How long should treatments be continued?

Data from randomised trials and cohort studies are needed to answer this question

BSIP, MAY/SPL

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To make evidence based decisions, clinicians and patients need to know the answers to three questions about an intervention. Does it do more good than harm? How intense should treatment be? For how long should it be given? In the linked study, Chen and colleagues tackle the third question by assessing relapse rates after a first episode of psychosis in patients who either continued or discontinued antipsychotic drugs after at least one year of treatment.[1]

Because of the explosion of randomised controlled trials and systematic reviews of trials in the past 50 years,[2] we have high quality evidence on the effects of many interventions. These days, almost all issues of major general and specialist journals will include at least one randomised controlled trial that will provide reasonable certainty about the effects of a treatment. Implicit in the design will be the dose or intensity of the intervention evaluated, which is informed by previous phase I and II studies and may be the subject of specific phase III trials.

In comparison, we know little about how long interventions should be given, both for common acute conditions like respiratory or urinary tract infections,[3 4] and for chronic conditions like mental illness, cardiovascular illness, and chronic kidney disease, where patients are exposed to potentially harmful interventions for months, years, or even decades. Trials are rarely designed to evaluate how long people should be treated. Does this matter? Yes. Interventions given for too short a time can result in preventable adverse outcomes, such as relapse or recurrence. If interventions are given for too long then patients are at unnecessary risk of adverse effects and money is wasted.

Chen and colleagues' randomised trial was unusual in that the research question was treatment duration.[1] They randomised patients who had recovered from their first psychosis to maintenance quetiapine or placebo, and they found that the risk of recurrence was 41% (95% confidence interval 29% to 53%) in the quetiapine group compared with 79% (68% to 90%) in the placebo group. The risk of discontinuation because of adverse events was about 10% higher in the quetiapine group (18% *v* 8%; relative risk 2.29, 0.99 to 5.28) over the next year, however. The trial provides reliable evidence on the benefits and harms of maintenance quetiapine and shows that psychotic relapse can be prevented by prolonged treatment with this drug.

How do we make informed decisions about the duration of interventions in the absence of such trials? The table details a suggested framework for answering questions about the duration of interventions.

Ideally, the effects of a shorter or longer duration can be compared directly, as in Chen and colleagues' trial.[1] Alternatively, the effects of different durations can be inferred from trials that evaluate a single duration of an intervention but display the control adjusted treatment course over time, usually as a survival plot. In Chen and colleagues' trial the outcomes are similar for the first 60 days of treatment and then diverge over the remaining period of the trial, which suggests many months of treatment are needed. In contrast, in a randomised trial of antibiotics to prevent urinary tract infection in children, most benefit occurs within the first six months of the 12 month randomised exposure period.[5] Although trials have not been specifically designed to determine how long women with early breast cancer should be treated with tamoxifen, data provided by the Early Breast Cancer Trialists' Collaborative Group clearly show improved survival with longer duration of exposure.[6] The third, but potentially biased information comes from indirect comparisons across different trials that have evaluated the same intervention but with different treatment durations. For example, a systematic review found that the most cost effective duration for trastuzumab as adjuvant treatment for early breast cancer was uncertain.[7]

A framework for making informed choices about treatment duration

Question	Study type	Design	Answer	Example
What do we know about the intervention?	Randomised controlled trials	Randomisation of different durations of the same intervention	Directly compares the effects of one duration with another	Short *v* long duration for symptomatic urinary tract infection in children and adults
		Randomisation of different interventions of the same duration	The effects of different durations can be inferred by analysis of time as a covariate (eg, survival curves)	Tamoxifen and early breast cancer
		Indirect comparison of trials of different durations	Comparisons are across trials and so are potentially confounded	Trastuzumab for early breast cancer
What do we know about the condition?	Cohort studies	Follow-up of people with the condition of interest	Elucidates the course of the condition	Anticonvulsants after first seizure
		Risk prediction using clinical marker of the condition	Monitors the current clinical status reliably	Clinical global impressions scale for acute psychosis
		Risk prediction using one or more biomarker	Can predict the course of the condition for an individual with reasonable certainty	Autoantibodies for systemic vasculitis

The course of the chronic disease can also help to guide the length of treatment. But experiencing a symptom for the first time does not necessarily imply that the disease will have a chronic course. After a first seizure, the two year seizure recurrence rate is 40-50%, so giving everyone an antiepileptic drug after a first seizure is unnecessary. This is illustrated by the Medical Research Council Multicentre Trial for Early Epilepsy and Single Seizures,[8] where patients were randomised to immediate or deferred antiepileptic treatment. Even though only 40% of patients in the deferred treatment group received an antiepileptic, seizure-free rate and quality of life at five years were similar in both groups.

Once it is known how chronic the disease is, the next question is whether it has a progressive or relapsing-remitting course. For patients with non-progressive infrequent relapses and full recovery in remission, evidence from trials of acute treatment can be directly applied. An example of such a situation is the use of triptans in acute migraine attacks.[9] However, most chronic diseases have a progressive course, with progressive deterioration. In a disease with progressive deterioration, treatment efficacy may decline as the disease worsens. In contrast, in some circumstances, such as childhood asthma, the underlying disease process may progressively improve over time, in which case withdrawal of inhaled corticosteroids may be safe.[10]

In some cases, treatment decisions can be individualised if the course of a condition can be predicted using periodic measurement of biomarkers of disease or monitoring.[11] Monitoring in chronic disease aims to guide treatment and control the disease or to predict relapse and re-establish control afterwards by measuring change in the disease marker. Disease markers are generally surrogate measures correlated with outcomes that are relevant to patients, usually through associations measured in cohort studies, but ideally within randomised trials, where a predictable and quantitative change in the biomarker correlates with patient outcome. However, most disease markers are imperfect, and true change can be hard to separate from expected variability and measurement error.[12]

More trials of the duration of treatment are needed. Until then clinicians, consumers, and policy makers may use existing trials and observational studies within the framework described to guide treatment decisions.

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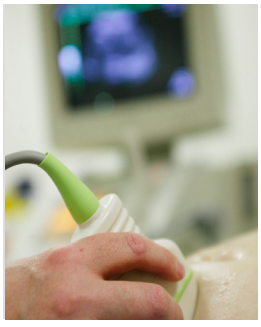
Miscarriage and time to next pregnancy

Women who conceive earlier may have better outcomes and fewer complications



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About half of women will miscarry at least once during their lives. Yet it is unknown how best to care for women and their families in such an event. Research has focused on the causes of recurrent miscarriage and possible ways to prevent it, but with limited success.[1 2] Increasing evidence supports the use of medical evacuation of the uterus and expectant care as alternatives to the more invasive and expensive surgical evacuation of the uterus that was the mainstay of care for decades.[3 4]

For women actively seeking to become pregnant, "how soon can we try again?" is a central question. To date, there is a remarkable lack of evidence on this question, especially from Western countries. In the linked retrospective cohort study, Love and colleagues assessed the optimum interpregnancy interval after miscarriage in a first pregnancy.[5] They found that women who conceived again within six months were significantly less likely to have another miscarriage, termination of pregnancy, ectopic pregnancy, or complications in pregnancy compared with women with an interpregnancy interval of six to 12 months.

Reliable data from birth registries show that, after a live birth, a further conception within 18-23 months is associated with the best outcomes for mother and infant in the subsequent pregnancy and birth.[6 7] Unfortunately, registries cannot answer the question of the optimum interpregnancy interval for conceptions after other pregnancy outcomes, particularly miscarriage, with similar validity and reliability. Unlike birth registries and data systems, those dealing with miscarriage are subject to lower data quality and incomplete data linkage.

The methodological difficulties of studying the course of miscarriage, such as accurate recognition, diagnosis, and recording of early pregnancy loss, in populations that are representative of women in the community, are well documented. Unlike pregnancies that proceed to birth, the documentation of pregnancies that end in miscarriage often depends on the woman's assessment and recall of timing and gestational age at which the loss occurred, or on the recording of the loss by a health service. Over recent decades the documentation of pregnancy loss has been affected by

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changes in technology, usual medical care, and the smaller number of pregnancies and births typical of the contemporary Western family, with the consequent greater attention paid to each pregnancy.

The ready availability of accurate pregnancy testing and the widespread use of ultrasound in early pregnancy have moved the recognition of pregnancy, and therefore pregnancy loss, to earlier gestations, resulting in shifts in diagnoses of early pregnancy losses from "spontaneous miscarriage" to "missed miscarriage." The effect of changes in usual care for miscarriage, however, is more difficult to assess. Often the documentation of pregnancy loss that allows linking of subsequent pregnancies with their outcomes will be restricted to those losses that lead to hospital care for the woman involved. Research in a range of countries over several decades suggests a substantial variation in the way miscarriage is managed in general practice and that most, but not all, women are referred to hospital.[8 9] Although changes in diagnosis may suggest an increase in hospital admission, changes in the management of miscarriage, ongoing improvements in the general health of women, and incentives to reduce pressure and costs of hospitals may mean that fewer women now receive hospital based care.

Interpreting the findings of the impact of the interpregnancy interval after miscarriage can be difficult. The literature is scarce and comes from a diverse collection of countries and contexts. Evidence on the optimum interpregnancy interval after a live birth may have encouraged practitioners to apply this knowledge to pregnancies with other outcomes.[10] Furthermore, some women who have had a miscarriage may be reluctant to become pregnant immediately, given the emotional, and for some, physical sequelae.[11] To add further complexity, researchers have shown that women who miscarry are slightly less fertile than their counterparts who proceed to a live birth.[12]

Perhaps surprisingly, given this heterogeneity and range of inherent methodological obstacles, findings suggest that a short interpregnancy interval after miscarriage may be preferable. However, all of the studies have selection and measurement biases that cast doubt on the value and generalisability of their findings. Of greatest concern is that women with short interpregnancy intervals are more fertile than those whose subsequent pregnancy occurs later because these women seem to have better pregnancy outcomes and fewer complications.

Further research into this question may need to wait for data from more sophisticated linked primary care and hospital datasets or specifically designed research studies that can measure and account for such differences, even if they will not be able to control for them.

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Unequal access to health care in England

Women, elderly people, and those in deprived areas continue to be worse off

RESEARCH, p 438

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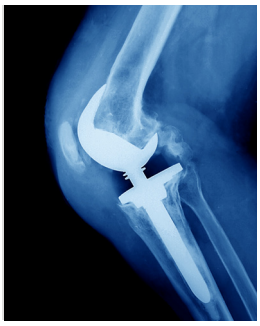
In the linked study, Judge and colleagues assessed the geographical and sociodemographic factors associated with variations in access to total hip and knee replacement surgery in England. They found inequity in access to both types of surgery by age, sex, deprivation, area of residence, and ethnicity.[1]

The 1989 report *Working for Patients* set out the responsibilities of health authorities.[2] These included assessing the health needs of their populations and ensuring that an appropriate range of services was available to meet them. It led to the development of a new set of methods, termed health needs assessment,[3] which was backed up by a substantial body of research. The process of methodological development provided a major stimulus to research into health services, and it brought together clinicians, epidemiologists, and a variety of social scientists. It led, among other things, to the publication of a multi-volume textbook that offered guidance to those commissioning health care.[4]

Assessing need and monitoring whether it has been met remains a core function of primary care trusts, the successors of those health authorities. Yet despite the work that went into methodological development in the 1990s, the task remains challenging. Firstly, we need to agree on the threshold for intervention. This can be difficult because much of the research on effectiveness is conducted in atypical subjects, few of whom have complex comorbidities. Secondly, we need to assess the need for health care in a way that can be measured in the population. A screening test that requires invasive investigations is of little value in this situation. Thirdly, we need to measure these indications in the population. And finally, if need is to be related to use, we need to determine the treatment rate in the population.

Judge and colleagues have tackled this challenge in an



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imaginative way.[1] They looked at disparities between the need for and use of total hip and knee joint replacement surgery—cost effective procedures that are undertaken for common problems, which can transform patients' lives by reducing pain and increasing mobility. They began by implementing and validating a simplified scale developed in New Zealand to identify patients who need major joint replacement. By applying this scale to subjects in the English Longitudinal Study of Ageing they developed a model that could be used with census data to estimate how many people in different parts of the country would need surgery and compare this number with how many operations were undertaken. Obviously, this approach has many limitations, as the authors recognised. Among the most important are the inability to determine whether everyone in need wants the operation and the absence of data on the 20% or more of procedures undertaken in the private sector. The limitations are unlikely to change the key findings, however.

Crucially, the study showed that, should you need joint surgery, the probability of getting it varies according to who you are and where you live. In particular, older people, women, and those living in deprived areas seemed to be disadvantaged, although the role of other characteristics varied between the two types of joint replacement.

These findings are consistent with existing research, especially studies showing that doctors in primary and secondary care are less likely to investigate and treat women and elderly people.[5] This is important because promotion of mobility and thus independence must be a core element of our response to population ageing.[6] The undertreatment of people in deprived communities is doubly unjust because they already face a greater burden of disease.[7]

Some findings are relevant to ongoing debates about hospital reconfiguration. Distance from hospital did not seem to be important, but the capacity to provide orthopaedic surgery (such as numbers of consultants and training status) did increase provision, strengthening the case for greater centralisation.

Although this study provides a major methodological advance, the implications of its findings for current policy are limited because the data are from 2002. Investment in the NHS has increased since then, and although health expenditure in the United Kingdom is still less as a share of national wealth than in other industrialised countries,[8] the level of provision has improved greatly. Hence the considerable under-provision recorded here is likely to have been alleviated to some extent, although we cannot be sure of this.

The authors should be congratulated for blazing a trail in conducting these analyses, but the NHS must now take on this task. In future, private sector data should be included that will build, for example, on the pioneering collaboration between the private sector and the London Health Observatory[9] or the growing number of national procedure registries that contain both NHS and private sector data. Without such analyses it is not possible to know whether the health needs of the population are being met and ask why any inequalities exist and how they can be tackled. This, however, raises one final question. So far, health needs assessment has been the responsibility of primary care trusts and strategic health authorities. Now that the Department of Health in England has signified its intent to move to general practice commissioning, who, if anyone, will have the skills or interest to take on this important role?

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From a cancer drug fund to value based pricing of drugs

Such pricing may be hard to implement and may not add value

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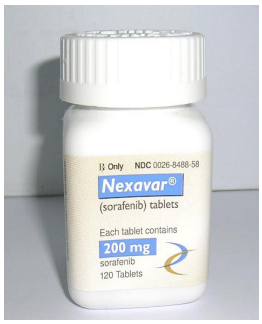
In late May 2010, the National Institute for Health and Clinical Excellence (NICE) decided not to support sorafenib (Nexavar) for use in hepatocellular cancer in England and Wales. NICE advised that the drug was not cost effective; it costs around £27 000 (€32 400; $42 500) for each course of treatment and improves median survival by 2.8 months in people dying of cancer (50% of people might be expected not to get this benefit, and 50% might get this benefit or more).[1] The media response was mostly an outcry, "Fury as new cancer drug is banned."[2]

Various patient groups and experts were also not happy with this decision. Professor Karol Sikora representing CancerPartnersUK said, "It is devastating that NICE has failed to use this opportunity to properly consider the very strong recommendations from UK oncologists who only want the best for their patients."[3] It is noteworthy that none of these emotive responses suggested or recognised that the drug may cost too much in relation to its limited benefit and that this money might be better spent elsewhere in the NHS—for example, on palliative care services, where arguably it might give better value for money.

NICE's most favourable analysis of the incremental cost per quality adjusted life year (QALY) for sorafenib versus best supportive care was £52 000, even with the drug com-



pany reducing the cost paid by the NHS by 25% as part of a patient access scheme.[1] Even using controversial "end of life" criteria, which enable NICE to value cancer drugs more highly than other types of drug,[4] this was considered too much to pay.

The timing may be a coincidence, but on the same day the newly installed coalition government began to flesh out the Conservative Party's pre-election pledge to make cancer drugs available on demand.[5] Despite the need for radical austerity measures elsewhere in public service, they promised £200m for England from April 2011 to provide a cancer drug fund for instances when doctors and patients insist the drugs should be used, even if NICE deems the treatment not cost effective. This suggests, at least in the short term, that drug companies can charge what they think fit and the NHS will pay regardless. It is not clear whether NICE should put on hold its decisions on cancer treatments given an open cheque for these in England in 2011. Also, will a similar provision be made elsewhere in the United Kingdom. In the interim, before this money is made available, the Department of Health has advised primary care trusts in England to consider carefully whether local or individual circumstances make it appropriate to fund drugs that NICE has been unable to recommend for routine use.[5] This reflects the new government's wish to allow local decisions and determination but seems to undermine the role of NICE, particularly where it seeks to create equity and avoid "postcode" prescribing.

In late July 2010, a report that received further media interest and criticism indicated that the UK was slow to adopt new cancer drugs compared with other countries in Europe.[6] Again, perhaps coincidentally, on the same day as the report, the government brought forward its plans for the cancer drug fund and announced its intent to provide £50m from October as "an emergency measure." It is difficult to see how this emergency measure will improve outcomes in cancer. The sting in the tale for the enthusiasts, largely missed by the press, is that it now remains unclear whether a sum approaching £200m will be made available in 2011 after all.

Alongside these changes, which are presumably interim, the coalition government has also advised that it will reform NICE and move to a value based pricing system for the NHS. Value based pricing was advocated by a report from the Office of Fair Trading back in 2007.[7] This report argued that the Pharmaceutical Price Regulation Scheme (PPRS) should be reformed and that drug prices should be set in the UK on the basis of an explicit assessment of the value they represent. The PPRS, which has run for more than 50 years, essentially allows drug companies to set their own drug prices for the NHS for brand products, although it attempts to restrict the overall profit an individual company can make from the now four separate NHS systems in the UK. The drug industry favours this scheme because it allows them to set high prices for certain drugs in the UK, and these prices may be reflected in the global marketplace, particularly as many health systems around the world use "reference pricing," which is based on how much is paid in other countries. It also helps the drug company to predict the future commercial value of their drug because clinical data are often lacking when the drug is launched, particularly for cancer drugs.

It is not yet clear how a value based system would operate, but the reformed NICE is likely to be involved in the process and a formal cost effectiveness appraisal carried out. One proposal is that the price could be set at launch (the Office of Fair Trading report used the term "ex ante") at the level that NICE or other drug appraisal bodies deem cost effective.[7] This means that an incremental cost effectiveness ratio per QALY threshold could be agreed—for example, at a specific point between the £20 000 and £30 000 per QALY threshold currently set as the conventional upper limit of cost effectiveness, and the price of the drug calculated from this point.

Whether a different threshold should be set for pricing cancer drugs and assessing their value compared with other treatment areas is controversial.[4] The cancer drug fund indicates that the government thinks that it should. Considerable problems can be envisaged with the value based pricing proposal. The first is that it may delay the availability of the drug while wrangling over the price takes place. The second is that it will require more robust trial data than is usually available when a drug is launched, although it could be argued that this requirement is no bad thing. Thirdly, the value of the drug may change over time as more information on effectiveness and safety becomes available; for example, if the need to monitor the drug or an adverse effect becomes evident after launch, the costs of this will need to be factored in. Revisiting the decision on price over time will be a complicated process. Fourthly, it is unclear how drugs currently available on the market will be assessed and valued, and this process could be time and labour intensive. Lastly, the drug industry may not be supportive, and in the face of resistance the new system may take a long time to set up, because although the 2007 Office of Fair Trading report recommended against it, a renegotiated PPRS was put in place to run for five years in 2009.[8] There are, however, legislative powers to enable renegotiation before this time. These and many other problems will need to be ironed out, and even if they are, it is still unknown whether value based drug pricing will truly add value.

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What does the white paper mean for hospital consultants?

Greater influence and greater accountability

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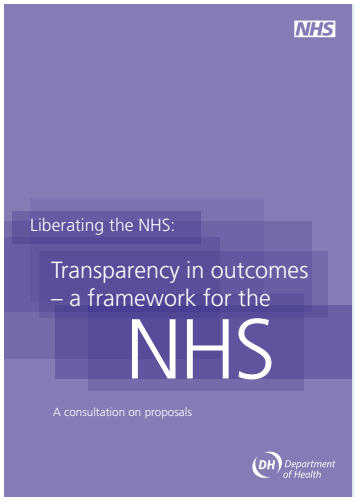
Since the general election the movement towards reform and reorganisation in the health service has been rapid. The recently published white paper and the subsequent *Transparency in Outcomes—A Framework for the NHS* could completely recast the way the NHS is managed, governed, and held to account.[1 2] Many commentators consider that a series of radical and far reaching changes to the NHS is under way.[3-5] Consultants and their patients are understandably concerned about what these changes mean for them. A consideration of the four broad themes that run through the white paper and its supporting documents is crucial to tackling these concerns.



The first of these, and perhaps the most important, is the principle that patient empowerment, facilitated by information and choice of health providers, is paramount. Second is the substantial strengthening and clarification at all levels of the purchaser-provider split. This will be supported by the third ambition, to free the provider market and promote greater choice. Finally, increasingly robust regulation will be directed towards internationally comparable quality outcomes and the effective use of resources.

Under this arrangement government will take far less of a day to day role and will concentrate on funding the NHS system, establishing a robust system of regulation, and holding the NHS Commissioning Board to account.

The ambition is once again to make the NHS the envy of the world, to put patients at the heart of everything, to have a relentless focus on clinical outcomes, and to empower health professionals to use their judgment about what is right for patients. Furthermore, the white paper says it will put clinicians in the driving seat and set hospitals and providers free to innovate while also providing a more transparent service, with clearer accountability for quality and results.[1]

Few, if any, consultants would not welcome and endorse such ambition and see within it the opportunity to offer better services to their patients and to be part of a system that routinely delivers world class care. However, there are those who rightly point out both the experiences of the past and the challenges that the proposals will face. Concerns include the scale of the change, which is substantial, its ambitious pace, and the potential reluctance of some general practitioners to become commissioners.[3-5]

Added to these concerns is the paucity of evidence to support further structural change.[4] It is difficult to conclude that the structural changes proposed are driven wholly by empirical evidence. This may alarm consultants who are trained to, and required to, base their practice on the best available evidence. However, government is elected and consultants are not. The politicians have a vision for the service, and consultants have been rightly urged to take the opportunity to play an active role in the consultation.[6]

But, after the consultation, assuming little of substance changes, what are the opportunities for consultants? General practitioners and consultants will undoubtedly need and wish to work together to develop the structures, processes, and outcomes of care.[2 7] General practitioner consortiums must assure a concerned public that there is clarity and transparency about who is responsible and available to provide patient care on a 24:7 basis, that the criteria for referral and discharge are consistent and routinely applied and that communication in both directions is fit for purpose.

Transparency in outcomes states that nationally the focus will be on outcomes rather than structure and process.[2] The delivery of outcomes will be directed by a suite of National Institute for Health and Clinical Excellence (NICE) quality standards, of which 150 will be developed over the next five years. Three current examples of these can be found in the care of stroke, venous thrombo-embolism, and dementia.[2]

These standards will be chosen by the Commissioning Board, after taking expert advice. General practitioner consortiums will be required to refer to these standards when commissioning services. They will be held to account for doing so by the Commissioning Board. The essential role of consultants will be to help the Commissioning Board in the choice of standards and then to work with NICE in drawing them up. For consultants this is an opportunity to shape the future of health care and should be seized.

As well as opportunity there is much mention in the consultation documents of accountability.[1 2] It may well be that the secretary of state for health wishes to have an NHS more shaped by the clinical profession's knowledge and expertise, and that should provide a much welcome opportunity. However, he also seems to have recognised that much power also sits with the clinical professions, notably doctors, and that there is a need to align power with accountability. Future governments, the public, and patients will hold doctors responsible not only for the care that individual patients receive but also for the efficiency and effectiveness of the system.

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