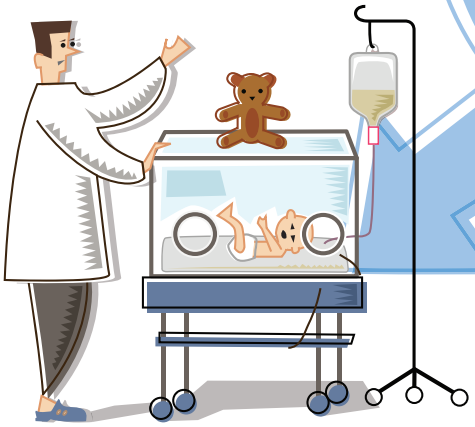
Health rationing in Europe: can cancer get a fair hearing?

Anna Wagstaff

Faced with escalating drug prices and rising patient expectations, Europe's governments are anxious to ensure value for money from their overstretched health budgets. But how can one measure the value of a few extra precious months of life, and could requirements to show strong evidence of value for money in the short term hinder the development of effective therapies over the longer term?

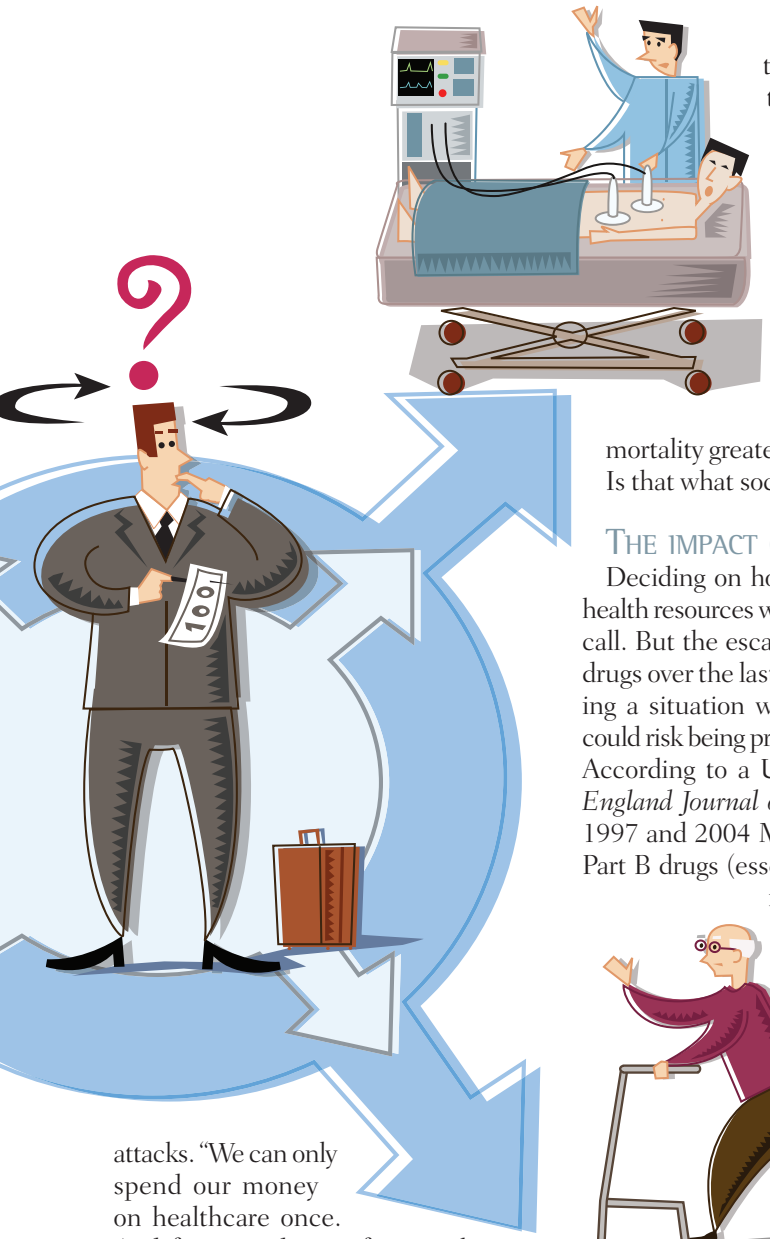


The value of good health is surely something we can all agree on. On a personal level, it contributes to wellbeing, long life, the ability to earn a living, enjoy leisure time, have children and raise a family. It is also good for the economy, reducing the amount of wealth needed for curing and caring, and minimising the number of people taken out of the workforce on grounds of ill health or to look after ill dependents.

It might come as a surprise to some, therefore, that a UK body set up with the laudable task of ensuring that available health resources are used to the best possible effect found itself, last August, being labelled 'barbaric', with one organisation in the US even equating it with a terrorist organisation.

The trigger for this outburst was a decision by the National Institute of Health and Clinical Excellence (NICE) to recommend against reimbursement of a number of new kidney cancer treatments, including the angiogenesis inhibitors Sutent (sunitinib) and Nexavar (sorafenib). NICE said that the cost of the treatments was significantly higher than the value they gave in terms of additional survival, adjusted for the improvements in the patients' quality of life. It justified its ruling by reference to the NICE social values document, which states that: "When there are limited resources for healthcare, applying the 'rule of rescue' may mean that other people will not be able to have the care or treatment they need." The rule of rescue, which had in fact been supported by a 'citizens council' set up by NICE in 2006, says that when someone's life is in danger there is a duty to try to help them no matter what the cost.

Barbaric? Or a brave decision in the interests of the greater good? As a spokesperson for the first explicit and unapologetic health rationing body in Europe, NICE chairman, Mike Rawlins, is no stranger to such highly emotive



attacks. "We can only spend our money on healthcare once. And if we spend it on a few people with rotten diseases, we will unquestionably deprive other people. Primary Care Trusts [responsible for the distribution of health budgets at a local level] are confronted with this problem all the time. I know a PCT that, because of increasing demands from funding these expensive drugs, has had to abandon improving arrangements for looking after children of immigrant parents who, in some parts of Britain, have a mortality greater than that in Kuwait. Is that what society wants?"

The impact of rising prices

Deciding on how to allocate limited health resources will always be a difficult call. But the escalating price of cancer drugs over the last decade or so is creating a situation where cancer patients could risk being priced out of the market. According to a US study in the *New England Journal of Medicine*, between 1997 and 2004 Medicare spending on Part B drugs (essentially cancer drugs) increased almost six times faster than its overall health spending (by 267% compared to 47%, adjusted for inflation).

Some of that will be down to an increasing incidence of cancer resulting largely from the increasing age profile of the population. Much of it, however, is due to the very high prices being charged for the new generation of targeted cancer drugs. In a credit crunch, the money to pay for these drugs will have to come from other areas of health spending. As a result, European governments and social insurance bodies are increasingly turning towards the use of health technology assessments (HTAs) – systems for deciding on the resource implications and the benefits associated with new drugs, diagnostics or other medical products – to inform decisions on what they will reimburse and at what price. Those who believe that they should continue to stump up for ever more pricey cancer therapies will have to make a strong case.

The value of life

One area of major battles for cancer patients has been over the use of the QALY (quality of life-adjusted life year) or DALY (disability-adjusted life year) to calculate the value offered by a given therapy.

From the perspective of getting the most out of a limited health budget, QALY-type measurements make perfect sense, and are used to inform decision making in many countries, including the UK, Sweden and the Netherlands. They provide a single measure that can be used to compare the benefit of any health intervention against any other, enabling health economists to evaluate in an objective way whether extending reimbursement of anti-cholesterol medication to those at lower levels of risk would offer greater value for money than using the same money to pay for Alzheimer's patients to receive an innovative therapy at an earlier stage, or for improving maternity services or introducing endoscopy screening for colorectal cancer.

ILLUSTRATION: FRED VAN DEELEN, WWW.ORGANISART.CO.UK

"We can only spend our money once. If we spend it on a few people with rotten diseases, we will deprive others"

Evaluation of health technologies across Europe

Criteria	AT	BE	CH	DE	FI	FR	NL	NO	SE	UK
Therapeutic benefit	●	●	●	●	●	●	●	●	●	●
Patient benefit	●	●	●	●	●	●	●	●	●	●
Cost-effectiveness	●	●			●		●	●	●	●
Budget impact		●			●	●	●	●		●
Pharmaceutical/innovative characteristics	●	●				●	●			●
Availability of therapeutic alternatives	●						●		●	●
Equity considerations								●	●	●
Public health impact						●				
R&D					●					

Source: Adapted from Zentner et al, 2005 (http://portal.dimdi.de/de/hta/hta_berichte/hta122_bericht_de.pdf) and case studies

HTA assessments that look at cost-effectiveness are likely to work better for cancer patients if they also take into account issues of equity (particularly important for patients with more rare diseases), the availability of therapeutic alternatives and the level of innovation

AT – Austria, BE – Belgium, CH – Switzerland, DE – Germany, FI – Finland, FR – France, NL – Netherlands, NO – Norway, SE – Sweden

The UK and the Netherlands both use a basic value of around €20,000 (£20,000 in the UK), for each extra year of life – higher if the extra survival is accompanied with an improvement in the patient's quality of life as well.

Cancer patient advocates argue that this is too low, and that tax payers and social insurance schemes are prepared to pay more to enable patients with life-threatening diseases enjoy an extra year. They point out that the state pays more than this to keep a prisoner in jail for a year, and question whether the government has got its priorities right.

NICE chairman, Rawlins, offers a different comparator. "The Ministry of Transport uses a similar figure when calculating the safety benefit of traffic schemes in terms of lives saved. The Home Office uses a slightly higher level for deciding how much to spend on keeping the streets safe. Maybe that's right, maybe it is a higher priority to keep the streets safe. It is a difficult area."

Patient advocates claim that the QALY lacks humanity because it fails to recognise the importance of an extra three months' life to a patient who has just learnt they have only six months to live. Those three months should not be valued the same as extending a person's natural life span by the same amount.

Denis Strangman, chairman of the International Brain Tumour Alliance, was one of the advocates who contributed evidence to the citizen's council set up by NICE in 2006 to review this issue. "The impact of the brain tumour journey, not just on the patient but on the family and the caregiver, is one of the most traumatic of any disease," he says. "Its onset tends to be extremely rapid, and affects not just the patient's mental and physical capacity, but their entire essence and being – a combination of the worst of the neurological diseases with the worst of the cancers."

Under these circumstances, says Strangman, being able to hold back the disease or its impact for even a matter of weeks can be immensely valuable to both patient and family.

The argument comes back to the 'rule of rescue' and the question of how much society is prepared to pay to help patients with a terminal disease. In practice, the Dutch, Swedish and UK systems do have some flexibility to take this added trauma into account. The Swedish Pharmaceutical Benefits Agency (TLV) identifies 'need and solidarity' as one of the principles for deciding on reimbursement, alongside

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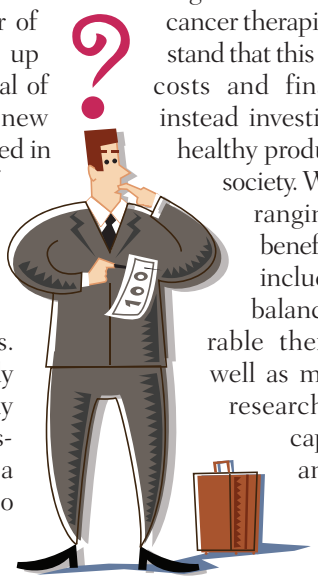
Cancer drugs tend to be trialled first in advanced cancers, where the benefit is much harder to prove

cost-effectiveness and equity. The Netherlands uses an 'index of severity' – which, in effect, lowers the value-for-money threshold for more serious or terminal diseases. NICE too has the flexibility to extend the QALY beyond the £20,000 basic threshold. Rawlins points out that cancer drugs are routinely given QALYs of £30,000 or more – £40,000 in the case of Glivec (imatinib).

Whether this is enough is a different question. The political fallout from the decision to recommend against reimbursement for the kidney cancer treatments led to the Minister of Health asking NICE to draw up new guidelines for the appraisal of end-of-life treatments. The new guidelines, which were published in January 2009, have the effect of treating some (rarer) cancers and other terminal diseases as a special case. The move, says Rawlins, was necessitated by the high price of cancer drugs. The same problem has already led the Netherlands to take many new cancer drugs out of the hospital drugs budgets and into a national system. Canada is also thinking of ring-fencing a budget exclusively for very high cost treatments.



Proving benefit: a loaded dice?

But there is more at stake than the immediate issue of access to the latest therapies. The complex process by which cancer therapies achieve successive improvements is intricately bound up with learning how to get the best out of new therapies – which can only be done when they are in widespread clinical use. Which patients, which dose, which stage of disease, which combinations, concomitant or sequential? Demanding too much from a drug too early could jeopardise the incremental improvements that have slowly but steadily improved outcomes for many cancers.

Andreas Penk, president of Pfizer Oncology Europe, worries that by focusing on short-term costs, HTA procedures could be damaging for the long-term development of effective cancer therapies. "We have to understand that this is not just a question of costs and financial burdens, but instead investing in the future of a healthy productive and progressive society. We need the most wide-ranging understanding of benefits possible, which also includes 'soft evidence' that balances costs and measurable therapeutic benefits as well as maintaining innovative research and manufacturing capacities of companies and ensures the long-term sustainability of the healthcare process." Some HTA procedures, he adds, "make proof of the benefits of specific innovation types more difficult, and consequently act as a deterrent to taking financial risk."

Some problems are fairly specific to assessing new cancer therapies. Simon Jose, general manager of GSK, UK, points out that new cancer therapies are almost always trialled in patients with advanced cancer, who have run out of recognised options. "It is much harder to demonstrate greater clinical value at this stage in this group of patients than if you had started earlier, because the earlier you intervene, the more responsive the disease is likely to be."

The problem is compounded by ethical imperatives in clinical trials. For example, in a trial of GSK's Tyverb (lapatinib) in combination with capecitabine in patients with HER2+ breast cancer who no longer respond to Herceptin (trastuzumab), a difference emerged during the trial in favour of the patients on the combination of drugs.

The data safety monitoring board recommended that patients on capecitabine cross over to the capecitabine plus Tyverb arm. The study was then closed, because it was no longer ethical to offer patients capecitabine alone. This was the right ethical decision says Jose, but it undermined the strength of the survival evidence. The statistical power of the study was weakened because recruitment stopped before the intended number of patients had enrolled.

In addition, because the outcomes were judged according to the 'intention to treat', rather than the treatment patients actually received, patients who crossed over to the drug combination were assessed as if they had taken capecitabine alone. Since some of them had in fact been on Tyverb for some of the time, that compressed the difference shown between the two arms of the trial.

"The data you end up generating is not as pure as you might like. While it is sufficient to get you through the regulatory process, it creates some issues for us

in the payer environment," says Jose. He accepts that it is fair for payers to ask for reasonable evidence of survival benefit. "The question is, are you happy with the 80:20 rule and accept the benefit that we can show, or do you have to search for the 100% and absolute certainty, which does not reflect the real world? The challenge is that you would never go back into that patient population and do another study like that because that wouldn't be ethical."

Because the progress offered by successive new cancer therapies tends to come in small steps, it can be quite a challenge to prove that new therapies really are worth their price tag. Jessamy Baird, HTA lead at Lilly UK, speaks from her company's long experience with lung cancer. "Lung cancer is hard, because it's picked up late, and you are looking at quite small changes, but they add up. We've gone from 5 months to over 12 months survival, and its better looking forward. But HTA bodies can find it very difficult to recognise the value of those incremental steps."

She argues that new therapies should be given the benefit of the doubt, where the evidence is less conclusive than one might like. "Unlike the legal process, in which you are innocent until proven guilty, in the pharmaceutical HTA assessment, you are guilty until proven innocent. If you say 'no' to medicines early on, you will never have the data to show they work further down the line."

From the perspective of NICE, Rawlins acknowledges that having to prove a drug's value in the sickest patients can load the dice heavily against making the value for money case. He believes the answer may lie in a flexible pricing scheme currently being discussed in the UK. "A new drug comes on the market – a good example would have been Herceptin for late breast cancer – and a manufacturer can bring it in at a relatively low price. Then when they demonstrate later on that it is curative in early cancer, they can negotiate a higher price."

Obstacles to generating robust evidence while keeping faith with the patients on the trial, he believes, will be harder to resolve. "It's not a case of wanting scientific purity. We want to find out in as decent and humane way as possible whether a drug should be used and whether it is good use of health service resources." Rawlins questions whether many of the trials that are stopped early because the experimental treatment appears to be superior are really able to provide this evidence.

"There is absolutely no consensus among the statisticians about when to stop. There is real worry that we may be stopping too early sometimes." Only one-third of cancer trials now go through to the end, he adds. "Very often we are talking about fairly modest changes, and nobody really knows how to distinguish a true positive from a true negative."

Various 'risk-sharing' or 'patient access' schemes have been proposed to address the lack of certainty. In Italy, Novartis has agreed a scheme for Tasigna (nilotinib, a drug for CML patients who are resistant or intolerant to Glivec), under which the company refunds the cost of treatment for every patient who does not reach an agreed haematological response after one month. A similar agreement was reached in the UK with Janssen-Cilag over the myeloma drug Velcade (bortezomib) two years ago, and more recently GSK proposed such a patient access programme for Tyverb, also in the UK.

Rawlins accepts there is a place for these sorts of agreements, but stresses the urgent need to improve the statistical basis on which many cancer drugs are now assessed.

As for the need to look beyond short-term value for money to provide an 'innovation-friendly' environment where companies feel they will be rewarded for taking risks and aiming high, Rawlins says that HTA bodies do want to back innovation, but it is not always clear how. France has traditionally been seen as a strong supporter of pharmaceutical innovation, and offers a price premium for drugs that are considered to offer something new. Belgium, Netherlands, Austria and the UK all take into account the innovative characteristics of new therapies. But, although support for innovation is written into the NICE remit, Rawlins points out that no one has ever explained exactly what that should mean. "What should we value about innovation? What is innovation? What aspects should we regard as important?" he asks. "Views range from: 'if it has got a patent, it's innovative,' to, 'well it acts in a different way and therefore it's innovative and you ought to give extra credence to it'." This is an area that NICE intends explore further in the coming year.

The benefits of saying 'no'

Despite resistance by many patient advocates, doctors and pharmaceutical companies, there are others who say that a well-designed HTA system is essential to deliver the best for patients on an economically sustainable basis.

"What should we value about innovation? What aspects should we regard as important?"

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Christina Bergdahl is patient representative on the Swedish Dental and Pharmaceutical Benefits Agency (TLV), which was established in 2002, in response to the rapid increase in drug prices, to decide which medicines should be reimbursed. She believes the new body is more democratic, transparent and effective than the previous system, where decisions on reimbursing drugs were taken by the national insurance agency.

As well as a patient representative, the 11-strong TLV committee includes a representative of the public, pharmacologists, doctors and health economists. Its brief is to appraise treatments according to three principles: everyone is treated equally regardless of age, gender, race and so on; people with more severe diseases are prioritised over those with less severe conditions; and the cost of using a medicine should be reasonable from a medical, humanitarian and socio-economic perspective.

Central to the appraisals, says Bergdahl, is evidence presented by patients about what the medicine actually does for them. "Does it enable them to go to work, or look after the children, or simply manage at home rather than being confined to hospital?" This helps to prioritise therapies that make a real difference to patients, says Bergdahl, and protects patients against pressure from politicians, and sometimes the media, to refuse to fund very expensive therapies, regardless of the benefits. This patient input, she believes, must be an essential element of any HTA system; she has even contributed to a European 'tool kit' designed to help patients present such evidence in the most effective manner (automatic download at http//tinyurl.com/HTA-toolkit).

So far, her experience of saying 'no' to some drugs has been entirely positive. By stopping reimbursement for drugs found to be less effective or more expensive than an alternative, TLV has saved €90 million. "When we do these big assessments [which assess all medicines for a given condition], and see that we can save, say 200 million kronor, I see that this money can be used for another patient group."

Bergdahl has not yet been confronted with the need to say 'no' to reimbursing a new cancer therapy that patients want, but which would impose additional costs that are considered out of proportion for the additional benefit. She recognises, however, that the day may come when she may have to do so.

A JOINED UP APPROACH

Even doctors, traditionally jealous of their right to treat patients according to their best judgement, are beginning to accept the need to take into account treatment decisions on the system as a whole. There is concern, however, that a lack of input from doctors with specialist knowledge of treating the disease – rather than just of the pharmacological properties of the drug – means that HTA and reimbursement decisions do not always get it right.

Paolo Casali, a sarcoma specialist at the Istituto Tumori in Milan, suggests it would be better for regulatory approval and reimbursement to be more closely linked with clinical guidelines specifying how the drug should be used. Without this link, he points out, the drug is approved for reimbursement not just for patients who are likely to benefit, but also for those in whom the clinical guidelines do not recommend its use. "Once it is approved and reimbursable, it is very difficult not to use it – not in a fatal disease," says Casali, "even if it's highly unlikely to be of any clinical benefit." The reverse, he points out, is equally true. There are many examples of guidelines, particularly for rarer cancers like sarcomas, which recommend use of drugs that are not reimbursed, because they have not been specifically approved for use in that setting.

"Approval, HTA and reimbursement, and clinical guidelines are all very much related," says Casali, "and should be dealt with together. An effort should be made to coordinate these steps."

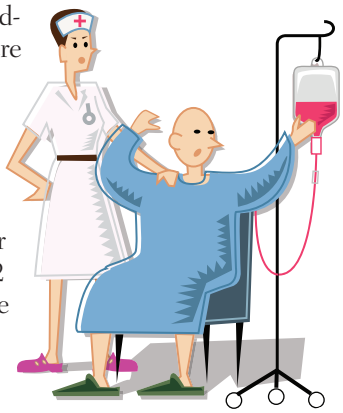
Pharmaceutical companies spent many years railing against HTA appraisals as a 'fourth hurdle' for drugs that had successfully completed phase I, II and III trials. They now seem resigned to the inevitable. Using the maxim 'if you can't beat them join them,' they have recently been snapping up many of the brightest young graduates in health economics, and are trying to have some say over the way HTA develops across Europe and beyond.

They are looking for more flexibility, with an emphasis on a greater level of interaction based on a shared commitment to the long-term goals of bringing new therapies to the market that meet the needs of patients and health services. "We need clear, reliable, innovation-friendly conditions in which to operate," says Penk from Pfizer. "It is imperative to view HTA as a consensus-oriented

"We need clear, reliable, innovation-friendly conditions in which to operate"

process, in which all relevant stakeholders in healthcare are involved. As a research-based company, we can and should contribute determinedly to initiating long-term, viable, constructive and patient-oriented solutions."

Jose from GSK agrees. "There are some real challenges and we need some flexibility around the edges when we are making decisions about patient access to these products. We accept that there are limitations regarding the data in these end-stage settings, as in the case of Tyverb. But in this situation we suggested that we would cover the cost of the first 12 weeks, to try to offset some of that uncertainty. Both parties have got to find a way around this. Ultimately the challenge has to be to get access for the patients who need it."



Guido Guidi, head of the European Oncology division of Novartis, calls for a much greater interactivity between companies and health authorities, including the possibility of informal discussions when the drug is still in phase II trials to identify what benefits the authorities are looking for, and what types of data they require to demonstrate those benefits. This, he argues, could help improve the correspondence between what companies are developing and the needs of health systems, which in turn could help cut down the amount of resources wasted on developing drugs that patients will never access.

He says that, like many companies, Novartis is conscious of the need to cut costs by, for instance, being more effective at weeding out unpromising drugs at an earlier stage of development. It is also engaged in trying to improve the value offered by new therapies, by finding markers that can identify patients most likely to respond, and is trying to address the uncertainty surrounding trials that have been stopped before they could generate strong survival data, by finding ways to demonstrate the link between progression-free survival and overall survival.

Novartis is even happy to discuss conducting additional studies after reimbursement, says Guidi. "We can fix reimbursement of a new drug and can then have a post-approval commitment where the company and payer fix some endpoint, and we can verify this at a certain time period. If it turns out to be more effective, you can add a premium; if it is less effective, you must agree a lower price. This way you can get the drug quicker to the patient, but continue to monitor the efficacy and safety of the drug, which is helpful to patients and the community."

There's plenty of room for finding flexible solutions, is the point he's making – but there needs to be a will on both sides. "I think we have to get out of a system where the different parts are fighting one against another," says Guidi. "Health authorities, physicians, pharma companies and patient advocates need to work together to ensure patients get access to effective drugs. If we don't, we are not doing our jobs. Sometimes I have the impression that the health authorities interpret 'no' as a success. But is this an optimal outcome?"

Squaring the circle

Could there ever be a dream HTA body that meets the demands of patients, provides an environment conducive to innovation and ensures that the maximum benefit is gained for every cent spent on healthcare? If so, what would it look like?

These questions have been exercising an increasing number of European minds – among them that of Panos Kanavos, a senior lecturer in international health policy at the London School of Economics. His answer to the first question is 'no' because health systems vary so much in the way they are organised and funded. Any HTA body that seeks to influence the behaviour of a health service needs to be moulded around that service – though there are opportunities for harmonising HTA structures across countries.

Yet, even if there is no blueprint for a perfect HTA system, it should be possible to reach agreement on some key qualities, and Kanavos has been working with Michael Drummond from the University of York, UK, and Ulf Persson from the Institute of Health Economics in Stockholm, Sweden, to see how this might be achieved, based on current practices in EU countries and previous work by other colleagues (see box). These are broadly outlined in a paper, *The Future of HTA in Europe*, which was presented in Prague in February 2009 as part of the Cox report, *Securing Europe's Healthcare Future:*

Chronic Disease Management and Health Technology Assessment. The paper also presents an overview of the experience of HTA in Europe, and tries to identify the potential for harmonising or approximating key areas of HTA focus and to suggest areas of collaboration.

Such harmonisation could be important in reducing inequalities in access to healthcare across Europe and minimising duplication of aspects of HTA analyses that don't necessarily have to be done at a purely national level. It could also be welcome for the pharmaceutical companies who are having to demonstrate the value of their products in an increasing number of countries.

Kanavos stresses that all of this is at a very early stage. Countries serious about introducing robust systems to ensure the best use of health expenditure will need to set aside serious resources, not least investing in training of health economists and supporting the facilities that carry out the HTA assessments. "The government of a European country asked us once to help them implement HTA and economic evaluation, and we asked: 'How many people do you have in the country who can read and understand economic evaluation and technology assessments?', and they said 'none'. I think they've made some strides since then."

Things are moving fast, he says. "Health economics is now one of the flagship sectors in academia, including in Eastern and Central Europe; many economists are switching to specialise in health. There are pockets of excellence and activity everywhere. And we've seen the establishment of agencies in many countries including Poland and Hungary; the Czech Republic is now is debating establishing one. These developments have happened literally in the past two to three years."

Kanavos talks in terms of "promoting a culture of assessing technologies" – not just medicines, but more globally. "From our perspective [at the LSE], from the way we deal with governments, institutions and insurers, the debate has already started: Are we maximising health benefits? Who benefits? Can we quantify these benefits? Can we measure performance? You don't expect a change in direction overnight, it takes a lot of time, a lot of debate and a significant amount of work to achieve consensus." Indeed the Cox report itself has not been greeted with universal acclaim, with many voices critical of the heavy emphasis on market mechanisms to stimulate innovation, and its failure to take a critical look at whether the high drug prices are really justified.

The coming three to five years, says Kanavos, are likely to shape the way all these issues are resolved for a long time to come. Those who care that the systems for technology assessment work well for cancer patients current and future will need to be a part of that debate.

WHAT MAKES AN HTA SYSTEM WORK?

- The goal of the HTA should be explicit and relevant – how will the findings be used?
- The process should be unbiased, rigorous and transparent – credibility will be undermined if the public believes hidden influences are at work.
- It should look at all relevant technologies – the value for money test should apply to all health expenditure, existing and new, and not just drugs.
- Assessments should be carried out by appropriately trained experts using rigorous methodology – this requires adequate resourcing.
- Evidence and data should be gathered from the widest range of relevant sources.
- Costs and benefits should be judged on a wide basis – there's no point cutting costs in one part of the system if the consequence is to raise them even more in another part.
- Uncertainty over estimates should be specified – manufacturers and HTA agencies should work together over issues of uncertainty and assessment of new data.
- All groups with a stake in the outcome should have an effective input into the process.
- The process of HTA evaluation should be carried out independent of the body that decides on pricing and reimbursement – questions of affordability are a matter for politicians.
- HTA systems need 'early warning' systems to identify emerging technologies that might require urgent evaluation – this can reduce the delay in getting effective new treatments and diagnostic products to patients.

Sources: Adapted from P Kanavos, U Persson and M Drummond (2009). *The Future of HTA in Europe*, www.sustainhealthcare.org; and M Drummond, J Schwartz, B Jönsson et al. (2008a) Key principles for the improved conduct of health technology assessments for resource allocation decisions. *Int J Technol Assess Health Care* 24:244–258

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