are increasingly involved as members of research teams to formally explore sensitive aspects of illness with patients and so improve the way in which trials are done. For a clinical trial in men with localized prostate cancer, researchers wanted to compare three very different treatments – surgery, radiotherapy, or 'watchful waiting' – and this presented difficulties both for clinicians offering the trial and for patients trying to decide whether to participate in it. Clinicians so disliked describing the 'watchful waiting' option that they had been leaving it to last, and describing it less than confidently because they had mistakenly thought the men asked to join the trial might find it unacceptable. Social scientists were asked to study the issue of acceptability to help determine whether the trial was really feasible.

The social scientists' results were a revelation.[21] They showed that a trial offering 'watchful waiting' would be an acceptable third option if described as 'active monitoring', if not left until last to be explained by the doctor when inviting the patient, and if the doctors were careful to describe active monitoring in terms that men could understand.

The research, bridging the gap between doctors and patients, had identified the particular problems that were presenting difficulties for both parties and that could easily be remedied by better presentation of the treatment options. One result was that the rate of acceptance of men invited to join the trial increased over time, from four acceptances in ten to seven in ten. This more

rapid recruitment meant that the effect of all these treatments for men with localized prostate cancer would become apparent earlier than would have been the case if the preparatory work had not been done. And, because prostate cancer is a common disease, many men stand to benefit in the future, earlier than they might have done.

WORKING COLLABORATIVELY BODES WELL FOR THE FUTURE

There are numerous ways in which patients and the public can become involved in testing treatments. As we have already outlined, they may be the prime movers – the ones who identify the gaps in understanding and the need to find new ways of doing things. Their input may be facilitated by researchers; they may be involved in some stages of the work but not others; they may be involved from the moment of identification of a specific uncertainty that needs addressing through to dissemination and implementation, and incorporation of the project's findings in an updated systematic review; and they may be involved in different ways within one project. Sometimes they initiate the work themselves. There is no hard and fast rule: the appropriateness of different strategies and approaches in a particular study will dictate those strategies chosen. As the localized prostate cancer trial described above illustrates, methods are evolving all the time – even within the course of a project.

When patients and researchers work together they offer a powerful combination for reducing treatment uncertainties for the benefit of all. Various methods for enabling this joint working, suited to individual studies as appropriate, with endorsement and support from national research organizations, bode well for the future.

KEY POINTS

- Patients and researchers working together can help to identify and reduce treatment uncertainties
- Input from patients can lead to better research
- Patients sometimes inadvertently jeopardize fair tests of treatments
- Relationships between patients' organizations and the pharmaceutical industry can result in distorted information about treatment effects
- To contribute effectively, patients need better general knowledge about research and readier access to impartial information
- There is no one 'right way' of achieving collaborative participation in research
- Patient participation should be appropriate for the specific research purpose
- Methods of involving patients are continually evolving