Investing in new medical technologies: A decision framework

Emma Cosh, Alan Girling, Richard Lilford, Helen McAteer and Terry Young

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Emma Cosh
has a BSc (Hons) in Production and Operations Management, an MSc in Operational Research and is currently working towards a Masters of Public Health.

Alan Girling
is a statistician and Senior Research Fellow in the Department of Public Health and Epidemiology at The University of Birmingham.

Richard Lilford
has been Professor of Clinical Epidemiology at The University of Birmingham since 2001. Since 2005, he has also been the Head of the Division of Primary Care, Public Health and Occupational Medicine. He is also Senior Investigator for the EU STEPS, EPSRC REMEDI and MATCH projects.

Helen McAteer
has a BSc (Hons) in Neuroscience, a Masters in Public Health and is now working towards her PhD at The University of Birmingham. Her work on the early evaluation of Regenerative Medicine products is being co-funded by the EPSRC REMEDI (Regenerative Medicine) project and the EU's STEPS (A Systems Approach to TE Processes and Products) project.

Terry Young
has a background in industry and moved to academia in 2001. He is now Professor of Healthcare Systems at Brunel University. He is also the coordinating director of MATCH (an EPSRC project).

Abstract

Purchasing and reimbursement decisions in healthcare systems with finite resources are increasingly influenced by formal health economic analysis. It is therefore sensible for a company considering the development of a new medical technology to assess its potential cost effectiveness as early as possible in the development cycle. This document describes a process by which an organisation can add rigour to decisions about which technologies to pursue, as well as creating a persuasive argument for outside investment. The process consists of a series of analyses that should be conducted before substantial investments are made. The stages of the algorithm are: strategic considerations, clinical problem definition, headroom analysis, return on investment analysis and further economic analysis. This paper concentrates on the clinical problem definition and headroom analysis aspects of the process. Two worked examples of calculating headroom for theoretical products in tissue engineering of urogenital tissue are given. The health gain in urethral tissue is unlikely to be sufficient to justify the cost of a regenerative medicine solution, whereas bladder substitution after tumour resection has the potential to be cost effective providing marginal costs do not exceed £16,000. The framework discussed here provides a structure for investment decisions that can illuminate a situation, which may otherwise appear hard to fathom. A headroom analysis is primarily useful as a barrier to misguidedly investing in those devices, which can never be cost effective.

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Correspondence: Helen McAteer, Public Health and Epidemiology Department, University of Birmingham, Edgbaston, Birmingham B15 2TT, UK
Tel: +44 121 414 8465
Fax: +44 121 414 6216
E-mail: hlm569@bham.ac.uk

INTRODUCTION

In a finite resource healthcare system, the cost effectiveness of a technology can be

compelling evidence for its adoption. The opportunity cost of a technology is based on its incremental cost effectiveness, that is, the cost associated with the benefits achieved from a technology compared to the next best alternative. The National Institute for Health and Clinical Excellence (NICE), for example, uses this approach for appraisal of potential new treatments for the English National Health Service (NHS). It therefore makes sense for a company developing a new technology to assess its potential cost effectiveness as early as possible in the development cycle. This will inform investment decisions and indicate which products and markets may prove most fruitful.

It is in the interests of patients, the supply side of the economy and the companies themselves to maximise the chance of picking winners. In an increasingly sophisticated third-party payer healthcare market, this requires a selection of applications that promise health benefits commensurate with their costs. Elegant technical solutions are not, in themselves, sufficient to drive investment. In commercial language, technologies that have the greatest 'value proposition' should be selected. At the early stages of technology development – when sometimes even the nature of the product is unknown – realistic estimates of effectiveness are, however, difficult to obtain. It is the purpose of this paper to describe an approach to this problem of conducting health economic analysis under circumstances where effectiveness is necessarily conjectural. We also show how this method fits into a framework for decision making in organisations. The suggested structure for decision making is laid out in Figure 1.

The following sections discuss each of the steps of the decision-making framework in further detail using examples from the nascent industry of regenerative medicine. Regenerative medicine makes use of human cells and tissues as functional support to the body in healing. Few products have yet made the transition from laboratory bench to large-scale fabrication and at least two companies have recently failed in their attempts to do so, due not to poor products, but insufficient marginal effectiveness delivered for the marginal cost incurred.[1] As with many new industries, the eventual success stories will be built on the foundations of numerous commercial failures.

STAGES IN THE DECISION ALGORITHM

Strategic considerations

An organisation needs to begin by asking itself questions such as the following: Does this technology fit with our skills and strategy? Who are our competitors? How will our decision influence competitor behaviour? What changes to the regulations are in the pipeline? Are similar/competing technologies about to be launched? Many management tools exist for structuring such processes, from PEST and SWOT analyses, based on research by Robert Stewart at the Stanford Research Institute in the 1960s,[2] which focus on the micro (Strengths, Weaknesses, Opportunities, Threats) and macro (Political, Economic, Social, Technological) environments, to Checkland's Soft Systems Methodology,[3] which is a framework for defining a business problem situation and specifying necessary changes to meet stated goals. Such analyses may do no more than formalise existing knowledge, but they serve to provide some rigour to the decision and exclude those schemes that are obviously futile. At the very least, they reduce the risk that some important considerations will be accidentally omitted from the deliberations. If the problem is not ruled out by strategic considerations, then the investigation should move to the next stage with a study of the clinical problem and an analysis of how the technology may help.

Refining the clinical problem

In some circumstances, the decision to invest in a technology can be made without recourse to any formal method of evaluation. If an unmet clinical need can be identified and resolved, such as curing a common, chronic disease at low cost – then the decision makes itself. For example, in 1895, when Roentgen's wife was persuaded to interpose her hand between his X-ray source

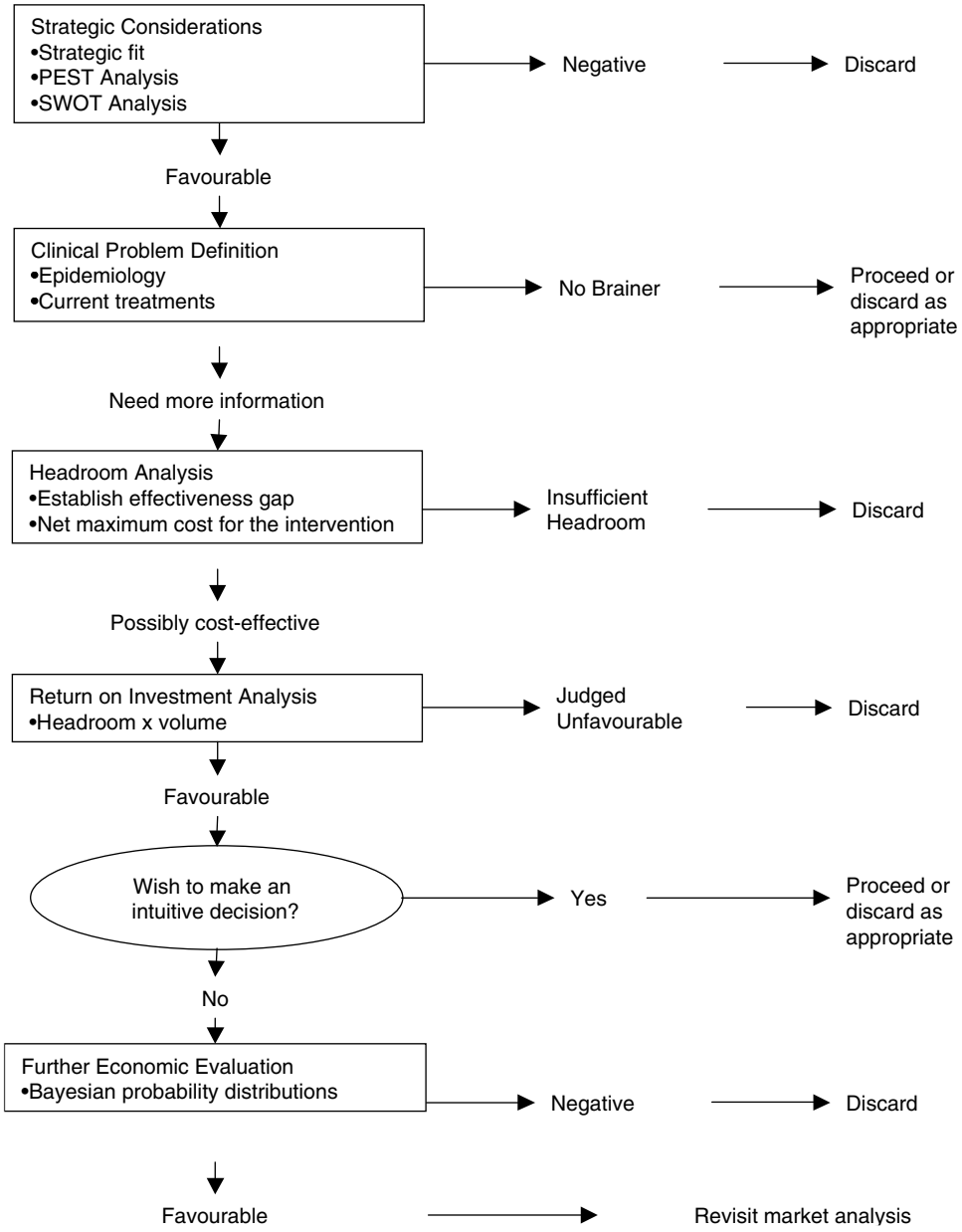

Figure 1: Algorithm for investment decisions for new technologies

and a photographic plate, he did not need a health economist to tell him he was onto a winner. These blockbuster discoveries come along only seldomly and the cost effectiveness of most proposed new technologies is much more difficult to predict. In such cases, it is important not to be carried away by enthusiasm for the technology *per se* or to over estimate the size of the potential market.

Enthusiastic supporters of a new technology may fall into the trap of superficial epidemiological analysis, leading to an overestimation of market size and value. For example, it appeared initially that the condition of chronic detrusor instability presented a large untapped market for a tissue-engineered bladder. On further examination, however, it was discovered first that only a small proportion of cases were sufficiently severe to require surgery and that secondly, botulinum toxin had recently been shown to be an effective and low-risk therapy for these hitherto intractable cases of this condition. It was immediately apparent that the scope for bladder resection and replacement with a tissue-engineered vestibule would be severely

curtailed.[4] Return on investment may be affected by the rarity of a condition or because it occurs only in economies unable to support high-cost remedies. For example, a tissue-engineered solution to small contracted bladders could not rely on treating Bilharziasis patients, since this parasitic disease occurs mostly in the world's poorest countries.

Thus, all the conditions where a new technology may have an application should be examined in turn, at least to the point where it is clear that there is a material clinical problem to be solved. It is important to be as specific as possible about the decision problem: a clearly defined clinical need based on a clear understanding of the strengths and weaknesses of current treatment is crucial to the uptake of any new technology. We suggest that the following issues should be clarified.

Statement of technology

The precise technology or technologies under consideration should be described as specifically as possible. For example, in the case of bone engineering, the technology may involve various combinations of scaffolds, cells and growth factors. The uncertainties should also be described. For example, the extent to which tissue-engineered bladder may become functionally innervated is uncertain.

Disease context

A precise description of the disease and its natural history should be given. In particular, thought should be given to whether the treatment would be suitable for all cases, or only the most severe. For example, guidelines for bladder excision and hence possible regenerative medicine solutions in neurogenic bladder are very restrictive[5] with surgical interventions being considered only where all medical therapies have failed.

Prevalence and incidence

Prevalence (number of people in a population with a disease) can be difficult to establish, especially when a particular subset is being targeted. Hospital Episode Statistics (HES) can be a useful source of data on the number of hospitalisations for a particular disease or operation in England. Crucially, no equivalent accessible data set exists for the USA. They should be used with caution and in conjunction with other epidemiological data, as varying interpretations of the classification codes can mask differences in severity or aetiology, which may have a large impact on the patients' suitability for RM.

Current treatments

The current gold standard treatment is the one against which any new technology will be compared. This may be gleaned from guidelines, such as those from NICE or NIH, expert opinion and systematic review of the literature. It is important to carry out a 'horizon scanning' exercise, that is, review new research as currently unlicensed therapies may change the shape of the market. It was in this way that the significant impact of botulinum toxin as a treatment for dysfunctional bladders was identified. Likewise, osteogenic growth factors may make certain types of bone scaffold obsolete or less widely applicable.

Cost effectiveness of available treatments

The costs, benefits, drawbacks and contraindications of the treatment described in the previous section must be examined in detail. It is the difference in performance between this and the proposed RM treatment, which will provide the headroom and justification for development. In principle, both the costs and benefits should be discounted as they are realised over a period of time.

Headroom analysis

What is headroom?

Cost-effectiveness analysis aims to quantify the incremental cost-effectiveness ratio (ICER), specifically the extra cost per unit of benefit when comparing one treatment, technology or programme against another – most often done on a cost per quality adjusted life year (QALY) basis. The comparator should always be the current gold standard treatment for a specific condition, as only an improvement on this performance will support the reimbursement of a new technology.

To calculate an ICER (Eq. (1)), the incremental cost (ΔCost) is divided by the incremental benefit (ΔQALYs) resulting in a 'cost per QALY'.

$$\text{ICER} = \Delta\text{Cost}/\Delta\text{QALY} \quad (1)$$

QALYs are calculated as the sum of the product of the mean utility of each health state and the mean duration of that state.[6–7] Quantifying the benefit of a treatment is, however, an inherently uncertain process; even when the product is finalised, effects will vary from one population to another and there are limits to the precision with which effectiveness can be measured. These problems are much greater for a treatment that does not yet exist. At this stage, there will be no head-to-head comparisons of the technology against an alternative and so, effectiveness estimates rely on conjecture.

As an alternative to a full cost-effectiveness analysis, at least in the first instance, we recommend a simple threshold approach, which we term the headroom method. There is always a prior limit to how cost effective a new technology may be – the epidemiology and clinical features of the condition in question limit the potential benefit. The headroom calculation is based on the most optimistic assumptions in the plausible range. The maximum net incremental cost (maxΔCost) for which the technology would still be considered cost effective (the headroom) can then be calculated.

If the willingness to pay (WTP) is £30,000, it follows that the headroom can be expressed as

$$\max\Delta\text{Cost} = 30{,}000 \times \max\Delta\text{QALY} \quad (2)$$

where maxΔCost is the headroom: the maximum *additional* cost of the new treatment over the comparator for the new treatment to be deemed cost effective.

If there is little or no chance that the technology could be marketed at a price that would keep the maxΔCost below the cost-effectiveness threshold, then the technology should not attract further investment. Since the ICER is calculated at the most optimistic end of the prior probability distribution for effectiveness, the headroom method is a cost-effectiveness analysis at the optimistic end of a conventional sensitivity analysis. It is important to note that maxΔCost is the net difference in cost (to the health service) of the proposed new technology. It thus includes any net savings or costs to the health service along with the costs of the product itself.

Estimating ΔQALY

The headroom, as we have seen, is based on optimistic but plausible estimates of effectiveness of the technology being assessed. Of course, a developer will always have optimistic hopes for their product, but rather than blind faith, this method aims to concentrate the mind on a realistic upper limit. The degree of formality used in eliciting these values is a matter for the decision maker(s) and dependent on the information and expertise available.

At one extreme, they (the decision makers) may simply use personal judgment. Having defined the clinical problem and its epidemiology (as described in Stage 2), the simplest situation is to assume that the outcome of the prospective treatment will be as good as the current treatment, and that there is no difference in mortality. In this case, only the period of time during which the QoL values of the two treatments differ need be considered (see Box 1). In other circumstances, where current treatment is less than satisfactory, an 'effectiveness gap'[8] can be estimated. That is, for those conditions with treatments that are ineffective for large proportions of patients, or have significant side effects, the maximum *potential* increase in effectiveness over current treatment may be used as the optimistic assumption. Alternatively, they can use empirical observation using formal methods. There are various methods for measuring preferences such as standard gamble and time trade-off[9]; however, the less time-consuming alternative is to use the pre-scored multi-attribute health status classification systems such as EurQol,[10] SF-36[11] or the health utility index.[12] There is, however, controversy regarding whether patients, the public or experts should be consulted for the utility values.[13] Since the headroom method is, however, a rough and

Box 1: Regenerative medicine for urethral stricture

A substitute for urethral tissue is needed in operations on lengthy strictures, and sometimes for epispadias and hypospadias (congenital defects resulting in the urethral opening on the top or bottom surface of the penis). Buccal mucosa, tissue making up the lining of the cheek, is becoming the gold standard substitute,[14] although it does have disadvantages, relating to morbidity at the donor site.

Estimation of parameters

We assume that a tissue-engineered substitute would avoid the donor site problems and perform as well as natural autologous tissue, with no difference in mortality. As such, parameter estimations will be required for the utility of avoiding donor site morbidity and the time over which the utilities for the treatments would differ, that is, the time over which the pain and swelling would have lasted.

A systematic review of the literature revealed no values for the QoL of patients after an urethroplasty using buccal mucosa. Instead, the quantity was elicited by our team[4] from the general public using the time trade-off method. The median utility found was 0.938. After consultation with clinicians, an estimation of 0.1 years was used as an estimate for the duration of the side effects.

These estimates give a ΔQALY of: $0.1\times(1-0.938)=0.0062$ which in turn suggests a headroom of: £$30{,}000\times0.0062=$£186 per patient treated

Box 2: Regenerative medicine for surgical treatment of bladder cancer

A tissue-engineered bladder substitute would most likely be used as an alternative to the use of bowel in substitution cystoplasty after resection for cancer. Other indications (dysfunctional bladder and bilharzia) are not propitious due to the existence of noninvasive treatments and market forces, respectively.

Estimation of parameters

Information regarding quality of life after cystoplasty is sparse, and those studies that do exist[15,16] are not easily translatable into QALYs. In the light of this and the complex nature of the medical conditions involved in cystoplasty, an estimate of its disutility was made via a survey of urologists. The median utility value found was 0.95. The mean age of the presentation of this condition is 72 years[17] and while reported survival rates vary widely, we may assume that patients suitable for a tissue-engineered solution will have a better than average five-year survival and will also be younger than average. Therefore, we assume a mean of ten years of life among this group.

These estimates give a ΔQALY of: $10\times(1-0.95)=0.5$ which in turn suggests a headroom of: £$30{,}000\times0.5=$£15,000

This, however, does not take into account savings by avoiding bowel surgery of £1,000 per patient. Headroom is hence £16,000 per patient treated.

ready method to decide whether to continue with development or further enquiry, less formal and inexpensive methods will often be fit for purpose.

Two examples of the headroom method from the field of regenerative medicine are given in Boxes 1 and 2. Both have 'passed' the strategic consideration stage and are under active consideration for development in industry. More detailed accounts of this work can be found in McAteer *et al.*[4] It can be seen from these examples that health gain in

the case of urethra is unlikely to be sufficient to justify the cost of a RM solution (confirmed by consultation with experts from the TE industry), whereas bladder substitution after tumour resection has the potential to be cost effective provided the marginal costs did not exceed £16,000. The latter is eminently achievable, especially as the alternative method, substitution cystoplasty, uses bowel tissue that adds to the surgical costs.

Return on investment

For those technologies that appear to have headroom (eg bladder tissue engineering for cancer), continuing development and investment would appear to be justified. A viable new business, however, requires substantial volumes to repay the return on investment. At this stage, our interest is focussed on whether or not this technology has the potential to succeed once it has been brought to market. Although future development costs will contribute to the decision to continue or abandon, these will largely be based on factors internal to the organisation rather than the technology itself and, as such, are not discussed here.

The market size for bladder tissue engineering relates mainly to patients with bladder cancer, most of who are treated by radical cystectomy and urinary diversion by ileal conduit. Only 4–19 per cent[18–24] are treated with the partial, or trigone-sparing cystectomy suitable for bladder substitution cystoplasty. If this practice continues, then only between 420 and 2,000 of the average 10,470[25] bladder cancer patients in a country of 60 million such as the UK will be eligible for RM bladders. This represents a small market and therefore, possibly not a very exciting investment opportunity. In some cases, however, a radical cystectomy can be 'nerve sparing' – retaining the innervation in urethral sphincter and thus providing an opportunity for an RM vestibule.[16] As Venn *et al.*,[16] however, note, 'there are very few centres where these procedures are actually performed. The vast majority of patients undergoing cystectomy still seem to be offered an ileal conduit and no alternative'. The potential market size for RM bladders is thus sensitive to the adoption of this technique. To an extent, therefore, any investors will be 'betting on' increasing use of the nerve-sparing operations and possible stimulation of this approach through the availability of a tissue-engineered bladder.

The revenue that can be generated is a function of headroom, the likely cost and volumes, represented by Eq. (3).

$$R = (\max\Delta\text{Cost} - C') \times V \tag{3}$$

where R is the revenue, ΔCost the headroom, C' the expected cost of production and V the cases per year. In the case of tissue-engineered bladder, assuming each device costs £8,000 and that there are 500 cases per year $R = (£16{,}000 - £8{,}000) \times 500 = £4{,}000{,}000$. The expected profit, however, must be discounted over a time horizon chosen to reflect the company strategy.

Next step if headroom and revenue analysis are favourable

The steps followed in this paper may show that a technology could be profitable. It is therefore a necessary but not sufficient basis on which to proceed. Two further possibilities exist. The investor may simply make an intuitive decision – if the headroom method shows that a strong revenue stream is possible then this may be enough to trigger investment. Alternatively, the potential investor/developer may wish to do a more formal value of investment analysis. This involves testing a more 'realistic' prior probability than that taken from the most optimistic end of the plausible range. In the case of bladder cancer, for example, it would not be assumed that the RM solution would work as well as hoped in all cases – some may undergo contracture, or leak and hence require further surgery, for example. In that case, the calculation of 'headroom' can be repeated over a range of probability estimates for effectiveness and a threshold determined where the technology would not be cost effective at its likely cost. To put another way, the probability that the technology would come into routine use would be derived. Next, 'expected' effectiveness contingent on this scenario

would be calculated. The expected 'headroom' under the assumption is then calculated along with the consequent revenue streams in a 'Value of Investment' decision. We give a full description and worked example of such an analysis in a forthcoming paper.

CONCLUSION

Where new medical technologies are competing for resources, a tool to prioritise those most likely to succeed is indisputably valuable. The framework discussed here provides a structure for investment decisions, which can illuminate a situation that may otherwise appear hard to fathom. This document has concentrated on the clinical definition and headroom analysis portions of the process suggested; however, each part of the framework plays an important role in supporting decision making. The key to this methods' successful exploitation is knowing which tools to use and when.

As development proceeds, it is important to revisit economic analysis with new information regarding the likely effectiveness of the technology as it becomes available. A headroom analysis is primarily useful as a barrier to misguidedly investing in those devices that can never be cost effective. As research progresses, estimates of costs and effectiveness can be updated.

It must be noted that the value of applying these methods at the supply side is dependent on the planned technologies being aimed at the third-party payer market. The value consumers place on a technology will undoubtedly be different to both NICE and each other as each individual has a different WTP.

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