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Inclusion of cost effectiveness in licensing requirements of new drugs: The fourth hurdle

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Abstract

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Inclusion of cost effectiveness in licensing requirements of new drugs: the fourth hurdle

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Increasing numbers of countries are considering cost effectiveness in decisions about which drugs to make available for prescription. How do the different approaches work and is it time for standardisation?

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Licensing is the main method of regulating and controlling access to pharmaceuticals. New drugs cannot receive a product licence until manufacturers provide evidence of their quality, safety, and efficacy. In a world of rapidly escalating global healthcare costs, evidence of a drug's quality, safety, and efficacy is no longer sufficient to ensure reimbursement for use in public markets. Increasingly, new drugs must show evidence of cost effectiveness. In other words, does the drug produce a useful health gain (over and above currently available treatments) for its additional cost? In industry circles this value for money requirement has become known as the fourth hurdle. In this article, we examine the international development of fourth hurdle policies, analyse their effect, and identify some of the future challenges and likely directions.

Emergence of the fourth hurdle

The first healthcare system to develop formal regulations governing the use of cost effectiveness evidence in reimbursement decisions was Australia. Since 1993, the Australian Pharmaceutical Benefit Scheme has insisted on appropriate economic evidence before authorising public funding of a new drug.¹ Once the Pharmaceutical Benefits Advisory Committee receives a submission from a pharmaceutical company, it is appraised in an explicit process that deconstructs the evidence provided by the manufacturer. The committee considers the evidence on cost effectiveness as one of several potentially important factors when advising the health minister on whether to list the drug for reimbursement. These include:

- The importance of the clinical area
- The availability of alternative treatments
- The likely effect of listing on the healthcare system and other therapeutic activities
- The investment of the sponsor in primary research.

The committee may therefore accept a higher price for a "breakthrough" product that has required the sponsor to invest substantially in primary research than for subsequent drugs with similar action ("me too" drugs) when these have an equivalent group effect. However, relative cost effectiveness is considered the most important criterion.

In September 1994, the Canadian Province of Ontario followed the Australian lead in issuing guidelines for the economic evaluation of a drug. Since September 1995, submissions for listing of new drugs on the Ontario provincial formulary have been deemed to be incomplete if they do not contain an economic analysis or justify its absence.²



Australia has required data on cost effectiveness of drugs since 1993

Global development

Faced with greatly increasing drug budgets (see box 1) many countries, particularly in Europe, have begun to use economic evidence in national reimbursement decisions.

Europe

Probably the most important fourth hurdle development in Europe has been the technology appraisal programme of the UK's National Institute for Clinical Excellence (NICE). In its first few years, NICE has attracted much attention and criticism and is seen by some as a potential model of a pan-European fourth hurdle agency.³⁻⁵

A few countries have introduced a formal requirement for the consideration of economic evidence as part of the pricing or reimbursement decision. These include Belgium, Finland, Norway, Portugal, and Sweden. The Netherlands has indicated the intention to introduce a formal requirement but has postponed this until 2005. Just recently, Hungary has become one of the first Eastern European countries to signal the introduction of a formal requirement for economic evidence. Germany has recently established an institute, which may have an evaluation function, and there is some health technology assessment at a regional level in Spain. In several other countries, including Denmark, France, and Italy, the submission of economic evidence (by companies) is voluntary, but may be considered when it is submitted.



References w1-w16, a comparison of Australian and UK systems, and figures showing the effect on drug prices are on bmj.com

Box 1: Why are drug budgets rising? (adapted from Stevens et al^{w15})

The unit cost of new drugs has been higher than that of the drug they replace—for example, selective serotonin reuptake inhibitors cost six times as much as the older tricyclic antidepressants,^{w1} taxanes are several thousand pounds per patient more expensive than previous anticancer drugs,^{w2} and two drugs for severe rheumatoid arthritis—etanercept and infliximab—can cost nearly £10 000 per patient for every year that they are treated.^{w4}

Drugs are being developed for many conditions that have previously had no treatment—for example, lifestyle drugs (such as sildenafil for erectile dysfunction^{w5} and bupropion for stopping smoking^{w6}) and designer drugs often produced by the biotechnology industry to treat uncommon diseases^{w7}

The introduction of a drug can place a demand on the use of other expensive technologies—for example, the effective use of the anti-flu drug, zanamivir, is aided by a near patient diagnostic test to confirm flu-like illness.^{w8} Moreover, delivery of drugs may depend on other medical technology—for example, insulin pumps for diabetics,^{w9} intrathecal morphine pumps for chronic back pain,^{w10} and, more recently, the development of drug eluting coronary artery stents coated with anticoagulant glycoproteins.^{w11}

United States

Like Europe, the United States has only recently started to use economic evaluation in drug listing decisions. In 1998, Regence BlueShield, a health management organisation, began requesting clinical and economic evidence from pharmaceutical and biopharmaceutical manufacturers as a condition for formulary review.⁶ In 2000, the Academy of Managed Care Pharmacy (AMCP), a national professional society of managed care purchasers, developed its own version of the guidelines—the AMCP format for formulary submission.⁷ Although an exact figure is not known, over 50 private and public sector healthcare purchaser organisations, covering well over 120 million lives, have adopted the AMCP format or a similar process.

Rest of the world

Little has been written about use of economic evaluation outside Australia, Europe, and North America. For example, Japan, despite being the second largest health care economy in the world, seems to have done little economic evaluation and currently has no system of limiting market entry of drugs based on their cost effectiveness.⁸

Many countries are now implementing formal or informal fourth hurdle systems that reflect the local health economy.⁹ Box 2 outlines the requirements of these systems (see bmj.com for illustration of the differing approaches to these requirements in the Australian and UK systems).

Effect of fourth hurdle

The ultimate goal of economic evaluation may be to maximise health for a given healthcare budget, but this is difficult to assess in practice. Here, we examine the effect of the fourth hurdle according to three outcomes: quality of evidence, effect on reimbursement policies, and effect on price

Quality of pharmacoeconomic evidence

The problem of quality and related biases in pharmacoeconomic studies has long been recognised. Friedberg and colleagues found that studies funded by the pharmaceutical industry were one eighth as likely to reach unfavourable qualitative conclusions, and 1.4 times more likely to reach favourable quantitative conclusions as non-profit funded studies.¹¹ The industry related bias in economic evaluation publications has been confirmed in several subsequent publications.¹²

Is the quality of pharmaceutical industry economic submissions to fourth hurdle agencies any better than published studies? Hill and colleagues examined all 326 submissions made to the Australian Pharmaceutical Benefit Scheme between 1994 and 1997.¹³ Of these submissions, 216 (67%) were considered to present “serious problems of interpretation.” The drug benefit plan committees in British Columbia and Ontario have confirmed this Australian experience. Anis et al reported that of the 32 pharmacoeconomic studies submitted to the two committees in 1996, only 21 could be used to make recommendations, the remainder being rejected because they contained incomplete or pending information.¹⁴

We were unable to find more recent publications examining the quality of pharmacoeconomics submitted to fourth hurdle agencies. However, our collective experience is that the quality of industry reimbursement submissions has probably improved. Nevertheless, complex decision analysis models are being increasingly used to support the acceptable (or not) cost effectiveness of drugs; this move is supported by the recent technical guidance released by NICE.¹⁵ The models vary in quality and many are not very transparent, making continued independent assessment of models essential within the fourth hurdle process.

Does cost effectiveness information influence reimbursement decisions?

A central premise of the fourth hurdle approach is that those drugs deemed to achieve acceptable cost effectiveness are recommended while those that fail to meet acceptable levels are more likely to be rejected. What might constitute acceptable cost effectiveness is beyond the scope of this article and has been discussed elsewhere.¹⁶

George and colleagues examined 355 submissions to the Australian Pharmaceutical Benefit System between 1991 and 1996 and found 26 that used cost per life year gained and nine that used cost per quality adjusted life year (QALY).¹⁷ Raftery conducted a similar exercise based on the decisions of the NICE technology appraisal programme up to March 2001.¹⁸ From these two studies it is possible to compare the cost per life year gained or QALY of drugs that have

Box 2: Stages in leaping the fourth hurdle

- Statement of information needs of decision maker
- Submission of evidence
- Critical assessment of evidence
- Appraisal or decision making
- Issuance of guidance policy

been recommended for funding versus those drugs that have been rejected. The threshold above which drugs were regarded as not providing good value for money seems to be \$A76 000 (£30 000, \$53 500, €44 000) per life year gained and \$A42 000 per QALY in the Australian study and £30 000 per life year gained or QALY in the NICE study.

Although broadly supportive of the objective of efficiency, both case series show that decision makers do not operate against a fixed willingness to pay threshold as an absolute decision rule. Other factors that can influence policy decisions include the overall budget impact of the drug (that is, the overall cost of introducing a drug to the health system); the rule of rescue (that is, funding a drug for a serious clinical condition on the grounds that alternative therapies are lacking or inadequate); and decisions around so called lifestyle drugs (such as sildenafil).

Effect of cost effectiveness analysis on price

An important potential consequence of including an assessment of cost effectiveness in licensing decisions is more efficient relative pricing. Indeed, reduced drug costs may be a specific objective in particular jurisdictions.

Drugs listed on the Australian Pharmaceutical Benefit Scheme have consistently been priced below the world average. The Bureau of Industry Economics estimated that in 1991 the prices of drugs in Australia were 30% below the European Union average and about 50% below the world average.¹⁹ A key question is whether the drug price differentials observed in 1991 have widened or narrowed as a result of the fourth hurdle requirement.

Australian drug prices have been compared with those in countries with similar and dissimilar subsidy arrangements.¹⁴ Prices have been compared for new innovative drugs, “me too” drugs, and generic drugs. Overall, the greatest price differentials between Australia and other countries are for “me too” and generic drugs (see bmj.com). Price differentials are smaller for innovative drugs with the exception of the United States (where prices are 104% higher). This is at least consistent with the objective of cost effectiveness in fourth hurdle systems, whereby price is set in relation to the value of the additional benefit of the drug with clinically superior drugs being rewarded with a higher price. This review of international drug prices concludes that “in very broad terms, it is difficult to find any obvious associations between the observed price differences and the types of subsidy and cost containment policies adopted in the comparison countries.” It may be that the biggest effect of fourth hurdle schemes on drug costs is not through individual drug prices but in better defining the appropriate clinical indications for the use of medicines.²⁰

Harmonising fourth hurdle systems

An inevitable consequence of the global growth of the fourth hurdle has been the development of a wide range of differing systems—both in terms of processes and methods. This is exemplified by the proliferation

Summary points

Licensing of drugs has traditionally been based on quality, safety, and efficacy

Faced with increasing healthcare costs, many countries are now also requiring evidence of cost effectiveness—the fourth hurdle

The limited evidence available suggests fourth hurdle policies have contributed to more cost effective use of drugs

Increasing international harmonisation and greater openness could improve the operation of fourth hurdle systems

of guidelines for economic submissions; a recent review identified over 25 different guidelines across Europe and North America.⁹

Several new drugs have been deemed to have acceptable cost effectiveness in one jurisdiction but been rejected in another (for example, zanamivir for the treatment of flu, riluzole for motor neuron disease, and interferon beta for multiple sclerosis). Variations in methods and processes across these countries may be contributing to these differences. A lesser but nevertheless potentially important effect of the differing fourth hurdle requirements across countries has been the inefficiency resulting from pharmaceutical manufacturers having to invest in often substantially differing submissions for a new drug in order to meet local requirements.

Although differences in decision making procedures and societal willingness to pay pharmaceutical policies between countries are likely to continue, the time seems right for a greater degree of harmonisation of methods. Drummond has recently outlined the issues to be considered in such a convergence of economic evaluation guidelines.²¹

Confidentiality and openness

A lack of confidentiality and openness presents challenges for the fourth hurdle.²² The Australian system is probably one of the starkest examples of a closed system that affords the industry a high level of confidentiality. Not only are the reasons behind its listing decisions not made publicly available, but, of even more concern, its negative decisions are not published at all. Should pharmaceutical companies be allowed to continue to submit data in confidence to public funding systems, including licensing?

Greater transparency in the decision making process will require industry to relax some of the constraints on the commercial in confidence nature of information they provide. Finally, openness encourages the considerable potential for collaboration between countries when evaluating pharmaceuticals.

Contributors and sources: All authors contributed to the design and writing of the article. RST is a member of the NICE appraisal committee and a member of the Birmingham Technology Assessment Group, which assesses technology on behalf of NICE. MD is a member of the NICE guidelines

review panels and a member of the York Technology Assessment Group. GS is an associate professor of health economics and a past member of the economics subcommittee, Pharmaceutical Benefits Advisory Committee, Australia. SDS is a member of the Premera Blue Cross Pharmacy and Therapeutics Committee and Director of the University of Washington Pharmaceutical Outcomes Research and Policy Program that undertake technology assessments for government and private concerns.

Competing interests: None declared.

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Q&A

Treating chronic inflammation of the Achilles tendon

Question

I have chronic Achilles tendinitis. An MRI scan has shown a few small foci of cystic degeneration within the thickened tendon. I am 63 and desperate to find a specialist in this field as I have had acute intermittent pain day and night for more than a year.

Elizabeth M Theo, *supply teacher, Surrey*

Answer

I recommend you to go to a physiotherapist and undergo phonophoresis with flufenamic acid gel. You may have to continue the therapy for at least two to three weeks, and you may feel an increase in your problem during the treatment days, but you will get better as the therapy ends. Please don't ever resort to a local corticosteroid injection.

Milind M Deshpande, *consultant orthosurgeon, Hubli, India*

Answer

May I add to the excellent advice of the previous correspondent. Once you have reached maximum medical improvement I would suggest you start a programme of gradually increasing barefoot walking. Choose irregular terrain, grass, sand, etc. Don't worry too much about impact on harder ground, even bitumen. I would do this on alternate days at first, later daily, but take the weekend or other two consecutive days off. Your feet will greatly appreciate being reminded of their original purpose and function and reward you richly. Needless to say, high heels would be as much a no-no as steroid injections.

Herbert H Nehrlich, *private practice, Bribie Island, Australia*

Answer

Have you heard of the Bowen technique? I have successfully treated a patient with a very thickened, scarred, and inflamed Achilles tendon. After pelvic, knee, and ankle procedures done over a short series of visits, this patient's Achilles tendon was far less inflamed and the patient was happily able to play tennis again.

The Bowen technique is a soft tissue therapy involving small and gentle moves across muscle and tendon fibres. Part of the aftercare involves walking, which backs up the second response to your question.

Isobel Knight, *Bowen therapist, Cambridge*

Answer

- 1 Use a soft shoe without a heel cap so as to reduce the mechanical inflammatory tendinitis
- 2 Use an ice pack daily for 15 minutes, moving it in circles
- 3 Apply diclofenac gel locally with gentle massage and stretch
- 4 Walk with a cane in the opposite hand.

Hesham Elsolamy, *rheumatology and rehabilitation, Cairo, Egypt*

http://bmj.bmjournals.com/cgi/qa-display/short/bmj_el;51396

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