Is the NHS willing to help clinicians and patients reduce uncertainties about the effects of treatments?

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ABSTRACT – Uncertainty is an inevitable component of clinical practice. Clinicians have a responsibility to minimise it by keeping up-to-date with current knowledge: but what is the responsibility of individual clinicians in reducing collective uncertainty? In all fields of medicine there are important questions relevant to both patients and clinicians, which can be answered only by clinical research. Unfortunately, much of the clinical research that attracts funding does not address the questions that both patients and clinicians regard as important. Furthermore, although the NHS has a proud record of innovation and clinical research, recent changes are jeopardising the ability and willingness of NHS clinicians to continue undertaking such work. A combination of increased bureaucracy in obtaining research ethics and local research and development (R&D) governance approval and the pressures on management to deliver service targets threaten to strangle research by NHS clinicians. Policy makers argue for informed patient choice, modernisation and improved quality. It is not in the interest of patients when research designed to address important therapeutic uncertainties is seen as an optional extra, rather than an intrinsic element of a health service interested in improving quality. The NHS needs to listen to its users, ie the patients, and to its clinical staff, and to encourage them to engage in research to help reduce those uncertainties.

KEY WORDS: health policy, NHS clinical research, patient involvement, psoriasis, uncertainty

The importance of addressing uncertainties about the effects of treatments

Clinicians and patients have to deal with several kinds of uncertainties when selecting treatments from among alternatives. Sometimes they are uncertain because they are unaware of the strength of existing evidence from research, as was the case for many years with thrombolysis in acute myocardial infarction.[1] Even if clinicians and patients are aware of relevant evidence, however, there will almost always be residual uncertainty about whether a treatment known to be helpful on average will help an individual patient: a patient's sensitivity to aspirin, for example, may preclude use of the drug to reduce the risk of cardiovascular disease.

Sometimes, a search for reliable evidence about the relative merits of different treatment options will make clear that no such evidence exists – a situation of 'certain uncertainty'. Choices among treatment options in these circumstances may sometimes be driven by strong patient preferences, for example, to avoid surgery. But what are the responsibilities of clinicians when patients have no strong preferences and little or nothing is known about the relative merits and disadvantages of different treatment options?[2]

Clinical practice would become impossible if clinicians tried to deal with all such 'informed uncertainties', and often little harm to patients will result from not doing so. However, acquiescence in 'informed uncertainty' sometimes results in avoidable suffering and death on a wide scale. For example, for over 30 years there has been uncertainty about whether systemic corticosteroids help patients with acute traumatic brain injury. This collective uncertainty has been reflected in variations in practice,[3] and the reason for these variations was made explicit when a Cochrane review showed that the evidence from controlled trials left doubt about whether steroids increased or decreased mortality after acute brain injury.[4] This systematic review prompted a large controlled trial of steroids in acute brain injury, which demonstrated convincingly that steroids were associated with increased mortality.[5] These findings implied that many thousands of patients have died unnecessarily because this particular therapeutic uncertainty had not been addressed decades ago.[6]

So what should responsible clinicians do when there are important uncertainties about the effects of treatments? The General Medical Council's booklet, *Good medical practice,* currently provides no clear guidance.[7] Indeed, the responsibilities of clinicians faced with informed uncertainty seems not to have received serious attention among medical ethicists and educators, nor among those who write about and develop policies intended to improve the quality of

care offered to people using the NHS. Because the issue is of such obvious importance, the recent decision by the College's Committee on Ethical Aspects of Medicine (2004) to tackle this issue is extremely welcome. The Committee recognised that questions relating to judgement in the context of uncertainty lay at the heart of the definition of a profession, and thus are of relevance to the College's Working Party on Professionalism.

In their discussion of uncertainty about the effects of treatments, members of the College's Committee on Ethical Aspects of Medicine identified three important strands:

(1) how the profession as a body could cope with uncertainty, and how coping strategies could be built into training and into the professional ethos
(2) the way in which uncertainty could be dealt with in the patient/doctor relationship
(3) systematic approaches to the reduction of uncertainty through research.[8]

It is this last strand – research as a strategy for dealing with uncertainty – that we wish to consider in this paper.

Confronting therapeutic uncertainties through research within the NHS

Ever since the inception of the NHS, consultants and junior clinicians working within the service have made important contributions as researchers. Their clinical research, sometimes combined with laboratory investigations, has occasionally led to important advances in understanding the aetiology and pathogenesis of disease.[9] In the first issue of *Clinical Medicine* this year, Peter Watkins' editorial noted that NHS consultants had done world-class clinical research of this kind in the past, often with limited resources, in an era when consultants in teaching hospitals were expected to undertake research.[10]

Important contributions have not been confined to teaching hospitals, however. NHS doctors working in district general hospitals and general practice have also made important contributions as researchers, in particular in developing and assessing treatments. Well-known examples include Charnley's development of hip joint prostheses at Wrightington Hospital, and Steptoe's development of *in vitro* fertilization in Oldham. But there are many examples of less dramatic, but nevertheless important, advances resulting from research done within the NHS, including in our own field of interest, dermatology. Despite a demanding clinical job, single-handedly serving the dermatology needs of Lancaster, Kendal and Barrow, Robert Seville was able to complete important work on dithranol therapy of psoriasis[11] and a pioneering study into the effects of stress on psoriasis.[12] Over the lifetime of the NHS, many clinicians have made their own individually small contributions to collaborative studies which have resulted in major changes in clinical practice (for instance, in demonstrating the beneficial effect of low-dose aspirin in myocardial infarction). There are still physicians willing to commit their energies to projects where the rewards are perhaps hard to measure, except inasmuch as the questions posed are considered important enough to be worth answering. A recent example is the collaboration among a number of enthusiastic dermatologists in district general hospitals in West Hertfordshire who questioned but then confirmed the value of serological testing for liver fibrosis as an alternative to liver biopsy in psoriasis patients receiving methotrexate.[13]

In spite of the creditable past track record of NHS clinicians as researchers, the potential for them to continue to contribute to treatment development and assessment has been severely constrained by over-regulation of clinical research. This trend has been characterised by Charles Warlow as 'a threat to public health'.[14] Those who have promoted recent trends in regulation appear not to have considered the responsibilities of clinicians faced with uncertainties about the effects of treatments. The situation has never been more succinctly summarised than by the paediatrician Richard Smithells, who declared 30 years ago: 'I need permission to give a drug to half of my patients, but not to give it to them all'.[15]

It is axiomatic that any clinician, faced with recurring uncertainty when treating patients for conditions with unpredictable responses to treatment, should feel some desire to lessen that uncertainty and thereby increase treatment success. To a certain extent, this can be achieved on an individual level by continual self-learning and the increased clinical acumen gained from experience. There are, however, obvious limitations in such individual approaches. So it is indeed 'a threat to public health' when the barriers to evaluating therapeutic options are increasingly outweighing the incentives for NHS clinicians to become involved in clinical research. Their ability to contribute to clinical research within the NHS and their enthusiasm for undertaking it is being eroded by a combination of recent factors, including the introduction of ever more stringent waiting-time targets for patients to be seen, more prescriptive job plans under the new consultant contract, and the daunting process of obtaining ethics committee approval, which can only serve to deter all but the most driven researchers.

Key Points

In all branches of medicine, both patients and clinicians are faced by important questions which can be answered only by clinical research

Reducing uncertainties of relevance to patients and clinicians should be an integral part of the practice of high quality medicine

Changes in the NHS are jeopardising the ability of NHS clinicians to contribute to the clinical research needed to achieve this

Identifying therapeutic uncertainties deemed important by clinicians and patients

As in the example of steroids and acute brain injury, systematic examination of the available evidence from research is helping to make explicit the extent to which there are variations in

practice and uncertainties about treatment effects in all branches of clinical medicine. Furthermore, the uncertainties rated important by clinicians and patients are often not those being addressed in research, which has become dominated by the interests of industry and its collaborators in academia.[16] A recent survey of people with Alzheimer's disease and their carers highlighted the divergence between assessments of benefit from anticholinesterase treatments (eg improvements in mood, reduction in fear and distress and improvements in confidence) and outcomes reported in clinical trials (mainly changes in cognitive functioning).[17]

We suspect that such mismatches are the rule rather than the exception. In part, this is because researchers too rarely invite patients and clinicians to identify the therapeutic questions that they regard as important. In addition, however, it reflects perverse and distorting influences on the research agenda:[8] for understandable reasons (principally the responsibility to shareholders), industry does research for industry's needs, which may, but frequently does not, coincide with those of patients. For less easily defended reasons, academics do research that will gain them credit with their employers, the universities, which have to compete for funding using criteria that have little to do with the direct needs of patients. The consequence is what one *BMJ* editorialist has referred to as 'The scandal of poor medical research'.[19] He called for less research, better research, and research done for the right reasons.

With the increase in medical student intake, the worrying reduction in numbers of medical academics and the narrow criteria by which universities measure academic success, academic medicine cannot be relied upon to undertake more than a small part of the necessary research, even if there were a willingness to undertake it. If their patients' best interests are to be served, NHS clinicians must be encouraged to contribute.

An exemplar: unanswered questions about the management of psoriasis

Psoriasis provides an apt model for discussion of these issues. It rarely leads directly to premature death but is common (its prevalence in Northern Europe is around two per cent) and may cause long-lasting misery to those afflicted by it. Extensive or disabling psoriasis can ruin lives by eroding self-esteem and self-confidence, and limiting normal social activities, career aspirations and earning capacity, causing disability as great as cancer, arthritis, heart disease, diabetes, or depression.[20] For many years, psoriasis has attracted rather little in the way of interest from major players in the healthcare industry. In the past five or six years, however, the biotechnology industry has fuelled a dramatic investment into clinical research for psoriasis and now several new and very expensive biological drugs have been granted product licences for treating severe disease.

As is the case with other chronic diseases, the management of psoriasis varies widely between countries, and between centres within countries. Few of these differences in practice have ever been formally evaluated. Newly introduced treatments are rarely compared to existing therapies. No biological drug has been formally compared with anything other than placebo. Even with as potent a drug as methotrexate, 40 years elapsed between its introduction and the first controlled trial of its use for psoriasis.[21] Most studies of treatments for psoriasis have looked at short-term responses, rarely more than three to four months, for a disease which commonly lasts decades, and few have attempted to mirror real life, where a combination of topical treatments with or without systemic medication is used. The authors of a recent survey of psoriasis trials commented that:

> *The development of new treatments for psoriasis follows a rather repetitive pattern where important questions for clinicians and their patients, like the comparative value of different treatment options and the long term impact of the treatment on the disease, are scarcely considered.*[22]

Less than 10% of the trials surveyed reported on patient preferences or satisfaction and only one considered impact on quality of life.[22]

Not surprisingly, psoriasis patients are commonly unimpressed by, and sceptical about the treatments made available to them. For example, the speed of action of a treatment or what counts as 'remission' may be of less moment to them than sustained duration of an ultimate effect. At the very least, patients do not want to find that treatment makes them feel worse, from either physical or psychosocial side effects, and they need to be reliably informed concerning the risk–benefit ratio and the longer-term uncertainties in that regard. It is, therefore, not surprising that patients' own judgements of severity often contrast strikingly with assessments made within the mainstream of dermatological research: rather than changes in physician-assessed severity scores, patients' subjective experience of itch, soreness, bleeding lesions on sensitive sites (genitalia, face, palms, soles), scaliness and social obtrusiveness all figure prominently, as do the inconveniences imposed by treatment which has offered only transient benefit.

It is not difficult to identify simple questions of relevance to patients with psoriasis which could readily be answered by appropriate controlled trials. UK dermatologists, both academic and NHS, working together with patient representatives have made a start at identifying important gaps in knowledge by forming a UK Dermatology Clinical Trials Network, coordinated at the University of Nottingham. Its aim is to conduct 'independent high quality trials on less common skin diseases and on cheap generic treatments and non-pharmacological interventions that industry is unlikely to fund'. For reasons that have been already been discussed, progress has, however, been slow to date. British dermatology can hold its head up high when its contribution to dermatology over the past 50 years is set against the tiny numbers of specialists in the UK; but despite a dramatic increase in dermatologist numbers in the past 10 years, competing claims for their time and energies now threaten to leave the specialty bereft of individuals willing to take the specialty forward by contributing to clinical research.

With the arrival of the new wave of biological treatments for psoriasis, patients and clinicians are being faced with a welcome expansion of choice of treatments for severe psoriasis. There is as yet, however, little to show that these new treatments genuinely and reliably offer better outcomes in respects valued by patients. Perhaps their high cost will, however, provide the impetus to address some of the unanswered questions about long-term management. It seems probable that the National Institute for Clinical Excellence (NICE) will demand that provision of biological therapy should be made conditional on registration in a

Biologicals Register, which is currently being set up by the British Association of Dermatologists. It has been proposed that a representative sample of patients commencing other systemic therapies such as methotrexate and ciclosporin should also be registered, to allow comparisons of biologicals with existing systemic therapies. This may provide a framework to use for making long-term controlled comparisons of the type which pharmaceutical companies themselves are unlikely to fund. Because treatment comparisons made using such observational may well present problems of interpretation, it is obviously important to ensure that the UK Dermatology Clinical Trials Network begins functioning effectively to produce evidence from randomised comparisons as well.

Concluding reflections

There has been increasing awareness among NHS clinicians and patients that treatment choices should be informed by evidence from research. This has been reflected in the preparation of clinical guidelines produced by the Scottish Intercollegiate Guidelines Network and the National Institute for Clinical Excellence, and in resources such as the *BMJ*'s *Clinical Evidence*, *The Cochrane Library*, the National Electronic Library for Health and DIPEx, a database of personal experiences of health and illness. However, there is still a long way to go before evidence from existing therapeutic research has been synthesised and made readily available to clinicians and patients. Although contributors to the Cochrane Collaboration have published, and are endeavouring to keep up to date, over 2,000 systematic reviews of the effects of healthcare interventions, it has been estimated that at least 10,000 reviews are needed to synthesise the findings from existing research.[23]

Some of the controlled trials organised by the Health Technology Assessment (HTA) Programme and the Medical Research Council clearly offer opportunities for the NHS to address uncertainties about treatment effects; but this does not mean that mechanisms are in place to encourage – let alone require – NHS trusts and their employees to ensure that these studies obtain the support that most of them deserve. For example, how many trusts could be (but are not) participating in the HTA trial addressing uncertainties about the relative merits of treatments for early prostate cancer? What are the responsibilities of managers, for example, when their institution has formally endorsed a multicentre trial addressing an important uncertainty of relevance to current and future patients in the NHS?[24] More than a decade ago, three Australian oncologists challenged their readers to consider the ethics of not inviting eligible patients to participate in established, ethically approved randomised trials:

> *Is not an institution obliged, once its ethics committee endorses a trial, to regard entry onto that trial as 'standard therapy' for eligible patients? By approving the trial the institution acknowledges that there is insufficient evidence to prefer one of the treatments over another. Moreover, the institution has committed itself to the use of scientific methods to discover which is the superior treatment. Should an institution not therefore scrutinise individual doctors who choose to treat eligible patients off protocol when an appropriate, approved trial is available? At a minimum should not the institution demand of those doctors an accountability of their action in the same rigorous way that is demanded of those entering patients on the trial?*[25]

Clinicians have sometimes shown important leadership in ensuring that significant uncertainties would be addressed. Paediatric oncologists are often rightly seen as exemplary in this respect, though such leadership is not confined to them. For example, when neonatal extra-corporeal membrane oxygenation (ECMO) – a treatment for severe asphyxia in newborn infants – was introduced, British neonatologists agreed that it should only be offered to NHS patients within the context of a randomised comparison with standard treatment, until more was known about its immediate and longer-term effects and its costs. They have adopted a similar approach to a randomised trial of cooling asphyxiated newborn infants.

The recent establishment of the James Lind Alliance, which aims to foster the development of working partnerships between patients and clinicians to identify their shared priorities for therapeutic research, is a step in the right direction.[26] But the main need is for serious consideration at a variety of levels of what clinicians and patients should do when their questions about the effects of treatments have not been addressed either in systematic reviews of existing evidence, or, if systematic reviews have made clear the need for it, in ongoing research. Patients' own support organisations must become more active and independent in seeking to influence the research agenda, resisting the temptation simply to welcome any enquiry on the false basis that any research is better than none at all. Where necessary, they must be constructively critical of the efforts of industry and the academic researchers supported by the companies.

The NHS needs to listen to patients and clinicians to learn what research they consider important. Indeed, how can policy makers argue for informed patient choice, modernisation and improved quality unless they do listen? Above all, this reality needs to be confronted explicitly by all those claiming to be committed to improving the quality of care offered to people using the NHS. It is not in the interest of patients when research designed to address important therapeutic uncertainties is seen as an optional extra rather than an intrinsic element of any serious quality improvement strategy.

The government has recently announced new money for clinical research. Those who have erected the bureaucracies making it so difficult for NHS clinicians and their patients to confront therapeutic uncertainties in research need to realise that the interests of current and future patients are not served by acquiescence in poorly controlled therapeutic experimentation when controlled experimentation is, in principle, possible. We need a wholesale reorientation of thinking driven by the shared interests of patients and clinicians.

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