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- The real problem that NHS patients face in accessing new medicines is the discrepancy between the price charged and how much the NHS can afford to pay for the benefits they offer.
- Recent policy initiatives have failed to address this fundamental problem.
- Linking the NICE appraisal to national rebates that reflect the discrepancy between the prices manufacturers wish to charge for their products and how much the NHS can afford to pay for the benefits they offer, would provide a sustainable solution for the NHS and for manufacturers.

Project team:

Karl Claxton.

For further information contact:

Centre for Health Economics,
University of York
Karl.Claxton@york.ac.uk

Pharmaceutical Pricing: Early Access, The Cancer Drugs Fund and the Role of NICE

The real problem that NHS patients face in accessing new medicines and that manufacturers face in getting market access and an early return on their investments has been, and remains, the discrepancy between the prices charged and how much the NHS can afford to pay for the benefits that new medicines offer.

An evidenced based and accountable assessment of the additional benefits offered by a new drug is required and the National Institute for Health and Care Excellence (NICE) has done an excellent job over the years in assessing those benefits; not just within the licensing trials but also taking account of other evidence to try to assess the longer run effects on survival and quality of life. NICE also assesses the additional cost to the NHS. Not just the cost of the drug itself but all future NHS costs, including any potential cost savings.

How much can the NHS afford to pay for the benefits offered by a new drug?

The Answer depends on what health could have been gained elsewhere if the additional resources required had been available to offer effective treatments for other NHS patients. We now know something about what the scale of these health opportunity costs are likely to be across the NHS. Recent research has, for the first time, estimated the effects of changes in NHS expenditure on the health of all NHS patients. [1] The evidence suggests that every £13,000 of NHS resources adds one Quality Adjusted Life Year (QALY) to the lives of NHS patients. So, for example, a new drug that costs the NHS an additional £10m each year is likely to lead to the loss of 773 QALYs each year, with increased mortality and reduced

survival in cancer, circulatory, respiratory or gastro-intestinal diseases and reduced quality of life in neurological diseases and mental health. [1,2]

What does this mean for the NHS? One thing it means is that increasing expenditure on the NHS appears to be very good value; £13,000 adds one QALY to the lives of NHS patients. We also have evidence that every QALY gained or lost through spending on the NHS is also associated with £13,000 of benefits in the wider economy.[2] In a sense, the NHS pays for itself. Recent research also suggests that NHS expenditure tends to reduce health inequalities. [3] You might think £13,000 per QALY is too low and the NHS should be able to afford to pay more for improvements in health. If you do, then you need to consider whether we should raise more taxes, extend public borrowing, or substantially reallocate public expenditure.

Implications for NICE and recent policy initiatives

What does this mean for NICE? NICE says it uses a threshold range of £20,000 to £30,000 per QALY when considering whether a new drug is cost-effective and should be approved for widespread use. This range is based on the values implied by the decisions NICE made between 1999 and 2003, [4] but over recent years it generally does not reject below £30,000 per QALY. In fact, the most recent evidence indicates that, on average, it approves new technologies at just over £40,000 per QALY. [5] This suggests that, on average, when NICE approves a new drug it does more harm than good to population health, with a ratio of QALYs lost to QALYs gained of at least three to one. [2] This means that without addressing the question of price, accelerating access by NICE

approving new drugs more quickly will simply accelerate the net harm and increase the scale of the net harm done to the rest of the NHS.

Recent policy initiatives, including the Accelerated Access Review, changes to the Cancer Drugs Fund as well as previous consideration of Value Based Assessment, have all failed to address this fundamental problem. Instead they appear to ignore or deny it. That denial over recent years has come in many different forms. For example, a claim that the discrepancy between the price charged and how much the NHS can afford to pay can be resolved by taking account of potential cost savings on the grounds that NICE has not previously done this, is profoundly mistaken. The principle of taking account of future costs savings has always been part of the methods used in NICE appraisals.

Some suggest that the measure of health adopted by NICE (the QALY) is the problem. But using other ways to measure health gained and health lost elsewhere is not going to overcome the fundamental difficulty either. We might wish to give greater weight to health effects where disease is severe. Again this won't solve the problem because, irrespective of the definitions of severity and the different weights that might be used, they would need to be applied equally to health gained and the type of health lost elsewhere, some of which is also in areas of quite high severity. [2] Considering the impacts outside the NHS on the rest of the economy won't resolve the issue either. Some new drugs offer benefits to the wider economy but some impose net costs. We also know that the health that we are likely to forego is associated with benefits in the wider economy. [2] So none of these considerations 'square the circle' of the current discrepancy between the prices charged for many new drugs and how much the NHS can afford to pay for the benefits they offer.

We are sometimes told that if costs can be reduced for manufacturers then prices will come down. The problem is that prices are not determined by the costs. The costs of developing new drugs are determined by the price that health care systems are willing to pay for new drugs. That's how capital markets work. If investors believe that health care systems are willing to pay more, more capital will flow into the sector and costs of development will rise until there is a normal return on those investments. Costs don't determine price. It's exactly the other way round.

Some express concern that unless the NHS continues to pay what are often unaffordable prices, innovation will not be supported and investment in research and development into the UK will be discouraged. Domestic prices have very little to do with the location of research and development. Much more important is investment in the type of basic science, which will provide the foundation of future innovation, and in evaluative research, so that the research environment in the UK is the best place to develop and evaluate new products. Using resources in this way will do much more to make the UK a more attractive place to invest than using the same resources to pay unaffordable prices for existing products.

¹ In 2013/14 the fund spent £231m treating 19,282 patients. An optimistic assessment of the benefits can be based on assuming an average 3 month overall survival benefit per patient (most funded drugs offered less than 3 months overall survival benefit) at a quality of life of 0.7. This suggests benefits of 3,374 QALYs but health opportunity costs of 17,821 QALYs lost elsewhere for other NHS patients, based on the recent estimate of £12,936 per QALY. [1,6]

The Cancer Drugs Fund

The Cancer Drugs Fund has been a real lesson demonstrating, beyond all reasonable doubt, that there is no blank cheque big enough to square this circle. The budget for the CDF rose from £50m in 2010/11 to £280m in 2014/15 but overspent by £136m. The budget for 2015/16 was increased to £340m but, despite a review of which drugs were funded, has significantly over-spent again.[6] The CDF has not been a sustainable solution to this problem and originally was never intended to be one. It was introduced as a temporary measure until pharmaceutical pricing was addressed through value based pricing [7]. But that fundamental issue remains to be resolved. As a consequence it has done considerable net harm to population health. Even an optimistic assessment of the QALY benefits of the drugs funded by the CDF suggests a ratio of harm to benefit of at least five to one.¹ [6] Although some manufacturers with oncology drugs have clearly benefited from the scheme, it has not been of particular benefit to the sector as a whole. It has offered perverse incentives and introduced unfairness between manufacturers because many that have not benefited from it have, nonetheless, paid greater rebates through the Pharmaceutical Price Regulation Scheme (PPRS) as a consequence. It wasn't intended as a long-term sustainable solution and it hasn't been, for the NHS or the pharmaceutical sector as a whole. Nor has it ultimately avoided the political difficulties of NHS patients facing restricted access to new cancer drugs.

What about the current plans to reform the CDF? Drugs which are not cost-effective even by NICE's standards will be funded within the scheme if there is a chance they might be shown to be cost-effective after data has been collected for two years. There are some good things. NICE will become responsible for the assessment of the benefits and costs of new cancer drugs. There's also a contingency which means that if the CDF budget is exceeded then manufacturers won't get the revenue that was initially expected and the budget will not overspend as it has in the past.

These two aspects of the reforms sound like good things but what are the incentives? The incentives for manufacturers are to provide as little evidence as possible at launch to make sure there is sufficient uncertainty at NICE appraisal to become eligible for CDF funding because there remains a chance that they might be cost-effective after two years of data collection. The second incentive is for manufacturers to price as high as possible. All manufacturers should expect the CDF budget to be exceeded and contingency funds to be withheld. To get the greatest share of the CDF budget, each manufacturer has an incentive to ensure their prices are as high as possible. Of course, there also remains a question of whether NICE will feel able to reject a drug after two years once it has become widely used. Recent history suggests it may not, in which case there is an incentive to establish a high price at the outset.

Possibly the greatest threat though is the faith in what's called 'real world' data. In the context of the CDF reforms, that appears to mean drug registries; observing what happens to patients using the new drug but without proper controls; observing similar patients not taking the new drug. Even if we have data from disease (rather than drug) registries we still need sufficient variation in treatment assignment, not different patients being treated differently, but the same type of patients treated differently. Without it comparisons will not be possible or will be biased because patients using and not using the new drug differ in important ways, some of which we can't observe. It becomes impossible to properly assess what would have happened to survival and quality of life without access to the drug. The presumption that we can necessarily gain useful and unbiased evidence in this way without seriously addressing these profound difficulties, ignores some of the basic principles of clinical epidemiology, what we know about good research design and Nobel-prize winning work on how to analyse observational data to understand causal effects. It ignores all the reasons why randomised controlled trials are, quite rightly, the cornerstone of evidence based medicine.

There is a real danger that these proposals will undermine the evidence base for clinical practice in the long run, which may be an even greater threat to health outcomes for cancer and other NHS patients than paying for cost-ineffective drugs through the CDF while the type of 'research' envisaged is undertaken. We will not know what works and what doesn't work and for whom. Nor will we have the opportunity to find out later once these products are in widespread use because it will be impossible to conduct the type of randomised trials that would be required. [8]

A mechanism to take a more sensible approach is available. It's one of the statutes on which NICE was founded, which says NICE has a responsibility to identify technologies that should only be used in the context of research and make 'only in research' recommendations. NICE asked the MRC to fund research to establish how NICE might make better use of these powers. [9,10] That research shows how the need for additional evidence might be judged and indicates that when we are unsure as to whether a new drug is worthwhile, and especially when the balance of evidence suggests it is not, NICE should make an 'only in research' recommendation which restricts use to within research that can resolve uncertainties. Restricting approval to only in research means that the type of randomised trials that are needed can be conducted. It also means that when the research reports, NICE is in a position to consider whether the drug should be approved for widespread use or rejected.

Of course, in making 'only in research' recommendations we do need to consider better and more innovative research designs, for example random allocation to groups that have access to current NHS care and those that also have access to the new drug. We also need to consider who will fund and conduct this research. Instead of paying for the widespread use of cost-ineffective drugs while

inadequate data is collected, the resources devoted to the Cancer Drugs Fund could instead be used to fund well designed independent research that would resolve some of these questions and have a much bigger impact on patient outcomes.

The Pharmaceutical Price Regulation Scheme

There is one good thing in recent history; at least there are some good elements to it. The current Pharmaceutical Price Regulation Scheme, which was negotiated in 2014, agreed caps on NHS spending on branded drugs. Rebates are paid at a national level by manufacturers based on their historic market share, when the caps are exceeded. It's good in two respects. It has protected the NHS somewhat and substantial rebates are being paid. Importantly it demonstrates that national rebate mechanisms are possible and can be agreed.

What are the problems with the PPRS? We don't know if the cap was set too high or too low because the cap wasn't based on an assessment of the value of the branded drugs the NHS currently pays for. It doesn't offer the right incentives either. It is unfair to manufacturers who produce valuable drugs and are responsible in their pricing. For example manufacturers with very effective drugs at reasonable prices are potentially paying higher rebates than those manufacturers with drugs offering modest benefits at unaffordable prices. It fails to distinguish the most valuable innovations compared to those of more limited value and again offers an incentive to price as high as possible to retain the greatest share of capped expenditure. Also, the rebate is paid at a national level so it doesn't reach the prescribers who still face (unrebated) prices and high prescribing costs that fall directly on their budgets. As a consequence there is no incentive for early uptake.

The PPRS will be renegotiated in 2020. At that point manufacturers could point to the fact that the caps on expenditure have been exceeded and should be increased. Unless the question of what price the NHS can afford to pay is addressed and some mechanism to adjust how much the NHS pays is in place, the Department of Health will not be in a strong position to resist these arguments.

This is especially acute as failing to agree continued rebates will remove the protection the NHS has had from cost-ineffective drugs that have become widely used. There is an urgent need to find a solution to this fundamental problem.

There is a solution

There is a solution and it has been available for some time. [7,11] It was set out in the consultation on value based pricing in 2010 but only now are all the elements required in place.[12] All that is needed is to link NICE appraisal of the costs and benefits of new drugs with the type of national rebate agreements in the current PPRS. The difference is that the rebates should reflect the discrepancy between the prices manufacturers wish to charge for their products and how much the NHS can afford to pay for the benefits they provide.

This would offer the right incentives for manufacturers. It would provide a clear and predictable signal of what the NHS can afford to pay for the benefits offered by developing a new drug, which is what is needed to make good long term investment decisions. It would also provide fair rewards for innovation, because those manufacturers that produce more effective drugs at affordable prices will not need to pay a rebate, but those that wish to maintain high prices for drugs of modest benefit will pay higher rebates. Manufacturers also need to be able to set prices for global markets without fear that offering lower prices in the UK will be referenced elsewhere. That's why rebates at a national level are so important. The current PPRS shows that how much the NHS ultimately pays for drugs can be adjusted through a national rebate agreement without asking manufacturers to change their prices for the UK.

Manufacturers also require some assurance that once they have developed an effective new drug and agreed a rebate, that there will be early uptake and they will get the volume of prescribing appropriate to its indication. For example, NHS England and the Department of Health could retain some of the expenditure on new drugs to fully reimburse those who prescribe products where a rebate agreement is in place. This would avoid the current problem of commissioners and prescribers facing high prices falling directly on their budgets. As a consequence, where rebates are agreed and local prescribing costs are fully reimbursed, there would be an incentive for early uptake and no reason why patient access should differ across the NHS.

This would mean that NICE could focus on what it does best: assessing the costs and benefits of new drugs based on the evidence. Manufacturers can then decide if they wish to agree to any rebate that might be required. If they do, prescribers would be fully reimbursed. If they don't wish to agree a rebate then their product would still be available for use but would not be reimbursed, so the full cost would fall on prescriber's budgets. NICE would no longer be placed in the politically difficult and potentially compromising position of being asked to approve or reject new drugs. Instead it can focus on an accountable and transparent assessment of the evidence.

Linking the NICE appraisal to value based rebates requires an assessment of how much the NHS can afford to pay for the benefits offered and that requires some assessment of health opportunity costs. For the first time we have an empirical estimate of the scale of health opportunity costs in the NHS. [1] Of course, as with any piece of empirical research, there are uncertainties. For example, currently we can only directly estimate the effect of changes in NHS expenditure on mortality outcomes. The important thing is that this research demonstrates that it is an empirical question that can be addressed and periodically re-estimated as more and better data become available. An ongoing evidence based and accountable assessment of health opportunity costs would give manufacturers the clear and predictable signal they need in making good investment decisions, aligning their incentives with what the NHS needs and how much it can afford to pay.

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UNIVERSITY of York

Centre for Health Economics
University of York
Heslington
York YO10 5DD

UK Tel: +44 1904 321401
Fax: +44 1904 321402
Email: che-news@york.ac.uk
www.york.ac.uk/che