Office of Health Economics Research

April 2014

Seminar Briefing 14

Real Option Value and Path Dependence in Oncology Innovation

Proceedings of an OHE Lunchtime Seminar given by Dr Joseph P Cook, Pfizer, Inc.[1]

1. INTRODUCTION

When a drug is approved, its direct implications for patients are considered based on the value expected from the approved indications at the time of launch. However, drugs can develop additional uses over time. Moreover, especially for oncology drugs, incremental innovation often proceeds in steps towards the development of major innovation with dramatic, curative effects. Evaluating the value of drugs only at launch, may then fail to capture the importance of a drug for future developments (defined as 'path-dependency'), leading to economic inefficiency. Hence, it may be possible to account for option—i.e. the value of developing a new use or of subsequent innovation—when assessing an incremental innovation at launch.

Rewarding path-dependent innovation in pricing, beyond the quality-adjusted life years (QALYs) delivered today, is an important topic. It has been debated at various times by the National Institute for Health and Care Excellence (NICE) as part of the 'value' in value-based pricing of medicines. From a payer's perspective, paying for option value can be considered valuable if this incentivises companies to invest in those products that would not be researched otherwise due to the high uncertainty of success in developing the future innovation. Moreover, paying for the option leads the firm to internalise the

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[1]Dr Joseph P Cook, Pfizer Inc., presented results from a study he published recently in the *International Journal of the Economics of Business* with Joseph Golec, John Vernon and George Pink (Cook et al., 2011). The views and opinions of the author expressed herein do not necessarily state or reflect those of his affiliation.

incentive to develop the intermediate innovation, speeding up or increasing the likelihood of attaining the future innovation. There is the potential for the issue of short-term self-interest: future drug developments may benefit only future generations, so purchasers may not have a strong enough incentive to pay now for benefits that will be recognised only in the long term ('myopia').

The concept of option value can also be applied to combinations of drugs: a new technology might be used in combination with currently available technology(ies) to produce major health benefits. In this case, the option value would be represented by the chance of successfully developing the combination technology.

A logical step forward is to explore how value can be rewarded. If that value is important to the drug coming to the market and there is no reward for it, then the potential benefit is lost or delayed. The next section investigates whether or not there is incremental value associated with a future use of a drug that is worth including in the current price.

2. REAL OPTION VALUE IN A SIMPLE MODEL OF A FIRM'S INVESTMENT DECISION

The role of the real option value in a firm's investment decision is illustrated simply in Figure 1.

Figure 1. Research path dependence for the discovery of new cancer therapies (adapted from Cook et al., 2011)

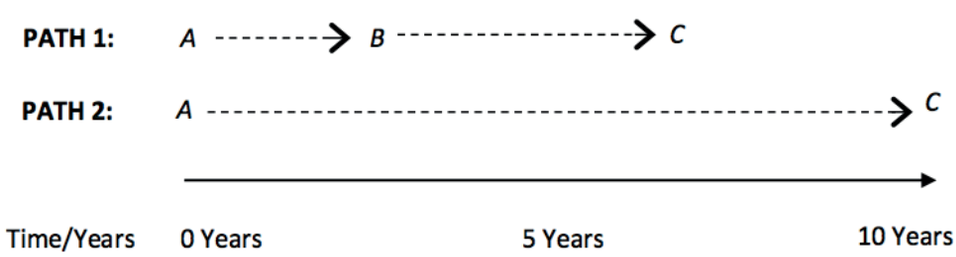


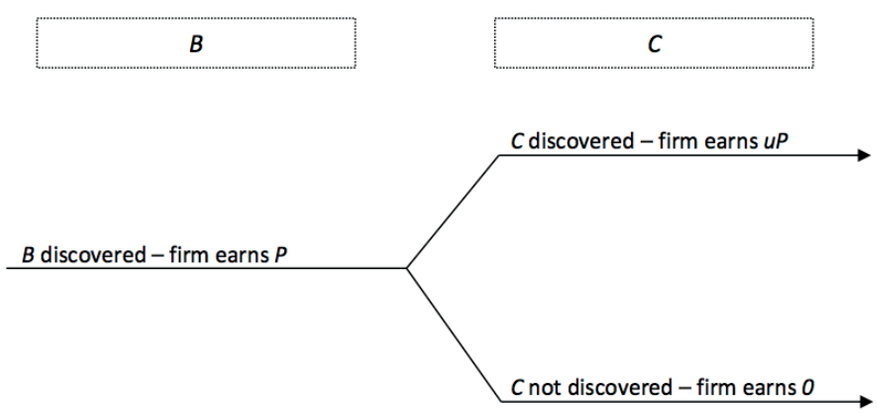
Figure 1 depicts two potential paths leading to technology *C*, a breakthrough that provides a bigger payoff than technology *A*. Both paths have the same starting position, where technology *A* is already available. Following Path 1, the manufacturer will develop technology *B*. *B* will give an option value to proceed to *C* at a faster rate and represents an intermediate, marginal improvement over *A* (it is not a great leap forward). Following Path 2, the manufacturer intends to go directly to *C*, skipping *B*. However, in this case it takes longer to develop *C*. This means that *B* provides a value beyond its therapeutic benefit, as the learning from *B* will help get to *C* faster.

The important question is how much innovation should be valued. In the early 2000s, Murphy and Topel estimated that a permanent 10% reduction in mortality due to pharmaceutical innovation was worth approximately $5 trillion in real US GDP (Murphy and Topel, 2003). A significant contribution

to this estimated decline in mortality comes from cancer research and development (R&D), which represents 17.9% of total global pharmaceutical R&D (Lichtenberg, 2010). In particular, combination therapies are becoming ubiquitous and are certainly common in cancer treatments (Reece et al., 2007) and in the treatment of malaria (Girardi et al., 2000). Another illustration might be tuberculosis for which three treatments are widely used. Although each treatment on its own may not appear particularly valuable, they perform well when used in combination. Therefore, it is important to understand how we should account for such synergistic values. HIV/AIDS is another good example of such synergies, well illustrated in Philipson et al. (2010).

The concept of net present value (NPV) in the standard capital-budgeting model is frequently used to assess the value of any technology—and to decide whether to progress it through the R&D process. Referring again to Figure 1, using the NPV would imply looking only at the value of *B* in terms of what it earns itself and not looking at its option value. The implementation of an option value approach would allow including future drug *C* in the decision tree. This is represented in a simple binomial pricing model in Figure 2, where the manufacturer decides to develop *B*, which can be sold at price P. In this example, if the sponsor does not research *B* first, the research for *C* is precluded. If *C* is developed, it replaces *B*, making *B* no longer necessary.

Figure 2. The firm's investment decision including real options (adapted from Cook et al., 2011)



Therefore, the investment in research for *B* opens up the possibility ('option') for the manufacturer to invest subsequently in the research for *C*. If this direction is eventually chosen (i.e. the option is 'called'), then research for *C* proceeds. The value of the call option depends on the price that the manufacturer would be able to charge for *C*: the higher the price for *C*, the higher the value of the option. In this case, the price the manufacturer can charge for *C* is *uP*, which is higher than the price P paid for the intermediate innovation ($u>1$). In particular, *u* represents the multiplicative increase in price above the price *P* of *B* that will be charged for *C*. The multiplicative factor also covers a risk-free rate of return (i.e. an investment rate of return with no risk of financial loss). The tree in Figure 2 considers the call option value, which is based on the upside value (*uP*) if *C* is discovered and the downside value (if *C* is not discovered), all discounted using a risk-free rate. Even assuming that the downside value is zero, the price of *B* is lifted higher to include the probability of successfully developing *C*. Therefore, *u* needs to reward the sponsor more than the risk-free rate; if that was not

the case, the sponsor would not exercise the option.

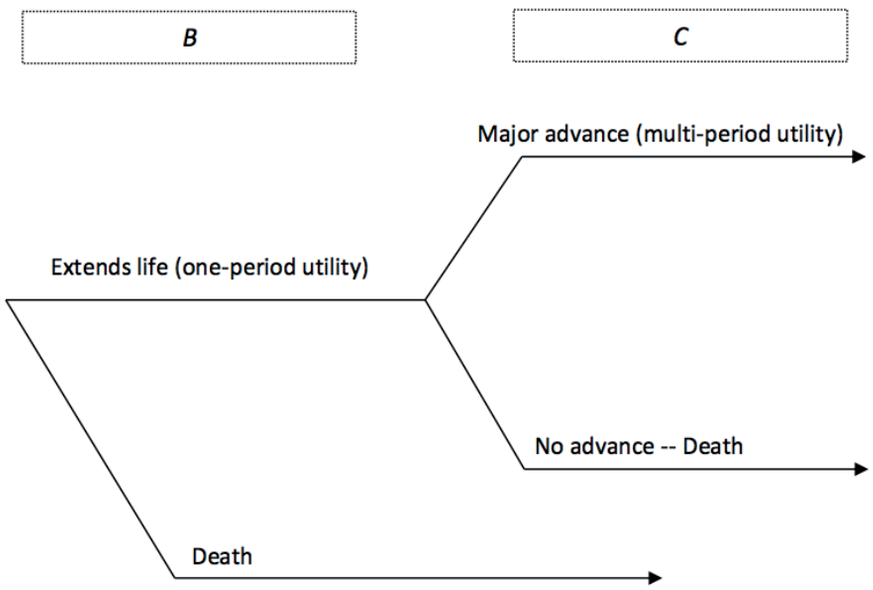
The above example holds true in a one-firm world. However, even if the discussion were extended to a competitive situation, the manufacturer of *B* would not be worried about competitors developing *C* before it does because it would hold the intellectual property (IP) to control both *B* and *C*. Moreover, *B* does not necessarily have to be a monopoly drug, meaning that there may be some therapeutic competition. In this case, therapeutic competition would be reflected in the price *P* and the option value would be scaled accordingly.

Lu and Comanor (1998) analyse therapeutic advances and observe that the value of the later-generation product is sometimes two to three times greater than the value of the 'intermediate step' product. This supports the argument that the option is valuable relative to the value of the initial product. Vernon, Golec and DiMasi (2010) apply the Fama-French model, following DiMasi, Hansen and Grabowski (2003), to analyse the profitability of different innovations. While DiMasi and colleagues find that three out of ten medicines provide positive returns to R&D investment, Vernon, Golec and DiMasi (2010) observe that only two out of ten are profitable. For the other eight (or seven) drugs that are being invested in, it would be consistent to say that some option value is being considered by pursuing them later on. Golec, Hedge and Vernon (2010) find a greater sensitivity in stock prices for firms that invest in more R&D, which is also consistent with the hypothesis that some development programmes take into account the option value.

3. REAL OPTIONS FROM A PATIENT'S PERSPECTIVE

Option value can be valuable from a patient's viewpoint as well. Philipson et al. (2010) look at HIV/AIDS and AZT (azidothymidine, a drug used to delay development of AIDS in patients infected with HIV) and calculate the impact of AZT on patients' survival (one or two extra years). Relative to the survival rate provided by the next generation of antiretroviral treatments (the HAART treatments), the improvement provided by AZT is considered marginal. However, the AZT treatment allows patients to live long enough to receive the new HAART antiretroviral. Therefore, patients should assign a value to the option because the first treatment (in Figure 1, drug *B*; in the HIV/AIDS example, AZT) not only provides some current benefit, but also increases survival rate, increasing the likelihood of benefiting from a better treatment in the future (see Figure 3).

Figure 3. The patient's drug consumption decision including real options (adapted from Cook et al., 2011)



4. REAL OPTIONS AND COST- AND COMPARATIVE-EFFECTIVENESS RESEARCH

In the US, comparative effectiveness research (CER)[2] is becoming increasingly important. Even if costs in principle are not considered under Medicare's current reimbursement and coverage decision system, in practice it is difficult for economists not to consider them. If we observe only the current value of a drug and ignore the option value, cost-benefit analyses based on a maximum threshold for approval might lead to the rejection of some innovations only because the option value is not recognised. Consideration of the option value would help rebalance cost-effectiveness decisions.

Oncology uses many combination therapies, mortality and morbidity can be very high, and evidence of path dependence on drugs exists. If all these issues were considered in CER by embedding the option value in the intermediate-step innovation, a more efficient allocation of R&D resources and a better mix of products may be possible.

[2] The Institute of Medicine defines CER as the 'generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat and monitor health conditions or to improve the delivery of care. The purpose of CER is to assist consumers, clinicians, purchasers, and policy makers to make informed decisions that will improve health care at both the individual and population levels'. National Research Council, 2009, p.29.

5. DISCUSSION

A number of practical issues arise in implementing an option-value approach. Four of the most important are summarised below.

The first is de-linking the payment for the option value from the sales volume of the intermediate innovation. Paying the option value as an increment on the price of the intermediate innovation implies that the payer cannot control the actual total amount paid for the possibility of achieving the future innovation, as this would be linked to sales of the intermediate innovation, which can fluctuate. This issue may be addressed by paying the sponsor a lump sum for the option value when the intermediate innovation is developed. This solution would require a different mathematical approach from the case where the reward for the option value is embedded in the price of the intermediate innovation. However, a lump-sum prize would still preserve the incentive to speed up or increase the likelihood of successfully developing the future innovation. A different solution would involve paying an additional amount for the future innovation to encourage the manufacturer to undertake the intermediate step, although compensation for the intermediate innovation would not be direct. In UK terms, this would require paying more for the future innovation than its QALY value.

A second issue is addressing the economic inefficiencies that may arise if the payer does not recognise or act on option value. For instance, a commercial payer in the US might not wish to reward an intermediate innovation because patients who would benefit would be covered by publicly funded Medicare by the time the future innovation was available. This would be different for people in their 20s, say, who might still be covered by private payers when the future innovation is available. Even if the people who receive the future innovation are not the same individuals as those who used the intermediate innovation, everyone benefits because insurance pools all the insured. Correcting for such economic inefficiencies, however, is possible, as it has been for orphan drugs, for example.

Third, valuations must account for the fact that a drug is under patent when evaluated, but eventually will not be. McKellar et al. (2012) look at the difference between prices after patents expire and consider that difference as a benefit. For instance, if a drug was worth $10 before patent expiry and the price is $0.10 after patent expiry, this means that after patent expiry the payer or consumer obtains $9.90 of value without paying for it, which represents a net gain. A method for estimating this net gain is partially considered in the Fama-French model (Vernon, Golec and DiMasi, 2010).

Finally, the resource constraints of consumers should be considered. If a consumer pays more for an intermediate innovation in anticipation of a future breakthrough, fewer resources will be available to spend on other innovations that might benefit that consumer. However, it is clearly also costly not to develop the breakthrough innovation or to wait longer for it. If it is optimal for the consumer not to have the future innovation, then the option should not be paid: option value should not be pursued simply because it exists.

6. CONCLUSION

The key message of this *Seminar Briefing* is that policy makers should consider option value when rewarding innovation. The future is important and it can, and should, be valued. This is not an easy task, but can help determine the appropriate balance in payment for drugs. In principle, option value could be determined case by case, but general rules could also be followed. For instance, NICE already uses option value in the pricing of drugs: it is option value that determines whether more research evidence is required before use of a technology is recommended (value-of-information approach). Although the issue of associating different option values with different development paths is taken into consideration in technology assessment, the way that NICE and other HTA bodies tackle this issue is not explicit.

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About this publication

This publication is based on a seminar at the Office of Health Economics entitled "Real Option Value and Path Dependence in Oncology Innovation".

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About the speaker

Dr. Cook is Senior Director, Global Health Technology Assessment Lead for Primary Care at Pfizer. Before joining Pfizer, he was a Vice President in an economics consulting firm, where he managed an economics group focused on producing high-quality research on complex issues that would be subject to adversarial review. His consulting and testimony involved a variety of industries with concentrations in telecommunications and health care, particularly pharmaceuticals. The issues addressed were principally those relating to the value of intellectual property, the nature of competition in a given market and antitrust or competition policy concerns, and the design of and strategic participation in auction and competitive tenders. He has been published in *the Journal of Political Economy, the Journal of Economic Behavior and Organization, American Law & Economics Review, PharmacoEconomics* and *Antitrust.*

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