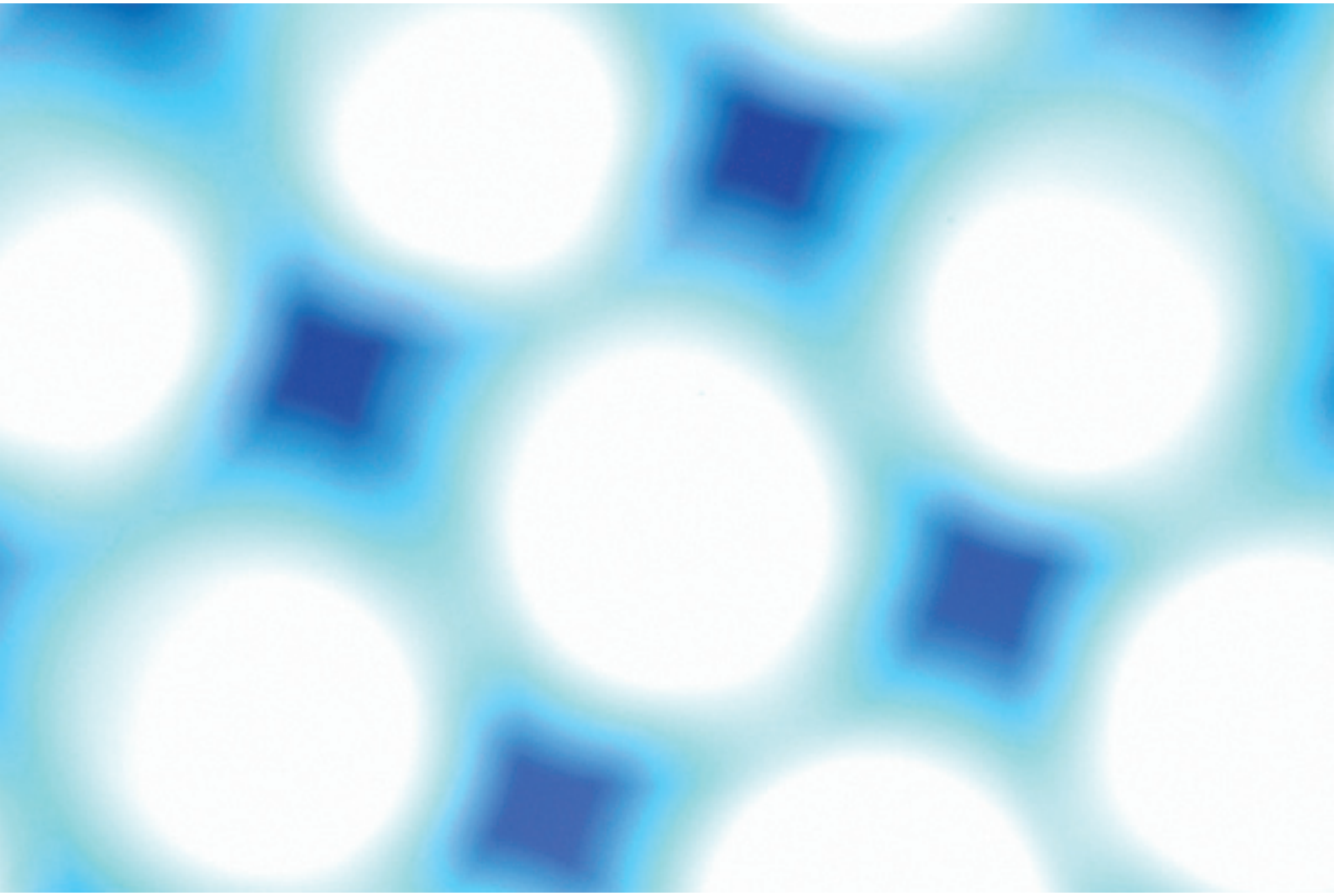
Medical Research: What's it worth?

Estimating the economic benefits from medical research in the UK



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For the Medical Research Council, the Wellcome Trust and the Academy of Medical Sciences

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Contents

Foreword

The UK Evaluation Forum was first initiated by the Academy of Medical Sciences, the Medical Research Council and the Wellcome Trust in 2004. Drawing together representation from Government, the research councils, medical charities and academia, the broad aim of the Evaluation Forum was to co-ordinate activity in determining the socio-economic benefits of UK medical research.

Following an initial mapping exercise of evaluation practices in member organisations, an international symposium was convened in 2005 to discuss evaluation needs and expectations amongst UK research stakeholders and to review what had already been attempted in demonstrating the socio-economic impact of health research in other countries. The outputs of the symposium, and the further deliberations of the Evaluation Forum, were published in the 2006 report *Medical Research: Assessing the benefits to society*.

Chapter 3 of that report summarised previous approaches to assessing the economic and financial impacts of medical research. Particular attention was given to the 'exceptional returns' work published in the United States, which suggested that investment in medical research is returned many times over in societal benefits. However, it was emphasised that the US work made a substantial number of important assumptions that may not be applicable to the UK situation. One of the five recommendations of our report was therefore "that research funders should support research to assess the economic impact of UK medical research".

So, in late 2006, the Academy of Medical Sciences, the Medical Research Council and the Wellcome Trust started a process to commission such research. The overall aim of the work was to compare the macroeconomic benefits accruing from UK medical research with the cost of that research – ultimately to give a *quantitative* assessment of the benefit of medical research to the UK. It was also expected that the research would critically appraise both the selected approach and previous attempts to estimate the economic returns from research. In this way, the goal was not to obtain a definitive answer about the returns on the investment in UK medical research, but to generate a piece of work that would help to move this young field forward and inform methodologies for future assessments.

The work presented in this report, carried out by a consortium involving the Health Economics Research Group at Brunel University, RAND Europe and the Office of Health Economics, certainly fulfils this hope. We are most grateful to the members of this consortium, led by Professor Martin Buxton, for the expertise, care and enthusiasm they have brought to the study. This is an enormously valuable contribution to an important issue for UK medical science and we look forward to working with our partners in the Evaluation Forum and elsewhere to take forward the research agenda presented in this report.

Professor Martin Roland CBE FMedSci

Director, National Primary Care Research & Development Centre, Manchester

Chair, Evaluation Forum Working Group

Executive Summary

Rationale and scope of the study

This report is the outcome of a one-year study commissioned by the Academy of Medical Sciences, the Medical Research Council and the Wellcome Trust to compare the economic benefits accruing to the UK from UK publicly and charitably funded medical research with the cost of that research. Understanding the nature, extent and processes involved in the return on investment in medical research has been largely neglected as an area of serious scientific study. Despite a growing international interest in this area there has been relatively little formal analysis of the returns to medical research, particularly in Europe. The study reported here represents an initial step towards rectifying that situation.

Past work in the USA and Australia – the 'exceptional returns' literature – has attracted publicity. But those analyses contain important flaws. While it is easy to identify the limitations of existing studies, it is less easy – but possible – to reduce these limitations. Our objective is to estimate the returns to UK public/charitable medical research in as transparent a manner as possible, in order to illustrate, to improve on and to explore these limitations and assumptions. This is not intended as a one-off exercise simply to produce a best estimate: rather it is offered as a contribution to an emergent understanding of the issues and as part of a process of establishing a research agenda which should contribute to the production of more robust estimates in future.

Economic returns to medical research comprise two, additive, elements:

- health gains net of the health care costs of delivering them
- GDP gains, that is to say the UK national income that results directly and indirectly from the medical research and the further activity stimulated by it.

Both elements are important.

Our approach is mainly bottom-up, in contrast to the top-down approach taken in most of the 'exceptional returns' literature. Thus we have undertaken detailed analysis of the important research-based changes that have taken place in the treatment of particular disease areas. The returns to medical research as a whole would be the sum of the estimates for each disease area. We initially analysed the returns to public/charitable research from one well-reported therapeutic area, namely cardiovascular disease (CVD), and then tested the same methods in the more problematic area of mental health.

We have addressed exclusively the question of what are the economic returns to the UK population and the UK economy from UK medical research. We recognise that UK health research benefits other countries, just as our analysis recognises that the UK benefits from research from the rest of the world. Indeed, some medical research is undertaken in the UK with the expectation that it will predominantly or exclusively benefit health care in other countries (for example most research on tropical diseases). However, benefits to countries other than the UK are outside the scope of this study.

The contribution our study makes

We provide a clear demonstration of an approach which provides an improved theoretical basis for empirically estimating the two main elements of the economic returns from medical research – the value of health gains and the impact on GDP.

Our main original contributions are:

- A consistent time series of estimates of public/charitable and private pharmaceutical industry expenditure on medical research in cardiovascular disease and mental health from 1975 to 1992, pieced together from a variety of sources. Given the expected lags between medical research and its impact, this is likely to be the most recent relevant period of research spending to investigate.
- A clear conceptual framework to underpin the concept of 'spillovers' from public and charitably funded medical research, based on an original broadly scoped literature review. The total social rate of return to an investment comprises the return to the organisation making the investment, the return to other organisations in the same sector (e.g. medical) and the return to all other parts of the economy. The last two are referred to in economic literature as 'spillovers', but that is not to imply that they are accidental. On the contrary, 'spillovers' are often an explicit objective of investment in research.
- Estimates of the magnitude of spillovers in the UK from public and charitable UK medical research, calculated in two different ways: (1) a two-step analysis of the relationship between public/charitable and private R&D and then of the relationship between private pharmaceutical R&D and GDP, and (2) based on the economic literature estimating the social rate of return to public R&D, whether medical or not.
- A 'bottom-up' approach to estimating the health gain from research. This is a significant improvement on earlier attempts to estimate the economic returns from research in that it is measured in terms of quality adjusted life years (QALYs) and is driven by evidence on the effects and costs of specific research-derived interventions, rather than by macro-level, temporal changes in mortality or morbidity.
- A successful test of this approach in two disease areas. The analysis of the gains for cardiovascular disease (CVD) was built up from evidence on 46 different patient indication/treatment combinations, and that for mental health from evidence on six such combinations.
- Analyses of UK clinical guidelines in the areas of cardiovascular disease (five guidelines) and mental health (12 guidelines), to provide indicators to inform the important issues of the lag between research

expenditure and health benefits and the attribution of benefits to UK, rather than worldwide, research.

- Computation of the internal rate of return (IRR) on past expenditures on research investment in the areas of CVD and mental health, allowing explicitly for the time lags involved and the level of attribution to UK research, with sensitivity analysis around key parameters. The IRR is a convenient way of representing the return to the original research investment, and has the pragmatic advantage that the published empirical literature on the GDP impact of research is expressed in terms of the IRR achieved by that investment. Expressing the return from health gains as an IRR allows it to be added to the IRR for GDP gains to provide an estimate of the total rate of return achieved by medical research. For example an IRR of 10% means that the return to an investment of £1 is equivalent to receiving thereafter an income stream of £0.10 per year in perpetuity.
- A comparison of the internal rates of return (IRRs) on research investment from the value of the QALYs gained in these two areas and with the new estimates of the rate of return in terms of GDP effect (which is not specific to individual disease areas).

Expenditure on medical research in the UK

Estimates of spending specifically on cardiovascular research are not readily available for either the public or private sectors and we provide here original estimates that have not previously been available. The construction of these estimates relies on data from a number of different sources and various assumptions regarding the split of medical research between different clinical areas.

Despite some inevitable uncertainties, we have a time series for total public/charitable research expenditure on cardiovascular disease which represents the research investment that we are studying, and also a series for research expenditure by the pharmaceutical industry. This feeds into our estimates of the indirect impact of public research on GDP. The private figures also make it clear that private sector R&D expenditure greatly exceeds public plus charitable expenditure.

We estimated the expenditure on cardiovascular research from the Medical Research Council, Higher Education Funding Councils, Department of Health, British Heart Foundation and Wellcome Trust. Our mid estimates of total annual funding for cardiovascular research in the UK from these public and charitable sources show that it increased from £26 million in 1975 to £88m in 1992 in cash terms, representing an annual percentage increase of circa 7.5%. Expressed in 2005 prices, this equates to a decrease in annual spend from £144m in 1975 to £121m in 1992, with a total expenditure over the period of £2 billion.

Pharmaceutical industry spending on cardiovascular research in the UK grew rapidly in this period: our mid estimate shows a rise to £213m in cash terms in 1992 – 2.4 times the level of public plus charitable expenditure.

On a similar basis, total annual public and not-for-profit funding for mental health research in the UK increased from £28m in 1975 to £93m in 1992, representing an annual percentage increase of around 7%. In real terms this equates to a *decrease* from £155m in 1975 to £129m in 1992. Private pharmaceutical industry expenditure on R&D in mental health was around three times this level in 1992.

The returns to public/charitable medical research

Our method

To estimate the net value of health gains in the area of CVD we:

- reviewed the economic evaluation literature to obtain published figures for the QALYs gained per patient from specific patient group/intervention combinations for cardiovascular disease over the period 1985–2005
- multiplied these figures by estimates of the numbers of users of each intervention, adjusted for compliance rates, to give an estimate of the total QALYs gained from each intervention
- monetised the total QALYs gained by multiplying these estimates by published figures on the opportunity cost of a QALY within the current NHS budget – central estimate £25,000 per QALY, i.e. the mid-point of the National Institute for Health and Clinical Excellence (NICE) threshold range of £20,000–£30,000 per QALY
- from a review of the economic evaluation literature obtained estimates of the incremental health care costs associated with each intervention and multiplied these by the numbers of users to quantify the incremental health care costs of each intervention.

Based on previous studies, we include interventions that are likely to have been important in terms of the health gains they have produced over the period 1985–2005.

We used essentially the same approach for mental health.

We drew on the extensive economic literature examining the so-called 'spillovers' from public/charitable research between organisations and between sectors to estimate the impact of this research on the UK's GDP. The literature is clear that the spillovers exist, but less clear about the relative importance of different transmission mechanisms. However the literature, especially that looking at the medical and biotechnology sectors, almost without exception takes the view that public research and private R&D are complements, not substitutes. Public research stimulates private, and vice versa. Both kinds of research lead to improved productivity and performance in the economy generally.

Results

All our work emphasises to us that our estimates of the rates of return need to be treated with extreme caution. Most aspects of the methods unavoidably involve considerable uncertainties. Therefore all quantitative results are no more than rough approximations. We have generally tried to provide a best/central estimate, and when in doubt have erred on the side of being conservative. In addition we provide high and low estimates around the best/central estimates and undertake sensitivity analyses.

The estimated rates of return were very sensitive to the assumed lag between the years when the research expenditure occurs and the years when the ultimate health benefit arises, and to the proportion of the benefit attributable to UK research as opposed to world research as a whole. The issue of lags has often been ignored in the past, but from a policy point of view may be crucial, especially in the context of the current agenda for translational research.

Cardiovascular disease

Our best estimate of the total value of the QALYs gained from the specific CVD interventions included in our analysis over the whole period 1985–2005 is £69bn (2005 prices). The upper and lower estimates are £91bn and £55bn respectively. The best estimate of the total incremental health care costs relating to those gains over the same period is £16bn (2005 prices), with upper and lower estimates of £17bn and £11bn respectively.

Based on our analysis of citations in UK clinical guidelines in CVD, combined with the findings of previous published studies, we assume that for CVD the proportion of UK health care benefit attributable to UK research lies in the range from 10% to 25% with a central estimate of 17%.

Similarly, from our analysis of CVD guidelines and from previous studies, we assume a mean lag between research and impact for CVD treatments of between 10 and 25 years, with a central estimate of 17 years.

Our best estimate suggests that for CVD the IRR from the value of UK net health gains alone (ignoring GDP impacts) is just over 9%. Most one-way sensitivity analyses place the IRR within the range of 5–15%. The 'optimistic scenario' we examined produced an IRR of over 25%, but in our 'pessimistic scenario' the cost of the research investment exceeded the value of the net health gain.

We estimated that the GDP gains that result from increased public/charitable medical research deliver an additional rate of return in the range 20–67% (with a best estimate of 30%). These figures are obtained from a small empirical literature, much of it US-centred and only a proportion of it specific to medical research. Hence the application to the UK and to medical research is at best tentative.

Nevertheless combining our estimates, the total health and GDP gains to public/charitable CVD research in the UK 1975–1992 give a total IRR of around 39%. In other words, a £1.00 investment in public/charitable CVD research produced a stream of benefits thereafter that is equivalent in value to earning £0.39 per year in perpetuity.

Mental health

For mental health research by the public and charitable sectors in the UK we found the IRR from the net health gains to the UK population for mental health of 7% to be somewhat lower than for CVD (around 9%). Most one-way sensitivity analyses place the rate of return within the range from a situation where the investment exceeded the net benefits to a positive rate of return of just over 11%. Our 'optimistic scenario' gave an IRR of over 15%.

Available evidence did not permit us to estimate different GDP returns according to the therapeutic area of research. Thus for mental health, as for CVD, our best estimate of the additional rate of return to the public/charitable research investment from GDP gains is 30%. This gives a total rate of return of 37% for mental health research.

These figures cannot be meaningfully compared with the estimates from most other studies, particularly the research from Australia, which not only uses different methods to estimate the returns but uses an unhelpful measure of return on investment.

Implications for the future research agenda

The limitations of available data, the questions around methodology, and the issues raised by our analysis lead us to identify some key elements for the future research agenda in this area, most prominently:

- research funders need to develop and use a standardised (and mapped) way of classifying research funding
- further research needs to be undertaken to understand the time lag between research expenditure and health gain
- the 'spillover' effects of public and charitable research expenditure on the national economy need further, UK-focused, empirical investigation
- a deeper understanding of the international flows of knowledge and influence would be valuable
- the importance of local research in terms of absorptive capacity: further research to test this would be very valuable, particularly to the health care system and the National Institute for Health Research
- we need to understand additionally, what are the *global* health benefits from UK medical research.

Chapter One

Introduction

KEY POINTS

- There is a growing interest in understanding and measuring the return to investment in medical research.
- There has been a tension between advocacy and more dispassionate analysis.
- Existing studies illuminate the issues but are all flawed.
- The aim of this study is to estimate the economic returns to the UK from health research in terms of two main elements: the value of the health gains to the UK population and the GDP gains.
- We take two areas of disease: cardiovascular, for which we anticipate there being relatively good data, and mental health, which we anticipate will be more problematic.
- In doing this as transparently as possible we hope to contribute to an emergent understanding of the methodological and practical issues.
- Additionally this report provides a future agenda for research in this area.

"UK research stakeholders should be more active in demonstrating the benefits that arise from medical research and making the case for continued investment."

(View of the UK Evaluation Forum underpinning its report *Medical Research: Assessing the benefits*, May 2006)

Background

Whether publicly and charitably funded research and the pursuit of new knowledge is seen as an end in itself or as an investment aimed at producing benefits for society, it is inescapable that the resources used to undertake such research could otherwise be put to other uses of benefit to society. In the language of economics: all uses of resources, including research, have opportunity costs. Research needs to be of demonstrable value to justify denying people the other opportunities to benefit that they forgo in order to pay for the research. In the medical field it is relatively easy to find examples of specific research that has led to enormous benefits in terms of a life-saving intervention or to major improvements in the quality of life of patients with a chronic disease. But understanding the nature, extent and processes involved in the return on investment in medical research has been largely neglected as an area of serious scientific study. Despite a growing international interest in this area (UK Evaluation Forum, 2006; European Science Foundation/European Medical Research Councils, 2005; Natural Environment Research Council, 2006), there has been relatively little formal analysis of the returns to medical research, particularly in Europe.

Different stakeholders have different reasons for understanding better the returns to medical research. In most cases, there is some tension between assessments to inform future decisions (about how much to spend, on what areas or categories of research, using which funding systems or mechanisms) and to demonstrate the value of past spending. With this tension also comes a narrow line between objective analysis and selective advocacy.

In the USA, it was an advocacy initiative of the Mary Woodward Lasker Charitable Trust, entitled Funding First, which commissioned from a group of leading US academic economists a series of papers. These were presented at a conference in December 1999, the summary of which was entitled 'Exceptional Returns' (Funding First, 2000). The subsequent book edited by Murphy and Topel (2003) provided a springboard for renewed interest in estimating the returns to health or medical research. In fact the book itself does not provide formal estimates of the return on investment in medical research. The 'exceptional returns' are implied by informal comparison rather than calculated in a systematic manner and come from the summary of the conference rather than from within the papers themselves:

> Using the methods of their earlier calculations, Murphy and Topel estimate that the total economic value to Americans of reductions in mortality from cardiovascular disease averaged $1.5 trillion annually in the 1970–1990 period. So if just one-third of the gain came from medical research, the return on the investment averaged $500 billion a year. That's on the

> order of 20 times as large as average annual spending on medical research – by any benchmark an astonishing return for the investment. (Funding First, 2000, p. 8)

Some of the key assumptions and limitations of this ground-breaking work, particularly when viewed from a less insular UK perspective, were highlighted by a study produced in Australia for the Australian Society of Medical Research (Access Economics, 2003). This built on aspects of the US analyses and produced estimates of the annual rates of return to Australian investment in health R&D. This study also concluded that the returns were exceptional, with a base-case estimate of a benefit to costs ratio for health R&D overall of 2.40 (with low and high estimates of 1.08 and 5.04). For 'cardiovascular' disease the ratio was 7.88 (3.55 to 16.56), but for research on 'nervous system and mental' the returns were much lower at 0.23 (0.10 to 0.48). But this study compared investment to the value of the health gain in the same year. This study has recently been updated (Access Economics, 2008). It uses a substantively changed methodology, comparing past health R&D expenditure with projected future health benefits. The estimated benefit to cost ratio for Australian health R&D as a whole is now estimated as slightly lower at 2.17 (with a range from 1.16 to 3.34). The new report downplays the significance of estimates for different disease areas.

It is easy to identify the limitations of these studies and possible, but less easy, to reduce the limitations. Our objective is to estimate returns in as transparent a manner as possible in order to illustrate, to attempt to improve on, and to quantitatively explore these limitations and assumptions. In doing this in an explicitly critical manner, we have undertaken this study, not as a one-off exercise to produce a best estimate but as a contribution to an emergent understanding of the issues and as part of a process of establishing a research agenda which should contribute to the production of more robust estimates in future. The estimation of returns should not be seen as some isolated (or even arcane) technical process. Rather, it brings together and encourages us to be explicit about our understanding of the way in which medical research may lead eventually to valuable outcomes.

Scope of the study

For this study we have conceptualised the economic returns to the UK as consisting of two main elements. Firstly, the value of the health gains to the UK population believed to be attributable to the UK research investment, and secondly, the GDP gains. Both are important. Most health researchers and research funders would probably see the objective of their research as being (ultimately) to lead to better health or better health care, and this is important from a national perspective as well, even though national accounts do not measure and value changes in the stock of the population's health. But governments also increasingly see investment in publicly funded research as having a major role in contributing to GDP via its effect through the private sector.

Given the scale of the commissioned study and our intended approach, it was clear that we could not address all areas of health research. Our approach is mainly bottom-up: it involves detailed analysis of the important evidence-based changes that have taken place in a particular clinical area. The overall returns to medical research would be the sum of the estimates for each clinical area. We therefore chose to focus initially on research in one therapeutic area, namely cardiovascular disease (CVD). This was a focus in the US study; it is an area where clinical developments have had a clear impact on morbidity and mortality and where there have been previous attempts to estimate the mortality impact of specific interventions (eg. Unal *et al*., 2004). Thus treatment and prevention of CVD provides an area which might be most amenable to rigorous and relatively robust estimation of returns. But this also means that it probably is not typical and any quantitative results may not be generalisable to other areas of medical research.

Therefore, in addition, we have taken the methods we develop for the cardiovascular area and have examined how they might be applied to the much more problematic area of mental health. Generally there has been less work on the relevant data for this area and fewer economic evaluations of specific interventions. Whilst the returns from mental health research have been previously considered, they are sensitive to assumptions about changes in the cost of services and rely much more heavily on estimates of improvements in quality of life rather than length of life. As a result studies of returns to research relating to mental health have shown very different results (Access Economics, 2003; Silverstein *et al*., 1995; Weisbrod, 1983).

An intentional but key limitation of our scope is that we have addressed exclusively the question of what are the economic returns to the UK population and the UK economy from UK health research. We recognise that UK health research may benefit other countries, just as our analysis recognises that the UK benefits from research from the rest of the world. Indeed, some medical research is undertaken in the UK with the expectation that it will exclusively, or predominantly benefit health care in other countries (for example most research on tropical diseases).

Structure of the report

Our study sets out to:

- review the literature and identify key issues for our study (Chapter Two)
- estimate time series for annual expenditures on medical research relating to cardiovascular disease from public and charitable sources, and present time series data on private sector research in the same area, both for comparison and to facilitate our calculations of GDP effects (Chapter Three)
- estimate what proportion of those gains should be attributed to UK research (Chapter Four)
- estimate the time lag between research expenditure and its clinical application (Chapter Four)
- estimate a time series for the annual value of health gains to patients in the UK from the most important interventions in CVD (Chapter Five)
- estimate the costs of delivering the health care that produced those gains (Chapter Five)
- estimate the effects on national income of the public/charitable research (Chapter Six)
- using data from earlier chapters estimate the return on investment in medical research in terms of the net value of health benefits and combine the estimates of health and GDP returns (Chapter Seven)
- test the methods used above in the context of mental health research (Chapter Eight)
- identify the key limitations in this approach and propose an agenda for future research (Chapter Nine).

Each step involves making estimates based on imperfect data. We have aimed to be explicit about these assumptions and the data weaknesses (in broad terms within the chapters themselves and in more detail in the supporting annexes). We have also aimed to err on the conservative side – avoiding underestimating the research investment or overstating the returns. We present 'best' estimates within a range where we feel able to do so. Where we simply have a range, and no other basis to judge, we present the 'central' estimate and the range.

Chapter Two

Overview of the existing literature and the issues raised

KEY POINTS

- A previous review of the diverse but limited literature on the economic returns from specific programmes of health research identified four main approaches: cost savings; benefits from a healthy workforce; the value to society of the health gain; and commercial development. The last two are now seen as the most promising approaches.
- Innovative ways of assessing the value to society of the health gain were developed by the Funding First team in the USA and in follow-up studies in Australia.
- Increasing attention is being focused on how research impacts on (creates GDP 'spillovers' for) the rest of the economy.
- A previous study, using bibliometric approaches to assess the contribution made by UK research to UK clinical guidelines, may provide an indication of the relative contribution of UK research to UK clinical practice.

Introduction

Several overlapping issues are relevant to assessing the economic benefits of health research. These include the items to be considered benefits and the ways of assessing them. There is no clear consensus about the best approaches to use. In the UK the Evaluation Forum (bringing together the Academy of Medical Sciences, the Medical Research Council and the Wellcome Trust) considered ways of assessing the benefits to society from medical research (UK Evaluation Forum, 2006). They recommended the "improved use of existing evaluation tools, greater sharing of good practice and the development of new approaches where required" (para. 5.3).

This Chapter reviews some of the main literature to assess current practice and highlight issues that need to be considered in our empirical analyses. It focuses, in particular, on studies on which our analyses build. A more detailed review, undertaken as part of our study, on the literature relating to the estimation of the contribution of research to GDP, is reported in Chapter Six.

Alternative measures of economic benefit

The report from the Evaluation Forum organised its analysis of the areas of economic benefits from health research around the approach developed by the Health Economics Research Group (HERG), Brunel University (Buxton *et al*., 2004). The HERG review of previous assessments of economic benefits from health research identified an extremely diverse but not very extensive literature and classified studies in terms of four main approaches to measuring economic benefits:

1 valuing direct cost savings to the health system

2 valuing benefits to the economy from a healthy workforce

3 measuring the value to society of the health gain

4 valuing the benefits to the economy from commercial development.

Valuing direct cost savings to the health system

Studies have shown that health research can lead to new treatments that reduce the overall cost per patient or the number of patients that need to be treated. Some of the clearest examples relate to vaccines or drugs that have resulted in significant reductions or the virtual elimination in some countries of diseases such as TB or polio. Research-based moves towards the control of Chagas disease in the Southern Cone countries of South America have led to considerable cost savings for these countries' health care systems (Moncayo, 2003).

Other areas of research from which cost savings have been identified include health technology assessments (HTAs). Jacob and McGregor (1997) looked at HTAs undertaken in Quebec, Canada, and found that several of these had directly influenced policy and contributed to health care cost savings.

Benefits to the economy from a healthy workforce

Measuring only health care savings is generally seen as too narrow a focus, and many studies also consider the benefits, or indirect cost savings, in avoiding lost production. Using the human capital approach, which values health gains in terms of the value of the production gained, Mushkin (1979) attempted, despite data problems, to calculate the economic benefits to the USA of all health research. In a series of calculations she estimated the economic value of the total reduction in mortality and morbidity in the USA between 1930 and 1975, and the value of the share caused by biomedical research and, after deducting the cost of the US research, produced a rate of return of 47%. At a smaller scale, a series of case studies by the US National Institutes of Health (1993) analysed particular pieces of research and included estimates of the saving from the lost production that had been avoided as a result of the research results.

There are two well-recognised problems in using this human capital approach (Drummond *et al*., 1992). While it tends to overstate the benefits at times when the lost labour can easily be replaced by unemployed people or through migration, it measures benefits from improved health only to those of working age, and ignores benefits to the rest of the population. Thus, as a measure of the value of any health-related activity it also has uncomfortable equity implications.

The value to society of the health gain

More recent studies have attempted to estimate a value of the health gain without resorting to human capital approaches. A major study that has attracted considerable attention is the Funding First report (2000), which was referred to in Chapter One. This piece of advocacy concluded that "the likely returns from medical research are so extraordinarily high that the pay-off from any plausible 'portfolio' of investments in research would be enormous". The basis for this and other such impressive claims lies in a series of highly technical papers, which, while broadly compatible in their approach, differ in terms of some of their detailed analyses and which were subsequently published in the book *Measuring the Gains from Medical Research* (Murphy and Topel, 2003).

A key element of the evidence base underpinning this work is the US research suggesting that individuals' average willingness to pay for small reductions in the risk of death is equivalent to a value of around US$5m to prevent a fatality or gain a 'statistical life'. This is then included in calculations of the economic value of the increasing longevity of the US population. The authors then consider what proportion of these gains can reasonably be attributed to medical research. In the area of cardiovascular disease, for example, they cite evidence to suggest that one-third of the decline in cardiovascular disease mortality is due to invasive treatment, one-third to pharmaceuticals and the remaining one-third to behavioural changes. But the complexity of the links between research findings and practice and behavioural changes are also emphasised; one paper, for example, looks at the impact of specific treatments in part of the CVD field and claims to demonstrate that sometimes clinical practice changes prior to formal clinical trials being conducted and at other times there are considerable lags (Heidenreich and McClellan, 2003). The importance of the diverse papers lies in their common use of a willingness to pay value of a statistical life (or life year), which enables the value of the health gain to be estimated. The robustness of the empirical value they use can be questioned, as can many more detailed assumptions they make in the Funding First report, which drew selectively on the series of papers. Nevertheless, this study provides an important influence on, and insights for, our study of the health benefits from research presented here.

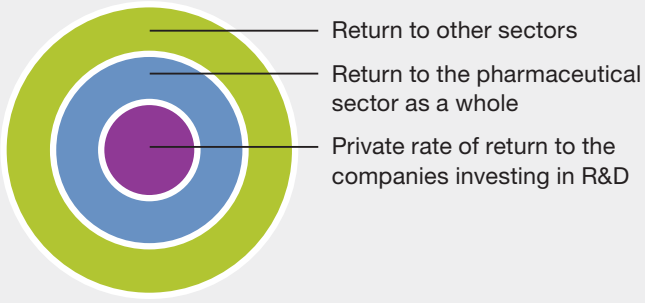
The subsequent extensive study in Australia built on the foundations of the US research and attempted to estimate the returns to investment in research in Australia for each main disease area. It used temporal changes in mortality and in morbidity by disease area. Like Murphy and Topel the Australian study used US$5m as the base-case value of a 'statistical life' which they calculated was equivalent to a value of a year of life of AUS$150,000. They extended this to allow for improvements in quality of life on the basis of an analysis of 'disability adjusted life years' (DALYs) in Australia which suggested that for each year of life lost due to premature mortality there was a further 86% of a DALY lost due to disability, worth AUS$129,000. They assumed this relationship held for all disease areas.

With these estimates they valued the mortality and (estimated) morbidity gains in Australia between 1960 and 1999, and noted that cardiovascular improvements accounted for one-third of these gains. On the other hand, using this approach, there were increases in mortality due to mental illness and hence a negative value to the measure of health 'gain' from mental health. (In the rates of return calculations, as quoted below, this fact was masked by combining the clinical areas of 'mental health' and 'nervous system' which taken together had a small positive health gain.)

Given they were starting from overall changes in mortality/morbidity it was then necessary to estimate what proportion of this should be attributed to health research, rather than general changes in economic wellbeing, education or diet for example. Despite recognising that there was no robust Australian or international economic evidence to separate out these effects and that "the eminent American economists were also not willing to hazard a guess", they took the view that "health R&D has directly, indirectly or serendipitously accounted for at least half of the gains" (Access Economics, 2003, p. 62). But they recognised that world pool of R&D was the main contributor, and used the proportion of Australia's contribution to biomedical research outputs (2.5%) as the percentage of the health benefits attributable health research that were attributable to Australian research.

A final key assumption relates to their handling of time lags. The overall analysis in the US study effectively ignored lags and compared gains over the same period as the research spend, and the Australian study adopts the same approach: comparing the gains estimated from the year 1999 with the R&D investment in 1998–99. This gave, for their base case, an overall benefit/cost ratio for health research of 2.40 (i.e. they estimated that the overall health gains – the benefit – in 1999 were valued at 240% of the value of the total health R&D –

Figure 2.1: Spillovers from private pharmaceutical R&D



the cost – in 1998–99). For cardiovascular the base case ratio was 7.88, whilst for nervous system and mental health the value was just 0.23. (They do not state, and it is not possible to estimate from the published figures, what the 'return' would be for mental health alone.)

This Australian study has recently been 'updated', but with substantial changes to the methodology used. The value of a statistical life year has been increased to AUS$266,843 (at 2008 prices) based on a new meta-analysis of studies and the Australian contribution to world R&D outputs has been increased to 3.04% based on more recent bibliometric data on clinical research. Most fundamentally, the analysis now deals with the issue of the lag between R&D spending and the health benefits that are attributed to that spending, by comparing R&D expenditure (in 1993–2005) with 'projected' health benefits in 2033–2045 (thus assuming an average lag of 40 years). These 'projected' health benefits are based on projections of the future burden of disease from the Australian Institute of Health and Welfare up to 2023, extrapolated forward further to 2033–2045. Thus their current estimate of the return to health R&D investment is not based on an analysis of what has happened but on estimates of what might happen in the future (and logically these estimates themselves should depend on assumptions about the effect of recent/current R&D on future health of Australians). Curiously the headline benefit/cost ratio remains similar (2.17 compared with the earlier 2.40) but this later report does not provide estimates of the return by disease area. One reason for this is that their estimates of 'projected' benefits indicate that the return if calculated would be negative for 'diabetes mellitus, endocrine and metabolic disorders', for 'mental disorders, nervous system and sense organ disorders' and for 'musculoskeletal diseases'. The report notes that this does not mean that R&D undertaken in these areas was not effective, but that "current R&D spending in these areas is not sufficient to outweigh the expected increase in these disorders". In which case, the figures for the aggregate of all disease areas also cannot be taken as an indicator of the effectiveness and hence the return on R&D.

In a recent study, Johnston *et al*. (2006) adopted a hybrid approach to assess the costs and benefits of phase III randomised trials funded by the US National Institute of Neurological Disorders and Stroke. Yearly total incremental net benefits of the programmes were calculated by combining trial costs and treatment costs with a monetary value for the QALYs gained from the implementation of the trial findings. The study used a value of a QALY based on US GDP per capita, suggesting that this reflected "the average yearly economic productivity of a US resident, regardless of employment or age".

Benefits to the economy from commercial development

A major UK review identified a range of categories of benefits to the economy but found that none of the studies provided a simple and comprehensive model (Salter and Martin, 2001). In its evidence to the US Congress, the National Institutes of Health cited several studies showing the importance of publicly funded research to the development of significant new drugs. In one study 15 of the 21 drugs identified as having had the most impact on therapeutic practice were developed with input from the public sector (Joint Economic Committee, US Senate, 2000). This study also stressed the complex interaction between publicly and privately funded research but it made no attempt to calculate the social rate of return.

For our study we undertook a review of the literature on how public research impacts, or 'spills over' to, the rest of the economy. This identified a clear consensus that the relationship between public and private research is complementary, though complex. Incremental public research is associated with increased private research. The published literature finds that the relationship between public and private research sectors works in both directions: public research stimulates private, and private research stimulates public. There is a small literature estimating the size of this complementarity and also a modest number of studies estimating the impact of GDP of public and private research.

Figure 2.1 illustrates, for the pharmaceutical sector, the concept of spillovers: R&D investment undertaken in one organisation not only generates benefits to itself (the 'private' return – shown in purple) but also could bring about economic benefits to other organisations operating in the same sector (shown in blue) and in other sectors of the economy (shown in green). The main sources of these positive externalities are scientific and technical advances and, more generally, knowledge flows generated and induced by R&D activity. The sum of all three sets of benefits represents the total 'social' return to the original investment in R&D.

Garau and Sussex (2007) provide an estimate of the spillovers generated by the (private) pharmaceutical R&D carried out by two major companies in the UK. The range of estimates is based on empirical economic literature looking at the rate of return to private R&D.

Key issues in estimating the return to R&D

Several issues emerge from this grouping of benefits. It is clear that both the second and third approaches place a value on health gain, but that these are alternatives: to use both concepts would involve double-counting. Furthermore, if the value of the health improvement can be measured by either of these approaches it will make a more significant contribution than the first area that concentrates on cost savings to the health care system. Moreover valuing the health gain is compatible with recent broad definitions of the economic impacts of research, such as that given in the Warry Report on increasing the economic impact from (all) research councils in the UK. This report suggests that the "effects on the environment, public health and quality of life" should be included (Warry, 2006).

The use of a willingness to pay estimate of the value of the health gained, as in the US study, has a clear logical basis in cost/benefit analysis, although there are well recognised problems in obtaining good empirical estimates, and available estimates vary considerably (Nordhaus, 2003). However, a value based on willingness to pay (or willingness to accept) is not necessarily the most appropriate for this purpose, particularly if the analysis is aimed to reflect the opportunity of investing in health research rather than directly in health care. In such circumstances, the amount the NHS would normally be prepared, and able given its budget, to pay for health gain might be more appropriate. This line of argument would point us towards the 'threshold' used by the National Institute for Health and Clinical Excellence (NICE) for the maximum value it is prepared to pay for a quality adjusted life year, which lies between £20,000 and £30,000 (NICE, 2004). Current research commissioned for NICE may indicate whether the NICE threshold approximates to a UK social willingness to pay value or not.

Where the focus is on the value of the health gain itself, some assessment has to be made of the cost of achieving this benefit. The main cost is likely to be to the health care system, but for public health and behavioural interventions the cost may be much more widely spread. It would seem logical to assess these costs and deduct them from the value of the benefits, as a necessary means to implement R&D. This was clearly done in the study by Johnston *et al.* (2006) but the Australian study appears to make no allowance for these costs of delivering health gain through the health care system. On the other hand studies assessing the return to investment in health care attribute the value of the health gain to the 'investment' in the health care system rather than to the research investment behind improved treatments etc. (Luce *et al.*, 2006; Cutler *et al.*, 2006).

The HERG review of studies of the economic benefits from health research (Buxton *et al.*, 2004) suggests that there are two issues of concern even before we get to the question of how we value the benefits.

Figure 2.2: Nationality of papers cited in 15 UK clinical guidelines published between 1996 and 1998 and world share of biomedical papers

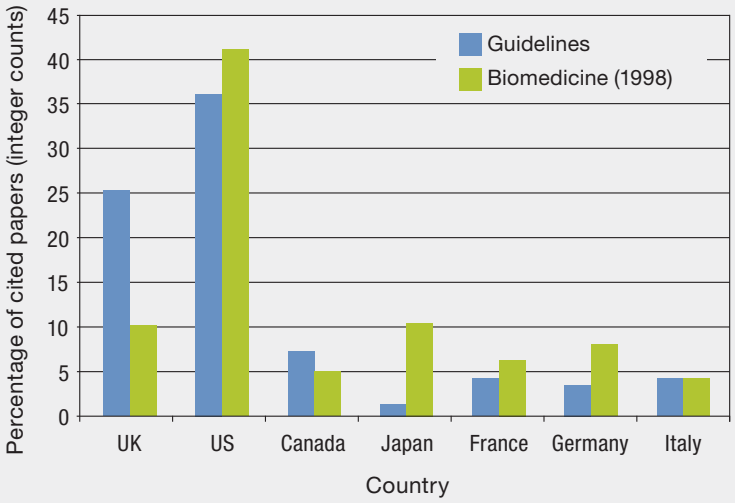
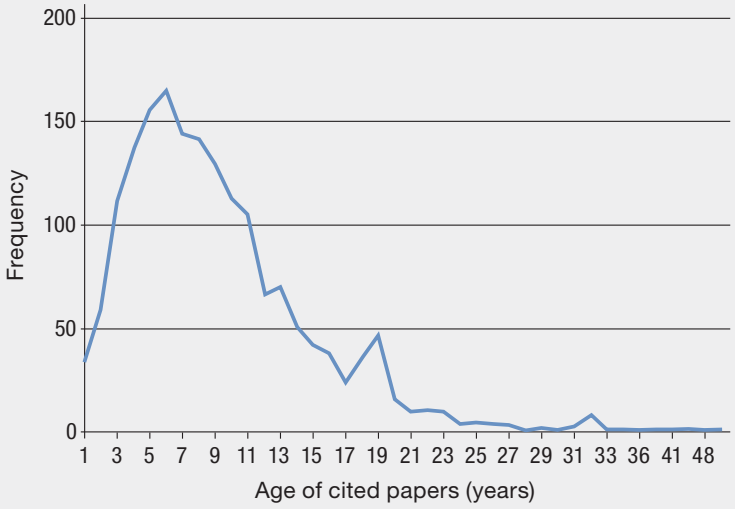


Figure 2.3: Age of papers cited on 15 UK clinical guidelines published between 1996 and 1998



The first concerns the inputs in question. A number of key science policy studies have emphasised the complexity and range of the research that can lie behind advances in health care (Comroe and Dripps, 1976; Raiten and Berman, 1993). It is often unclear precisely which research has contributed to specific health advances. In the studies examined in Buxton *et al.* (2004), the breadth of the research considered varies considerably. Some studies consider the impact from specific research projects or programmes, while others look at a broad field of research (e.g. cardiovascular research) and a few have attempted an overall assessment of medical research.

The second issue relates to the relationship, or attribution, between the research inputs and health and other outcomes. Overall, it is not known for certain how far research, from whatever source, has contributed to advances in health. For example, McKeown (1979), in an analysis challenged by Mushkin (1979) and more recently by Sussex (2000), suggested that during the 20th century much of the reduction in mortality was due not to medical advances and medical research, but to improvements in general living standards. If temporal change in health is used as a measure of benefit then some of that change should probably be attributed to broader factors other than simply medical research.

This latter point is an example of the general issue that we can only observe the events and outcomes that followed past investment in research: we cannot observe what would have happened without that research. Any analysis of returns on that research involves an explicit or implicit assumption of the counterfactual – what would have happened if the research had not been undertaken. As a result there will always be difficulties in establishing unequivocal links between research and its impact. The problem of attributing benefits to specific pieces of research is a particularly acute problem and has led some authors to question the value of attempting to assess the health and economic benefits from research (Royal Netherlands Academy of Arts and Sciences, 2002). There have been criticisms of some series of case studies, including those undertaken for the National Institutes of Health (NIH, 1993; Johnston *et al*., 2006), because they seem to have made assumptions about the level of implementation of NIH research. It is claimed that one way of attempting to address these problems of attribution in case studies is through use of the payback framework (Buxton and Hanney, 1996; Hanney *et al*., 2004; Wooding *et al*., 2005).

We have already noted the problem that the research from any one country adds to the international pool of knowledge. Whilst perhaps this problem can be ignored in the USA, which produces a sizable proportion of global health research, elsewhere it must be addressed. The Australian study used its proportion of world health research output as a proxy for the indicator of how much of the benefit could be attributed to Australian research. The analysis of papers cited in national clinical guidelines provides information that could offer an alternative estimate to help link research to practice and inform estimates of the economic return from research. Whilst the UK contributes about 10% of the global scientific research effort (King, 2004), we know from previous work that UK guideline authors disproportionately cite UK research (Grant *et al*., 2000). In that study the authors examined the bibliographical details of 15 disease management guidelines that covered a range of conditions seen in family practice in the UK. All the cited papers were looked up on the *Science Citation Index* and additional bibliographic information, including authors' addresses, was captured. The country of authorship was derived from an analysis of the addresses showing that 25% of papers cited in a sample of UK guidelines had authors with a UK address, whilst the UK only contributed 10% of the world's biomedical research papers (Figure 2.2).

These data might suggest that between 10% and 25% of health gains could be attributed to UK research. This analysis of guidelines is repeated in Chapter Four and Chapter Eight for cardiovascular and mental health guidelines respectively.

A further issue that has been addressed is the proportion of UK research that is funded from public and charitable funding and the proportion funded by industry. Dawson *et al*. (1998) reported that of biomedical papers with a UK address 18% of cardiology papers and 17% of neuroscience papers acknowledged industry funding, most but not all which came from the pharmaceutical industry.

The analysis of guidelines described above calculated the median time lag between guideline date and publication date of cited papers. This provides one estimate of the time lags between when R&D spending occurs and when society benefits from that R&D as a result of the adoption of new interventions or treatment strategies. Grant *et al*. (2000) estimated that the median 'knowledge cycle time' for all 15 guidelines was eight years, with 25% of papers cited being more than ten years old and 4% more than 25 years old (Figure 2.3).

Conclusions

Our brief selective reviews of the various literatures suggest that no single existing study adequately addresses the issue of the economic returns to health research. We see the way forward as being to build on, but significantly improve, the methodology of the most promising and relevant approaches, and using them to produce empirical estimates for the UK. Clearly reliable estimates of past UK research investment are required for our two areas of focus: cardiovascular research and mental health research. These are developed in Chapter Three. We then focus on the two main elements of economic benefit which represent the returns on this investment: 1) the net value of the health gain attributable to UK public/charitable research investment and 2) the GDP effect of that investment. These are conceptually quite different and potentially additive in assessing an overall return on research investment. Our chosen methodological approaches to these are set out in Chapters Five and Six. In the final Chapter we summarise the key developments to previous methods that we have made in this study.

Chapter Three

Expenditure on cardiovascular research

KEY POINTS

- We estimated the expenditure on cardiovascular research from the Medical Research Council, the Higher Education Funding Councils, the Department of Health, the British Heart Foundation and the Wellcome Trust.
- Total annual funding for cardiovascular research in the UK from these public and charitable sources increased from £26m in 1975 to £88m in 1992 in cash terms, representing an annual percentage increase of circa 7.5%.
- In 2005 prices, this equates to a decrease in annual spend from £144m in 1975 to £121m in 1992, with a total expenditure over the period of £2,026m.
- Pharmaceutical industry spending on cardiovascular research in the UK grew rapidly in this period and rose to £213m in 1992 – 2.4 times the public/charitable expenditure.

Figure 3.1: Total estimated cardiovascular research spend (public and non-profit), by source of funding, 1975 to 1992, at current prices

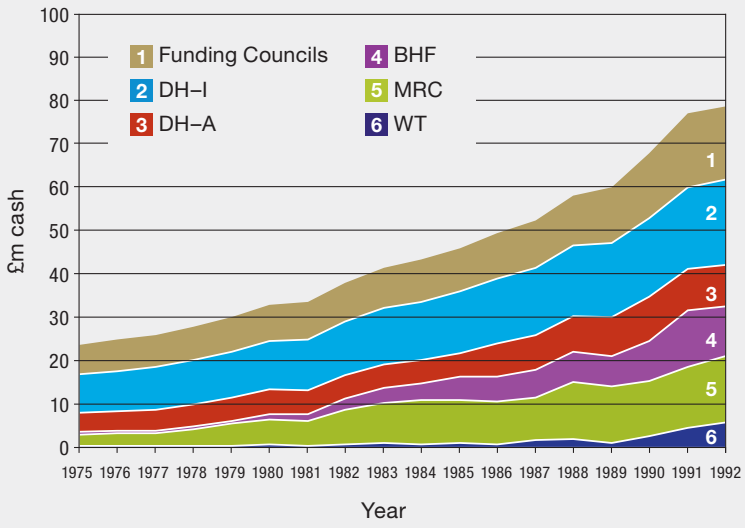
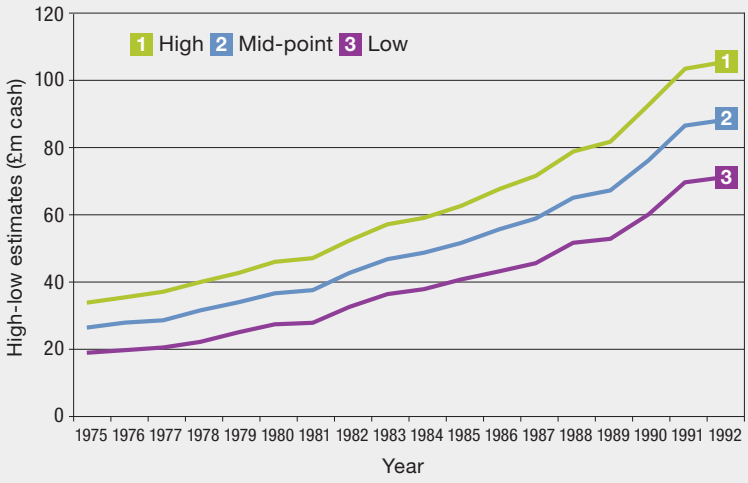


Figure 3.2: High and low estimates for public and non-profit cardiovascular research expenditure, 1975 to 1992, at current prices



Introduction

The focus of our study is the impact of publicly and charitably funded R&D expenditure in the UK. A part of that impact is mediated through the interrelationship between public/charitable medical R&D and private sector medical R&D, and the literature suggests that a proportion of private R&D is likely to have been stimulated by public/charitable R&D. The direct returns from private sector R&D are reflected in the costs associated with interventions that result in cardiovascular health gains and these are therefore netted off from our estimates of monetary value of health gains (see Chapter Five). In addition, public/charitable research may have a more general effect on GDP through its impact on the productivity of private sector R&D (see Chapter Six). In this Chapter we provide estimates of the magnitude of past spending on cardiovascular research from both the public/charitable and for-profit (pharmaceutical industry) sectors.

Estimates of public/charitable funding

Figure 3.1 illustrates the expenditure on cardiovascular research from 1975 to 1992 by six sources of funding from the government and charitable sectors. These graphs are based on a number of overarching assumptions about the nature of R&D funding in the UK. First, we have assumed that the Medical Research Council (MRC), Department of Health (DH) and Higher Education Funding Councils are the sole government funders of cardiovascular research in the UK. This will cover most of total government funding in this area, although it should be noted that there may be small pockets of relevant research funded by other Research Councils or by other Government Departments that we have not captured.

For the non-profit funders we have assumed that cardiovascular research is supported principally by the Wellcome Trust and the British Heart Foundation (BHF). There are, of course, other non-profit funders of cardiovascular research (such as the Stroke Association) but data available from the Association of Medical Research Charities website indicate that the Wellcome Trust and BHF currently account for 95% of funding by medical research charities between them[1], and for this reason we have focused on these two organisations.

Finally, we have assumed that the definitions of the cardiovascular field used by the research funders we

include capture the range of the basic research that may have contributed to developments in this area. Our impression from scanning the grant titles included suggests that this is the case, and that even fairly fundamental basic research tended to be classified into clinical fields. This is an important consideration since the difficulty of establishing clear links between basic research and applications means that a proportion of contributing basic research will inevitably be excluded by restrictive field definitions.

The data presented in Figure 3.1 derive from a number of different sources and, of necessity, include further assumptions and extrapolations in some cases. We describe these in further detail below; on this basis, we provide a 'high' and 'low' scenario for total cardiovascular research expenditure as shown in Figure 3.2.

- **Wellcome Trust (WT)**. Wellcome Trust expenditure on cardiovascular research is derived from the Wellcome Trust grants database using a combination of key-word searches and classification terms developed and used by the Trust. Historically grants have been classified by Grant Officers using a thesaurus of terms. We selected all grants that had been classified as 'CARDIOLOGY', 'VASCULAR DISORDERS', 'CARDIOVASCULAR DISEASE' and 'VASCULAR SYSTEM'. In addition a list of search terms developed for a bibliometric search filter for cardiovascular research was applied to the titles of awarded grants (a full list of key words is available from the authors).
- **Medical Research Council (MRC)**. Between 1972 and 2005 the MRC has used five different systems for classifying grants. The longest time series is for 1976/77 to 1992/93 and this was the series used for the basis of our estimates. For this period annual spend on funded grants was classified in two ways; the first was based on the primary purpose of the research and provided an 'exclusive' measure of spend by a number of headings (in this case 'CARDIOVASCULAR SYSTEM'). The second was a more 'inclusive' measure where spend could be placed against a number of different categories. For the current project we have used the 'inclusive' measure as this is the larger value and errs on the side of caution in our ultimate aim of generating a measure of the rate of return on investment.
- **British Heart Foundation (BHF)**. The BHF data are taken from their annual reports for the years 1975 to 1985 and 1989 to 1992. We assumed that all BHF grant expenditure was directed at cardiovascular research. Data for the intervening period 1986 to 1988 were interpolated using a linear function.
- **Department of Health – activity (DH–A)**. The DH data include the NHS (which was only collected from 1995) and Department expenditure. The NHS data have been 'backcast' (using an exponential function) for 1975–92, using 1995–2005 data published in the online version of the Science Engineering and Technology Indicators (SET) Statistics.[2] The DH data for 1986 to 1992 are taken from the online version of the SET Statistics, and for 1981 to 1985 from a published report of the SET Statistics.[3] The 1975–80 period is interpolated (using a linear function) from these two series and a 1973 data point estimated in a one-off survey of R&D expenditure in government (Maddock, 1975). This means that we deliberately risked over-estimating expenditure, with the aim of taking a cautious approach to the estimated rate of return.

Once the data series for the NHS and DH were derived, we split the NHS expenditure by a ratio of 20% of activity funding and 80% for infrastructure. The activity element of the NHS was combined with cardiovascular-specific DH data, derived by multiplying the DH figures by an estimate of cardiovascular activity.

In deriving a figure for cardiovascular activity, we settled on a central estimate of 9% of total research, and we also assumed it to be constant over the time period. This estimate of 9% represents a middle ground between a number of independent data points:

- the MRC's spending on cardiovascular research (using the 'exclusive' definition described below) ranged from 6% to 9%
- WT cardiovascular funding was more erratic, ranging between 2% and 19% of expenditure being on cardiovascular research
- the proportion of peer reviewed research papers in the cardiovascular field as a percentage of all biomedical outputs ranged from 8% to 9% between 1988 and 1995 (Dawson *et al*., 1998)
- the proportion of peer reviewed research papers in the cardiovascular field (as a percentage of all NHS research outputs) was 11.5% between 1990 and 1997 (Wellcome Trust, 2001)
- in a short, one-off report, *NHS R&D Annual Reporting 2002/03*[4], 63 out of 764 programmes (8.2%) were classified under the heading 'cardiovascular and heart disease'.

Given the importance of this estimate of the proportion of research activity that is cardiovascular (where we have no actual breakdown), Figure 3.2 presents the data also using high and low estimates of 6% and 12% respectively, and these are used in subsequent sensitivity analyses.

- **Department of Health – infrastructure (DH–I)**. This is calculated as 80% of the total NHS R&D spend, again multiplied by 9% for estimated cardiovascular research activity. The total NHS R&D expenditure is derived from the SET statistics as described above.

- **Funding Councils (FC)**. The Higher Education Funding Council for England (HEFCE) directly provided us with funding data for biomedical subjects from 1989/90 to 2007/08. The data for 1989/90 to 1992/93 were for the University Funding Council (UFC) and covered Great Britain. From 1993/94 onwards the data here were for England alone. Biomedical research was defined by the cost centres/unit of assessments used at the time.[5] To estimate a time series for 1975 to 1992, we used Funding Council data for the period 1989–2007 (with adjustments to include data for Wales, Scotland and Northern Ireland where otherwise not taken into account) and then back-cast these figures using an exponential function to generate data for the period in question. These data represent the total biomedical spend during our period; they have been multiplied by 9% to give estimated cardiovascular research activity.

Figure 3.3 presents the total public and charitable spending on CVD research, as shown in Figure 3.2 but in constant prices. This emphasises that the growth in cash terms apparent in Figure 3.1 masks the fact that in real terms spending fell from 1975 to 1981 and whilst it rose again to 1991, it had still not got back to the levels of real spending of 1975. In more detail, between 1975 and 1992, total annual cash expenditure by public and charitable funders of cardiovascular research increased three-fold from £26m to £88m. Total estimated cardiovascular expenditure over the period was £900m in cash terms. During the period growth rates for the different components varied: total MRC expenditure increased by an average of 10.5% a year, Wellcome Trust by 23.1%, Gross Expenditure on Research and Development (GERD) by 6.8% per year and Government GERD by 3.5%.

Figure 3.3: Expenditure on cardiovascular research by public and non-profit funders, 1975 to 1992, at constant 2005 prices

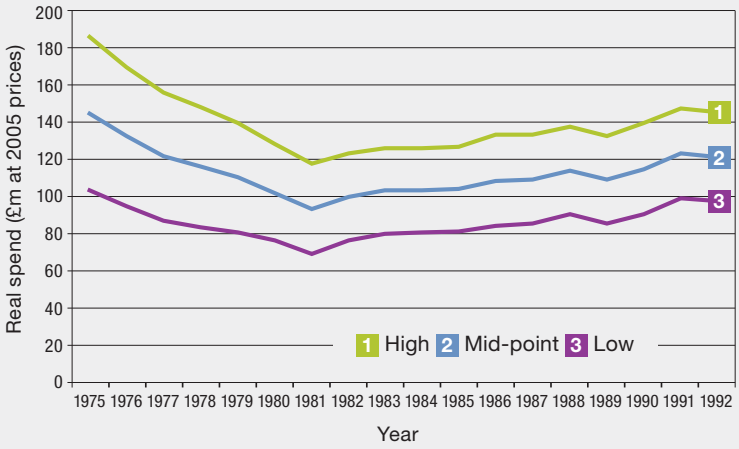
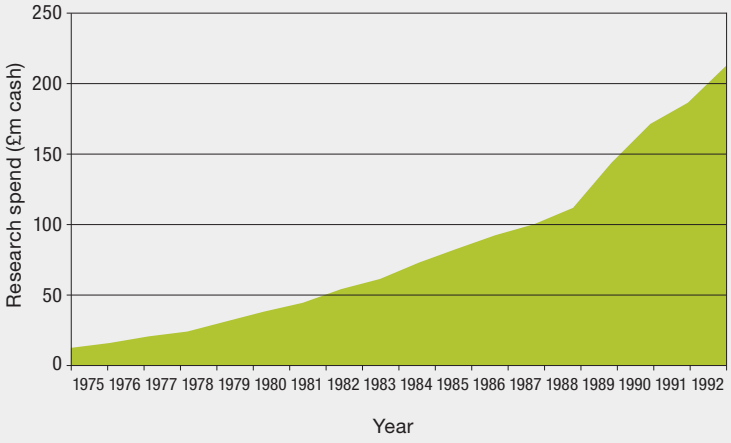


Figure 3.4: UK pharmaceutical industry expenditure on cardiovascular research, 1975 to 1992, at current prices



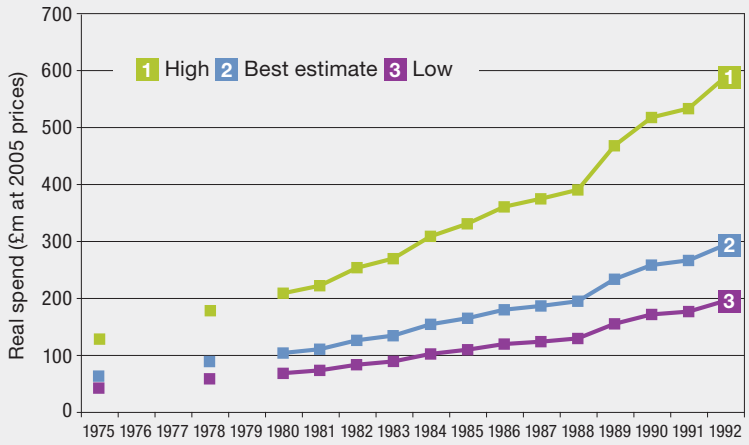
Estimates of 'for-profit' sector funding

To provide comparative figures for the 'for profit' sector, we have assumed that cardiovascular research is principally supported by pharmaceutical companies in the UK. We note that the total non-pharmaceutical health care industries' expenditure is equivalent to around 4% of that of the pharmaceutical industry. Although we discuss the derivation of this figure in more depth below, we have not included it in our analysis because it cannot be broken down by therapeutic area.

Our detailed sources and assumptions for this sector were as follows:

- **The pharmaceutical industry**. The Association of the British Pharmaceutical Industry (ABPI) compiles and publishes data on total R&D expenditure in the UK by the pharmaceutical industry, but does not disaggregate them between different therapeutic target areas. We were unable to find any such disaggregated data for the UK elsewhere. Estimates of worldwide R&D expenditure by broad therapeutic area were provided for the last three years, 2003–05, by CMR International from their survey of approximately 20 multinational pharmaceutical companies.[6] These showed cardiovascular R&D accounting for 10% of total worldwide private pharmaceutical R&D expenditure over those three years. Ward and Dranove (1995) present similar estimates, for the years 1966 and 1988, for the therapeutic categories of R&D spend by members of the Pharmaceutical Manufacturers of America association, covering global spend by US companies and US spend by non-US companies. Ward and Dranove quote 14% of pharmaceutical R&D going to cardiovascular in 1966 and 30% in 1988. Thus, we assume overall that cardiovascular may account for anything between 10% and 30% of total pharmaceutical sector private R&D spending. On the basis of the estimates provided above, however, we conclude that an estimate of 15% is more likely to be representative of industry cardiovascular research expenditure than a strict 20% mid-point, and this is the figure we have used in our calculations of the 'spillover' effects described in Chapter Six.

Figure 3.5: UK pharmaceutical industry expenditure on cardiovascular research, 1975 to 1992, at 2005 prices



- **Private, non-pharmaceutical health care sector expenditure**. Data on R&D spending by the private non-pharmaceutical health care sector are even scarcer than for the pharmaceutical sector. We were not able to find specific data on UK R&D expenditure. The only available data, which are published in the Department for Innovation, Universities and Skills (DIUS) R&D Scorecard,[7] give total annual R&D expenditure figures by the health sector (excluding pharmaceuticals) for the period 1990–2006, on the basis of worldwide spend by UK-based companies plus spend in the UK by non-UK-based companies. The same source presents equivalent data for the pharmaceutical sector which makes clear that health care industry R&D is very small relative to pharmaceutical R&D, being only around 4% of the size of pharmaceutical R&D. Given its small scale and the unavailability of any estimates as to the therapeutic area breakdown of that spending, we have treated non-pharmaceutical health sector private R&D as de minimis for the current exercise.

Figures 3.4 and 3.5 summarise the data. Figure 3.4 shows that our best estimate of private pharmaceutical industry cardiovascular R&D expenditure increased steadily in cash terms from £12m in 1975 to £213m in 1992. When expressed in constant 2005 price terms (Figure 3.5) this becomes an increase in our best estimate from £65m in 1975 to £295m in 1992.

Conclusions

Estimates of spending specifically on cardiovascular research are not readily available for either sector and we provide here original estimates that have not previously been available. The construction of these estimates relies on data from a number of different sources and various assumptions regarding the split of medical research between different clinical areas.

Despite some inevitable uncertainties we have a time series for total public/charitable research expenditure on cardiovascular disease which represents the research investment that we are studying, and also a series for research expenditure by the pharmaceutical industry. This feeds into our estimates of the indirect impact of public research on GDP. The private figures also make it clear that private sector R&D expenditure greatly exceeds public plus charitable expenditure.

1 See: www.amrc.org.uk.

2 www.dti.gov.uk/dius/science/science-funding/set-stats/.

3 Annual Review of Government Funded R&D (Cabinet Office, 1984).

4 www.dh.gov.uk/en/Researchanddevelopment/Researchanddevelopmentpublications/Informationfromresearch/DH_4078384 [accessed 12 February 2008].

5 These were: Clinical Medicine, Clinical Dentistry, Pre-Clinical Studies, Anatomy and Physiology, Pharmacology, Pharmacy, Nursing, Other Studies Allied to Medicine, Biochemistry, Psychology, Other Biological Sciences for the UFC; and Clinical Laboratory Sciences, Community-based Clinical Subjects, Hospital-based Clinical Subjects, Clinical Dentistry, Pre-Clinical Studies, Anatomy, Physiology, Pharmacology, Pharmacy, Nursing, Other Studies and Professions Allied to Medicine, Biochemistry (Discontinued in RAE2001), Psychology, Biological Sciences for HEFCE.

6 M Ogg, personal communication, 28 November 2007.

7 www.innovation.gov.uk/rd_scoreboard/ [accessed 23 April 2008]. This area was previously under the purview of the Department for Trade and Industry (DTI).

Chapter Four

Analysis of cardiovascular guidelines

KEY POINTS

- In this Chapter we look for evidence to suggest what proportion of the impact of all (world) cardiovascular research might reasonably be attributed to UK research. We also estimate a mean time lag between research expenditure and its impact on health.
- Analysis of UK cardiovascular clinical guidelines indicates that the proportion of the cited evidence base attributable to UK cardiovascular research is 17%, ranging between 12% and 23% for different guidelines.
- Combining this evidence with findings from previous studies and other data points, we assume that the proportion of UK health care benefit attributable to UK research lies in the range of 10% to 25% with a mid-point estimate of 17%.
- Analysis of cardiovascular clinical guidelines suggests that the time lag between research spending and citation on a clinical guideline (a proxy for health gain) is around 12.5 years, ranging between nine and 17 years.
- Combining this with findings from previous studies and other data points, we assume a mean lag between research and impact of between ten and 25 years, with a mid-point of 17 years.

Introduction

As introduced in Chapter Two, to estimate the returns from cardiovascular research we need to know what proportion of health gained can be attributed to UK research and the time lag between when R&D spending takes place and the time that society obtains the health benefits.

At one level, both pieces of information can be generated heuristically. For example, the UK accounts for roughly 10% of the global research (King, 2004), and the time lag between research and impact is often quoted as in the order of ten to 20 years. However, to both validate and improve on these estimates, and to allow for the possibility that these parameters might vary between clinical areas, we undertook an analysis of cardiovascular guidelines based on the approach developed by Grant *et al*. (2000) and discussed in Chapter Two.

Analysis of UK clinical guidelines relating to cardiovascular disease

We identified seven national clinical guidelines which provide a broad representation of current cardiovascular practice (see Table 4.1 below), focusing on UK guidelines only since we are concerned with UK practice. Five of the seven were published by the National Institute for Health and Clinical Excellence (NICE), one by the Royal College of Physicians (RCP) and the other by the Scottish Intercollegiate Guidelines Network (SIGN).

The references were extracted from the electronic (PDF) version of each guideline using a bespoke computer program and then matched with the bibliometric database developed and maintained by the Centre for Science and Technology Studies (CWTS) at Leiden University in the Netherlands.[1] Of the 2,881 references on the seven guidelines, 2,793 (97%) were extracted by the program, and 2,064 (74% of the extracted papers) were indexed on the CWTS database and were used as the basis of our analysis (Table 4.2). Those references that were not on the database will include non-serial outputs (such as books), journals that are not captured by CWTS in their source databases, or incorrect (and therefore un-matchable) references. In the sections that follow, on country of authorship and knowledge cycle time, our analysis looks only at the numbers of cited papers, and makes no judgements about their relative importance in contributing to the guidelines in question.

Table 4.1: Guidelines analysed

Guideline	Source	Publication date
Angina	www.sign.ac.uk/pdf/sign96.pdf	2007
Atrial fibrillation	www.nice.org.uk/nicemedia/pdf/cg036fullguideline.pdf	2006
Chronic heart failure	www.nice.org.uk/nicemedia/pdf/Full_HF_Guideline.pdf	2003
Hypertension	www.nice.org.uk/nicemedia/pdf/HypertensionGuide.pdf	2006
Post-myocardial infarction	www.nice.org.uk/nicemedia/pdf/CG48FullGuideline.pdf	2007
Venous thromboembolism	www.nice.org.uk/nicemedia/pdf/VTEFullGuide.pdf	2007
Stroke	www.rcplondon.ac.uk/pubs/books/stroke/stroke_guidelines_2ed.pdf	2004

Country of authorship

Figure 4.1 shows, for the seven clinical guidelines, the distribution of the addresses of the authors cited for G7 countries.[2] Most papers were published by authors living in either the USA (35%) or the UK (17%; ranging from 12% for the atrial fibrillation guidelines to 23% for the stroke guideline). The G7 countries accounted for 71% of authors. By comparison, Grant *et al.* (2000) reported that 36% of papers had an author with a US and 25% an author with a UK address. Both sets of figures suggest a higher than expected level of citation for papers of UK origin – which may reflect either perceived greater relevance of UK evidence to UK context, or simply parochial preference.

To get a better understanding of what lay behind these findings, a more qualitative analysis was undertaken of the research cited on one of the guidelines, that on hypertension.[3] This detailed analysis highlights that there are varying degrees of UK involvement in the research. A few studies are clearly fully funded by traditional UK funders and conducted solely in the UK. A greater number, however, are international with varying degrees of UK input – and often funded by the pharmaceutical industry. Taken together this analysis suggests that UK-based research probably constitutes well over 10% of the research on key trials cited on the guideline.

Discrepancies between the figures derived from the two analyses to some extent reflect problems of attribution inherent in bibliometric analysis of authorship – particularly that addresses of all authors may not be listed. Thus, in the quantitative analysis, both the UK and the USA would be 'credited' equally for a paper with six authors, five of whom were at a UK institution and only one of whom was in the USA, although the UK contribution would arguably have been much greater.

Combining these various estimates, we assume that 17% of the health gain to the UK population might reasonably be attributed to UK cardiovascular research and this proportion might range between 10% and 25%.

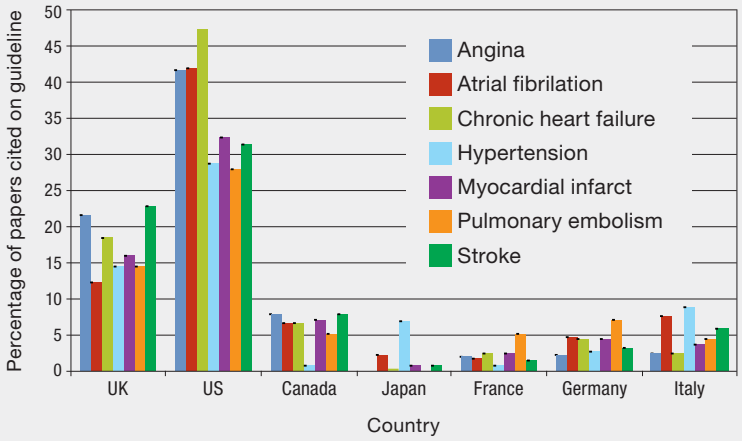
Knowledge cycle time

The age of the papers cited on a clinical guideline is known as the 'knowledge cycle time', and this is illustrated in Figure 4.2. The mean knowledge cycle time for all seven guidelines is around 9.5 years, ranging from just over six years (for the chronic heart failure guideline) to just under 14 years (for venous thromboembolism). A third of references were over ten years old, and 2.5% over 25 years old. It is notable that these figures are similar to those reported by Grant *et al.* (2000), where the median age was eight years, with 25% over ten years and 4% more than 25 years old. Given a plausible approximate time lag between research expenditure and publication of around three years, we can assume a total time lag of around 12.5 years, ranging between nine and 17 years.

Table 4.2: Number of references, papers and found papers, by guideline

Guideline	Number of references	No (%) of extracted papers	No (%) of matched papers
Angina	311	305 (98%)	241 (79%)
Atrial fibrillation	505	478 (95%)	324 (68%)
Chronic heart failure	349	323 (93%)	255 (79%)
Hypertension	81	74 (91%)	65 (88%)
Post-myocardial infarction	269	258 (96%)	194 (75%)
Venous thromboembolism	588	579 (98%)	390 (67%)
Stroke	778	776 (100%)	595 (77%)
Total	**2,881**	**2,793 (97%)**	**2,064 (74%)**

Figure 4.1: Nationality of papers cited in seven cardiovascular clinical guidelines published between 2003 and 2007



To complete our understanding of the time lags involved we also looked at the literature on product development – complicated both because it takes time to obtain a tangible research output (e.g. a new medicine) and because maximum uptake of new products is far from immediate. A highly cited estimate of drug development costs and timelines is DiMasi *et al.* (2003). In this work, the authors look at development costs and timelines for a sample of new drugs first tested in humans between 1983 and 1994. They estimate that the time between the start of clinical testing and submission of a new drug application (NDA) or a biological licence application (BLA)[4] with the Food and Drug Administration (FDA) is 72.1 months. On top of this, they estimate that the approval phase lasts on average 18.2 months. Combining these two results, the time from the start of clinical testing to marketing approval in their timeline for a representative drug averages 90.3 months. In an earlier paper (DiMasi *et al.*, 1991), where the authors look

at a sample of new medicines first tested in humans between 1970 and 1982, they estimate that the time from start of clinical testing to marketing authorisation was 98.9 months. Within this earlier time period, the approval phase was estimated to be much longer (at 30.3 months) than in the later period.

It is important to remember that time lag estimates generated in this way represent *proxies* for the real values since other factors are often involved. For example, there may be a gap between guideline publication and translation into practice, suggesting that we may be underestimating the time lags. On the other hand, interventions may come into use *before* guidelines outlining them have been published – suggesting that we may overestimate time lags in some cases.

We also recognise that time lags will vary considerably between different types of research. Basic research will precede the health impact that might follow from technologies it underpins by a much longer period than, for example, a health technology assessment confirming in which patients a new technology might be most cost-effective. Equally, it may be that research uptake is better in some fields than others.

In the absence of better evidence, however, and combining the various estimates we presented above, we assume the lag between when public and charitable R&D spending on cardiovascular research takes place, and the time that it benefits society through measurable health gains, to be 17 years, ranging from ten to 25 years. Aware of the importance of this evidence to our overall estimate of returns, and the paucity of data that it is derived from, in Chapter Eight we undertake an analysis of the sensitivity of time lags on our final results.

Analysis of cited reviews

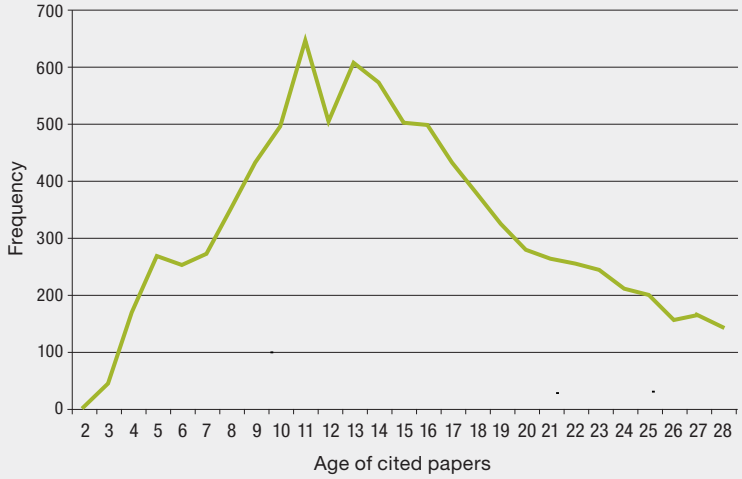
We initially planned to undertake an analysis of the papers cited by the papers cited on clinical guidelines to understand the 'generational' effects of the flow of knowledge (as initially done by Grant *et al.*, 2000). However, we began to question the additional utility of this analysis on adding to the estimates derived above, so instead focused our analysis on cited reviews. Within the CWTS all publications are classified as being, for example, original papers, reviews, letters, editorial etc. To our surprise, of the 2,064 references only 122 (or 6%) were reviews, hence we question the value of this additional analysis for the information we are trying to generate. The 122 reviews cited a further 35,774 papers of which 12% were UK (range: 5% for artrial fibrillation to 18% for stroke), and 45% US. An age distribution for these cited papers is presented in Figure 4.3. The mean knowledge cycle time for reviews from these guidelines was found to be around 13 years, varying from just under nine years for those reviews on the hypertension guideline (an outlier), to 14 years for chronic heart failure. Given the approximate time lag between research expenditure and publication of three years stated above, we conclude that total lag time for the review was around 16 years,

Table 4.3: Estimated time lags for pharmaceutical product development

	Time between the start of clinical testing and submission of an NDA/BLA (A)	Approval phase (B)	Time from start of clinical testing to marketing authorisation (A+B)
DiMasi *et al.* (2003)	72.1 months	18.2 months	90.3 months
DiMasi *et al.* (1991)	68.6 months	30.3 month	98.9 months

Figure 4.2: Age of papers cited on seven cardiovascular guidelines published between 2003 and 2007

Figure 4.3: Age of papers cited by review papers on seven cardiovascular guidelines published between 2003 and 2007



ranging between 12 and 17 years. This gives a best estimate similar to the knowledge cycle time for papers cited directly suggesting that citation through a review does not significantly change the speed of uptake of research findings.

Conclusions

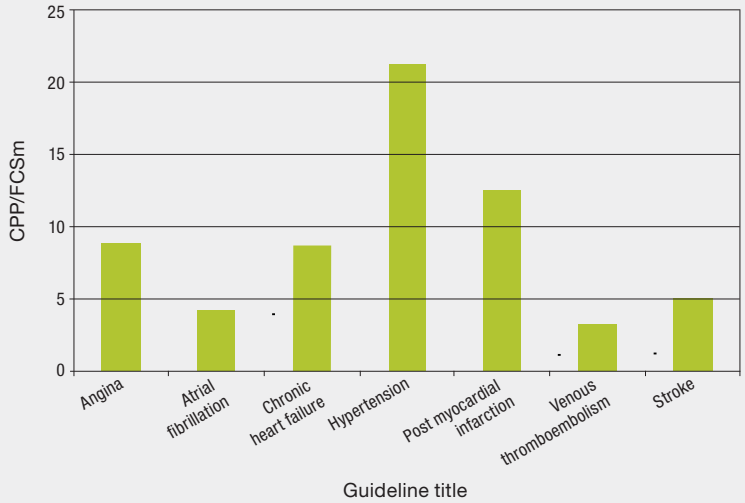
Although the evidence is limited and our indicators are proxies for the parameters in question, we conclude that for the analysis in this report:

- the proportion of the cited evidence base attributable to UK cardiovascular research will be assumed to be 17%, ranging between 12% and 23%
- mean lag between research and impact of between ten and 25 years, with a mid-point of 17 years.

Postscript: A note on citation impact

Although not of direct relevance to the current study, it was notable that the papers cited by the cardiovascular clinical guidelines were themselves extremely highly cited. CWTS considers papers with 20% more citations than the field average as of high relative impact. The group of papers cited by the guidelines had on nine times more citations than would have been expected in their field. As citation patterns differ by field, and subfield, it is important to normalise any citation measure by the mean field citation score (FCSm), i.e. the average number of citations to each paper in the field. In detail, if CPP is number of citations per paper then the ratio of the two measures – CPP/FCSm – gives a relative estimate of impact. If the ratio is 1.0 then the number of citations per paper is equivalent to the expected number for a given field; a figure above one implies a higher relative impact and a figure below one a lower impact. As illustrated in Figure 4.4, the average ratio for papers cited on cardiovascular guidelines was 9.1, ranging from 3.1 (for venous thromboembolism) to 22.0 (for hypertension).[5]

Figure 4.4: Citation impact compared to world field average



1 The Centre for Science and Technology Studies (CWTS) maintains a bibliometric database of all scientific publications (including health and biomedical research) for the period 1981 to 2004. This dataset is based on the journals and serials processed from the CD-ROM versions of the Science Citation Index and associated citation indices (CI): the Science Citation Index (SCI), the Social Science Citation Index (SSCI), and the Arts & Humanities Citation Index (A&HCI), extended with six so-called speciality Citation Indices (Chemistry, Compumath, Materials Science, Biotechnology, Biochemistry & Biophysics, and Neuroscience). Currently, CWTS is changing its database towards the Web of Science version (the internet version) of the Citation Index(es), which covers the period 1981 to 2005, and has a somewhat different journal set coverage. The construction of this database, and the indicators operating on it, are described in various scientific publications (Moed *et al.*, 1995; van Leeuwen *et al.*, 2001; van Leeuwen *et al.*, 2003).

2 Because of the way the databases are constructed authors are not linked directly to addresses. Two separate lists are presented: the authors' names and a list of addresses; no direct link is made between the two. The countries of authorship are taken as the addresses listed for each paper.

3 Full findings are reported in the Annex to Chapter Four.

4 Once drug developers believe that they have enough evidence of safety and efficacy, they will compile the results of their testing in an application to regulatory authorities for marketing approval. In the USA, manufacturers submit a new drug application (NDA) or a biological licence application (BLA) to the FDA for review and approval.

5 The field definitions used by CWTS are the same as those used by Thompson ISI.

Chapter Five

The value of the health gains in cardiovascular disease and their associated health care costs

KEY POINTS

- We use a bottom-up approach to estimate the vale of the health gains from specific interventions to treat or prevent cardiovascular disease over the period 1985–2005, and the health care costs incurred in the achievement of these gains.
- From published economic evaluation studies, and estimates of usage, we calculate the quality adjusted life years (QALYs) gained from a series of 46 combinations of patient groups and specific interventions.
- These QALYs are valued at £25,000 – the mid-point of the 'threshold range' used by the National Institute for Health and Clinical Excellence (NICE). This value represents a measure of the opportunity cost if, rather than investing in R&D, the resources had been used directly in the NHS.
- Our best, though conservative, estimate of the value of the QALYs gained from the specific interventions included in our analysis over the whole period 1985–2005 is £69 billion. The upper and lower estimates are £91bn and £55bn respectively.
- Our best estimate of the total incremental health care costs relating to those gains over the same period is £16bn, with upper and lower estimates of £17bn and £11bn respectively.

Introduction

In this Chapter we estimate the monetary value of health gains from specific interventions to treat or prevent cardiovascular disease (CVD) over the period 1985–2005, and we also estimate the health care costs incurred in the achievement of these gains. As discussed in Chapter Two, previous attempts to value health gains from investment in medical research have tended to use a 'top-down' approach, monetising the health gains from reduced morbidity and mortality at the macro level and then making assumptions about the proportion of these that can be attributed to medical research. In this Chapter we use a 'bottom-up' approach that considers the effects of specific interventions and then sums these to generate an overall estimate.

In doing this we use quality adjusted life years (QALYs) as the measure of health gain. Although QALYs have their critics and do not necessarily capture all aspects of the health benefit offered by new interventions in all clinical areas, they are widely used to measure health gain and are the measure favoured by NICE in its appraisals of health technologies. As a result there is a substantial evidence base estimating the QALYs gained and costs associated with treatment of various diseases, not least for CVD.

To estimate the monetary value of health gains from specific interventions to treat or prevent cardiovascular disease we:

- review the economic evaluation literature to obtain published figures for the QALYs gained from specific interventions for cardiovascular disease over the period 1985–2005
- multiply these figures by estimates of the numbers of users of each intervention, to give an estimate of the total QALYs gained from each intervention
- monetise the total QALYs gained by multiplying these estimates by published figures on the opportunity cost of a QALY within the current NHS budget
- from the review of the economic evaluation literature obtain estimates of the incremental health care costs associated with each intervention and multiply these by the numbers of users to quantify the incremental health care costs of each intervention.

Based on previous studies, we include interventions that are likely to have been important in terms of the health gains they have produced over the period 1985–2005.

In Chapter Seven we deduct the total incremental health care costs estimated in this Chapter from the monetised total QALYs gained. We then combine the result with estimates of the costs of UK medical research, and we produce an estimate of the returns to UK medical research accounting for both the time lag between the research investment and the net returns and for the proportion of health benefits that can be ascribed to UK medical research.

As noted in Chapter One, our estimates focus on the returns to UK public and charitable investment in research. The costs of private sector R&D investments are accounted for in our analysis because they are included in the incremental health care costs. These include the prices of interventions manufactured in the private sector, which include a return on its investment in research.

Overview of methods

Our analysis is derived from, but ultimately different to, the approach used in the IMPACT Study (Capewell *et al.*, 2007), which *inter alia* tries to explain the decline in coronary heart disease mortality in England and Wales between 1980 and 2000. We extend the analysis by considering a wider range of interventions for cardiovascular disease, by focusing on the UK, by measuring costs and benefits during the period 1985–2005, by quantifying the cumulative benefits and costs over the whole period rather than the difference between the two end points, and by calculating the QALYs gained rather than the deaths prevented or postponed and life years gained.

To estimate the monetised health gains from specific interventions for CVD over the period 1985–2005 we:

1 identify specific interventions for patients with CVD

2 estimate the QALYs gained for each intervention in each patient group

3 estimate the numbers of patients in each patient group

4 adjust for overlapping patient groups

5 estimate the uptake of each intervention by each patient group in each year

6 compute the numbers of users of each intervention in each patient group

7 compute the numbers of new users each year

8 adjust for compliance with treatment

9 adjust for polytreatment

10 compute the total QALYs gained from each intervention

11 monetise the total QALYs gained

12 undertake a sensitivity analysis.

From our review of the economic evaluation literature we also obtain estimates of the incremental health care costs associated with each intervention and multiply these by the numbers of new users who are compliant with treatment to quantify the health care costs associated with each intervention.

Estimating the monetised health gains from specific interventions for CVD over the period 1985–2005

Stage 1: Identify specific interventions for patients with CVD

At the first stage we identified specific interventions for patients with CVD to be included in the analysis. The patient groups and treatments were selected according to whether or not they were likely to have been important in terms of the total health gains they have produced in the UK since 1980.

At the outset we used patient groups and interventions that were used in the IMPACT study (see Box 5.1), which focused on interventions that were important in terms of the total health gains they have produced since 1980. We excluded from our analysis a number of CVD risk factors that were included in the IMPACT study (obesity, physical activity, diabetes) because the prevalence of these has worsened over time and so the health gains in terms of the QALYs gained from research into these diseases is deemed to have been zero. This is possibly conservative because the increasing prevalence of these conditions may have been even higher without UK medical research. We also did not include deprivation, taking the view that the level of deprivation is unlikely to have been affected by UK medical research.

Box 5.1: The IMPACT study

The IMPACT coronary heart disease (CHD) mortality model (Capewell *et al*., 2007) combines data from various sources on patient numbers, treatment uptake, treatment effectiveness and risk factor trends to estimate the numbers of CHD deaths prevented or postponed over a pre-defined time period due to specific interventions and modification of CHD risk factors. It has been used to estimate the proportion of the decline in CHD mortality that might be attributed to treatments or risk factor changes and has been applied to data from Europe, New Zealand and China (Capewell *et al*., 1999, 2004; Unal *et al*., 2004, 2005; Laatikainen *et al*. 2005).

The model includes a range of patient groups and interventions including: treatment of acute MI (cardiopulmonary resuscitation, thrombolysis, aspirin, primary angioplasty); secondary prevention of CHD post-MI (aspirin, beta blockers, ACE inhibitors, statins, warfarin, rehabilitation); revascularisation (CABG surgery, angioplasty); treatment of unstable angina (aspirin, glycoprotein IIB/IIIA antagonists); treatment of chronic stable angina (aspirin, statins); and treatment of heart failure (ACE inhibitors, beta blockers, diuretics, aspirin, statins). It also includes treatment of hypertension and hypercholesterolaemia for primary prevention of CHD and the modification of a number of CHD risk factors (smoking, deprivation, obesity, diabetes, physical activity).

The model has been extended to include stroke (Zhechun *et al*., 2006), with the following patient groups and interventions: treatment of acute stroke (aspirin, anticoagulants, tr-PA, stroke unit, early diagnosis and treatment); secondary prevention of stroke (rehabilitation, aspirin, statins, warfarin, antihypertensive drugs). It also includes use of warfarin and aspirin plus treatment of hypertension and hypercholesterolaemia for primary prevention of stroke, and population diabetes control.

We added interventions for treatment of arrhythmia (implantable cardioverter defibrillators [ICDs]), treatment of heart failure (cardiac resynchronisation therapy [CRT] devices [CRT-P], CRT devices plus ICDs [CRT-D]) and heart transplants. We also added clopidogrel, which is used to treat CVD. The interventions we added were not included in the IMPACT study but are likely to have generated health gains over the period 1985–2005. The patient groups and interventions considered are in Table 5.1 column 1. Note that some treatments are considered more than once because they are used in different patient groups.

We have not included all CVD interventions provided by the NHS in the UK – it would be impractical to do so. We assume that the monetised total QALYs gained minus the incremental health care costs of the interventions not included directly in our analysis is equal to zero. The effect is that these interventions are assumed to be neutral in terms of their impact on the calculation of the net returns to research. This effectively assumes that the net benefits to society from the provision of these interventions (value of health gains minus costs) are zero.

Stage 2: Estimate the QALYs gained for each intervention in each patient group

We undertook a systematic review of the economic evaluation literature to obtain figures for the QALYs gained for each intervention in each patient group. We systematically searched the economic evaluation literature using three databases:

- published reports from the NIHR Health Technology Assessment Programme (www.ncchta.org/project/htapubs.asp)
- the NHS Economic Evaluation Database (NHS EED) at the Centre for Reviews and Dissemination at the University of York (www.york.ac.uk/inst/crd/crddatabases.htm)
- PubMed (www.ncbi.nlm.nih.gov/sites/entrez?db=pubmed).

We also searched the reference sections of retrieved papers from these databases to identify additional papers. We selected studies according to whether or not they focused on the specific intervention in the particular patient group, and whether or not they focused on UK patients. If we were unable to find studies that focused on interventions in the particular patient group then we considered studies that investigated the same intervention in other similar patient groups. If we were unable to find studies that focused on UK patients then we considered studies that used non-UK patients. We preferred studies that focused on interventions in the particular patient group over UK studies. If we found more than one study that focused on the specific intervention in the particular patient group and that used UK patients then we used the most recently published study.

Where a range of baseline estimates of QALY gains were reported, we took a conservative view and always used the lowest value. The estimates of the QALYs gained from each intervention in each patient group are in Table 5.1 column 3. See Annex 5A for further details of the studies used to generate these estimates. Because we focus on new users, all the studies would ideally consider a lifetime time horizon. Not all did, and the studies varied in terms of the time horizons they considered and the discount rates they used.

Stage 3: Estimate the numbers of patients in each patient group

To calculate the total QALYs gained we multiplied the QALYs gained for each specific intervention by the numbers of new users of that intervention in each year. For some interventions we have data on the numbers of new users directly, but for the majority of interventions we do not have this information and we model it as a function of the numbers of patients in each patient group and the uptake rate for each specific intervention. We therefore require estimates of the numbers of patients in each patient group in each year, which we call the numbers of eligible patients. These data were obtained from systematic searches of the literature.

In some cases we were able to find data on numbers of eligible patients for England and we applied these figures to UK population data. In the majority of cases we were unable to find figures for the entire period 1985–2005 in which case we modelled the numbers of eligible patients in other years: we extrapolated the percentage of the UK population in each patient group to UK population figures in these time periods with missing data. See Annex 5B for further details on how these estimates were generated.

Stage 4: Adjust for overlapping patient groups

The strategy described above for quantifying the numbers of eligible patients is likely to overestimate the total because some patients will feature in more than one group (e.g. some patients with chronic stable angina will also have a revascularisation procedure). We adjusted for this overlap by reducing the numbers of eligible patients in some patient groups according to the criteria used in the IMPACT study. See Annex 5C for details on these criteria.

Stage 5: Estimate the uptake of each intervention by each patient group in each year

We obtained figures for the uptake of specific interventions in each patient group based on systematic searches of the literature. As with the data for eligible patients, we were unable to find complete data for every intervention. In all cases we were able to identify when the intervention was first used and so we knew the time period before which the uptake rate was zero. We were also able to identify non-zero figures for one or more later time points. In the absence of additional data we generally linearly interpolated uptake rates where there was a gap between two time points and we assumed a constant uptake rate at later time points. Where it was used the latter is probably a conservative assumption in that generally uptake increases over time and so it will underestimate the numbers of users of each intervention. See Annex 5D for further details on how these estimates were generated.

Table 5.1: Summary of results by patient group/intervention, 1985–2005

1	2	3	4	5	6	7
		QALYs gained			Incremental costs	
Patient groups/interventions	Compliant new users (000s)	Per new user	Total (000s)	Total monetised (£ million)	Per new user (£)	Total (£ million)
Treatment of acute MI:			**196.6**	**4,916.1**		**58.7**
Community resuscitation	24.0	0.220	5.3	131.7	1,491	35.8
Hospital resuscitation	32.6	0.619	20.2	504.5	1,491	48.6
Thrombolysis	767.2	0.058	44.1	1,103.4	141	108.0
Aspirin	575.5	0.213	122.4	3,060.7	-289	-166.2
Clopidogrel	54.6	0.077	4.2	105.4	546	29.8
Primary angioplasty	4.9	0.084	0.4	10.4	543	2.7
Secondary prevention of CHD post-MI:			**662.2**	**16,553.8**		**3,178.2**
Aspirin	1,737.5	0.213	369.6	9,240.3	-289	-501.7
Clopidogrel	73.1	0.038	2.8	69.6	925	67.6
Beta blockers	695.6	0.142	98.5	2,462.4	773	537.7
ACE inhibitors	327.1	0.180	58.9	1,471.8	1,919	627.7
Statins	1,225.5	0.103	126.2	3,155.5	1,680	2058.4
Warfarin	22.6	0.006	0.1	3.4	56	1.3
Rehabilitation	648.9	0.009	6.0	150.7	597	387.2
Revascularisation:			**186.5**	**4,662.3**		**3,748.8**
CABG surgery	408.6	0.400	163.4	4,085.9	6,301	2574.4
Angioplasty	384.3	0.060	23.1	576.4	3,056	1174.4
Treatment of unstable angina:			**215.8**	**5,396.2**		**28.9**
Aspirin	834.6	0.213	177.5	4,438.7	-289	-241.0
Clopidogrel	72.9	0.077	5.6	140.8	546	39.8
Glycoprotein IIB/IIIA antagonists	329.3	0.099	32.7	816.7	699	230.1
Treatment of chronic stable angina:			**328.1**	**8,202.6**		**1,675.8**
Aspirin	981.2	0.213	208.7	5,218.1	-289	-283.3
Clopidogrel	40.3	0.038	1.5	38.4	925	37.3
Statins	1,144.1	0.103	117.8	2,946.1	1,680	1921.8
Treatment of arrhythmia:			**21.0**	**525.2**		**1,363.5**
ICD	19.8	1.060	21.0	525.2	68,805	1363.5
Treatment of heart failure:			**142.0**	**3,550.6**		**375.2**
ACE inhibitors	171.6	0.110	18.9	471.9	1,919	329.4
Beta blockers	39.1	0.137	5.4	133.9	773	30.3
Diuretics	335.6	0.130	43.6	1,090.7	-592	-198.7
Aspirin	271.0	0.213	57.6	1,441.1	-289	-78.2
Statins	109.4	0.103	11.3	281.8	1,680	183.8
CRT-P	3.1	0.700	2.2	53.8	11,630	35.8
CRT-D	3.1	0.990	3.1	77.4	23,320	73.0
Heart transplant:			**5.1**	**128.0**		**127.9**
Heart transplant	3.5	1.475	5.1	128.0	36,824	127.9
Treatment of acute stroke:			**217.9**	**5,448.7**		**-201.8**
Aspirin	452.8	0.013	5.9	147.2	-289	-130.8
Anticoagulants	457.8	0.090	41.2	1,030.0	-178	-81.5
tr-PA	756.5	0.036	27.5	686.5	141	106.5
Stroke unit	464.6	0.190	88.3	2,207.0	305	141.7
Early diagnosis and treatment	705.7	0.078	55.1	1,378.0	-337	-237.7
Secondary prevention of stroke:			**166.1**	**4,153.6**		**1,745.0**
Rehabilitation therapy	1,037.1	0.009	9.6	240.8	597	618.9
Aspirin	413.4	0.013	5.4	134.4	-289	-119.4
Clopidogrel	22.6	0.038	0.9	21.6	925	20.9
Statins	358.1	0.103	36.9	922.2	1,680	601.5
Warfarin	172.2	0.006	1.0	25.8	56	9.6
Antihypertensive drugs	793.5	0.142	112.4	2,808.8	773	613.4
Primary prevention of CVD:			**289.8**	**7,244.6**		**3,221.3**
Treatment of hypertension	4,197.8	0.060	251.9	6,296.7	760	3190.3
Treatment of hypercholesterolaemia	122.3	0.310	37.9	947.9	253	30.9
Primary prevention of stroke:			**61.2**	**1,530.7**		**57.5**
Warfarin	71.9	0.810	58.3	1,456.7	1,393	100.2
Aspirin	148.0	0.020	3.0	74.0	-289	-42.7
Smoking cessation:			**262.7**	**6,568.1**		**248.5**
Quitting smoking	265.4	0.990	262.7	6,568.1	55	248.5
Total	**21,780.2**		**2,755.2**	**68,880.6**		**15,627.4**

In column 1 the patients groups are highlighted in bold. CHD = coronary heart disease; MI = myocardial infarction; ICD = implantable cardioverter defibrillator; CRT-P = cardiac resynchronisation therapy device; CRT-D = CRT device plus ICD; CVD = cardiovascular disease.

Stage 6: Compute the numbers of users of each intervention in each patient group

We computed the numbers of users of each specific intervention in each patient group by multiplying the numbers of non-overlapping eligible patients in each time period by the uptake rate for each intervention in that time period.

Stage 7: Compute the numbers of new users each year

The estimates of the QALYs gained for each intervention obtained from the systematic review usually adopt a time horizon that is greater than one year. Since the numbers of users of a given intervention in each year will include a proportion who started using the intervention in a previous year, to avoid double counting we focus only on the numbers of new users.

We computed the numbers of new users each year by subtracting from the numbers of users in each year the numbers of users in the previous year, also accounting for the numbers of deaths from all causes among users in the previous year. The numbers of deaths were obtained from life tables produced by the Government Actuary's Department (www.gad.gov.uk/Demography_Data/Life_Tables/). For simplicity, we assumed a constant annual mortality rate of 1%, which is the rate for males aged 60 years and females aged 65 years in the UK. Males and females older than these ages have a higher mortality rate and so the numbers of deaths, and therefore the numbers of new users, will be underestimated in these groups. In addition, these annual mortality rates are for the general population; among patients with CHD the annual mortality rate is likely to be higher. Hence, our mortality rate is probably conservative, which means that we underestimate the numbers of new users each year.

Stage 8: Adjust for compliance with treatment

Not all new users will benefit from treatment because a proportion will be non-compliant. We searched the economic evaluation studies used to obtain the QALYs gained estimates for each specific intervention. In some of these non-compliance was accounted for in the analysis. Where it was not accounted for we applied compliance rates used in the IMPACT study. See Annex 5E for details on the values used. Accounting for compliance gives an estimate of the numbers of compliant new users of each specific intervention in each year. These are reported for each specific intervention in Table 5.1 column 2.

Stage 9: Adjust for polytreatment

A polytreatment adjustment is considered because patients in a particular patient group may receive more than one intervention. Ideally we would have data on the numbers of patients receiving every combination of interventions, but invariably we do not have these data. Hence, we need to account for the use of multiple interventions in some other way.

We adjusted for polytreatment in three ways:

1 we assumed there was no polytreatment

2 we assumed there was maximum polytreatment and that the QALYs gained from each specific intervention are additive

3 we assumed there was maximum polytreatment and that the QALYs gained from each specific intervention are not at all additive.

Options 1 and 2 yield the same results and are used to derive our best estimates of the total QALYs gained. Option 3 is used in the sensitivity analysis (see below) to generate a lower estimate. (See Annex 5F for a more detailed description of the methods used.)

Stage 10: Compute the total QALYs gained from each intervention

We compute the total QALYs gained from each intervention in each year by multiplying the numbers of new users in that year by the QALYs gained from each intervention. We then summed the result across the period 1985–2005 to calculate the total QALYs gained. These are reported in Table 5.1 column 4. Our best estimate of the total QALYs gained over the whole period 1985–2005 is 2,755,223.

Stage 11: Monetise the total QALYs gained

We monetised the total QALYs gained by multiplying the estimated total QALYs gained by published figures for society's willingness/ability to pay for a QALY within the current NHS budget. According to the *Guide to the Methods of Technology Appraisal* published by NICE:

> Below a most plausible ICER [incremental cost-effectiveness ratio] of £20,000/QALY, judgements about the acceptability of a technology as an effective use of NHS resources are based primarily on the cost-effectiveness estimate. Above a most plausible ICER of £20,000/QALY, judgements about the acceptability of the technology as an effective use of NHS resources are more likely to make more explicit reference to factors including:
>
> - the degree of uncertainty surrounding the calculation of ICERs
> - the innovative nature of the technology
> - the particular features of the condition and population receiving the technology
> - where appropriate, the wider societal costs and benefits.
>
> Above an ICER of £30,000/QALY, the case for supporting the technology on these factors has to be increasingly strong. (NICE, 2004, p. 33)

This evidence indicates that NICE is prepared to recommend interventions that cost up to £20,000–£30,000 per QALY gained, and we therefore interpret these figures as estimates of the willingness/ability of the NHS to pay for a QALY given the current NHS budget. They therefore reflect the opportunity cost of a QALY if the investment in research were instead to be directly invested in health services. We use the middle of the range, £25,000, as our central estimate. Hence, we multiply the total QALYs gained by £25,000 to generate a monetised value of the total QALYs gained. The results are reported in Table 5.1 column 5. The total monetised QALYs gained over the whole period 1985–2005 are estimated to be £68.9bn.

Figure 5.1 plots the estimated total QALYs gained for each year. See Annex 5G for the estimates used to generate the figure. The trend is broadly upwards from left to right. The variation in the trend from year to year is due to the numbers who quit smoking, which according to our calculations are very erratic, and also due to the conservative assumptions we have made regarding the numbers of new users each year (in particular the assumption that uptake rates are constant where no data for these rates is available).

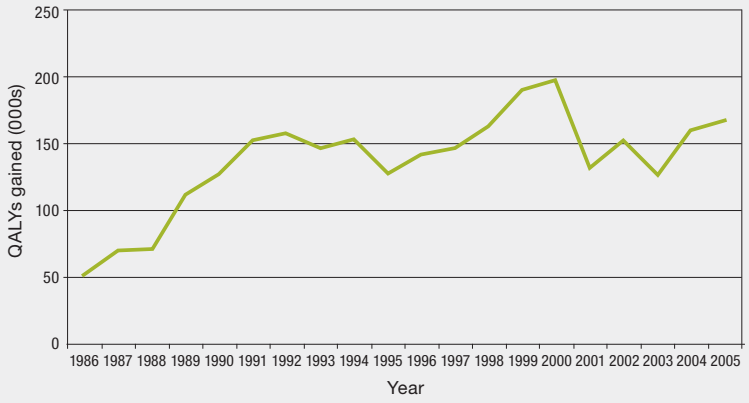
The figures for smoking cessation are based fundamentally on the prevalence rate of smoking measured in the General Household Survey. The trend in the prevalence rate is generally downward, but in some years it increased and in others it remained constant. In these years we set the numbers of quitters to zero. This is probably conservative because even in years when the prevalence increased there may have been people who quit smoking due to medical research, but there were fewer of these than the number of people who started smoking (who did not start due to medical research).

Stage 12: Undertake a sensitivity analysis

At the final stage we undertook a sensitivity analysis to generate upper and lower estimates of the total QALYs gained around our best estimate. These were calculated as follows:

- **Upper estimate**: smoking cessation is an important component of the total QALYs gained. We assumed in our best estimate that 22–25% of people who quit smoking did so as a result of medical research, based on the numbers of quitters who were told by medical services to quit smoking for medical reasons. This may underestimate the contribution of medical research because some people may quit smoking for medical reasons without being told to do so by the medical services. Hence, to generate an upper estimate of the total QALYs gained, we assumed that 100% of people who quit smoking did so as a result of medical research.

Figure 5.1: Total QALYs gained by year



- **Lower estimate**: we calculated the lower estimate of the total QALYs gained by assuming there was maximum polytreatment and that the QALYs gained from each specific intervention are not at all additive (see Annex 5F for a more detailed description of the method).

As noted above, our best estimate of the total QALYs gained over the period 1985–2005 is estimated to be 2,755,223 QALYs and the total monetised QALYs gained are £68,880.6m. Using the approaches described above the upper estimates over the whole period are 3,648,331 QALYs and £91,208.3m and the lower estimates are 2,195,732 QALYs and £54,893.3m (see Annex 5J for further details).

Estimating the health care costs from specific interventions for CVD

From our review of the economic evaluation literature, we also obtained estimates of the incremental costs associated with each intervention.

Where UK papers were used to generate the QALY gains estimates we used the same papers to obtain the incremental cost estimates. Where non-UK studies were used to generate the QALYs gained we attempted to find cost estimates from UK cost studies or UK economic evaluations with outcomes other than QALYs. If we were unable to find any UK studies then we used the non-UK study that was used to generate the QALYs gained estimates and converted the costs to UK£.

Where a range of baseline incremental cost and QALYs gained estimates were reported we used the cost value that was commensurate with the QALYs gained estimate used in our analysis.

All costs were converted to 2005 UK£ using NHS pay and prices indices (Curtis, 2007) and where appropriate GDP purchasing power parities published by the OECD (OECD, 2008). The estimates of the incremental cost of each intervention in each patient group are in Table 5.1 column 6. Note that in some cases the incremental costs are negative because the intervention is cheaper than the alternative. See Annex 5H for further details on the studies used to generate these estimates.

We then multiplied the cost estimates by the numbers of new users to quantify the health care costs associated with each intervention. We used estimates of the numbers of users who are compliant with treatment on the basis that non-compliers are unlikely to continue to incur treatment costs over a prolonged period. We computed the total incremental costs of each intervention in each year by multiplying the numbers of new users in that year by the incremental costs of each intervention. We adjusted for polytreatment using the same methods as for the total QALYs gained. We then summed the result across the period 1985–2005 to calculate the total incremental costs. These are reported in Table 5.1 column 7. Note that in some cases there are cost savings because the incremental costs per new user are negative.

The total incremental health care costs over the whole period 1985–2005 are estimated to be £15.6bn. Figure 5.2 plots the total incremental costs for each year (see Annex 5I for the estimates used to generate the figure), which generally increase over time.

We also computed upper and lower estimates around our best estimate using the same approach that was used for the total QALYs gained. The upper estimate over the whole period was estimated to be £16.5bn and the lower estimate £10.8bn (see Annex 5J for further details).

Figure 5.2: Total incremental costs by year

Example One: statins for secondary prevention of CHD post-MI

Ward *et al*. (2007) undertook an economic evaluation of statins for the primary and secondary prevention of coronary events in the UK. On the basis of their modelling work, and using a lifetime time horizon, they report lifetime QALY gains associated with statin therapy in secondary prevention of coronary events in the range 103–493 QALYs gained per 1,000 patients, depending on the age and gender of the patient. We used the lowest figure (which applies to males aged 85 years) to give a conservative estimate of 0.103 QALYs gained per patient with statins over their lifetime.

The numbers of patients eligible for statin therapy was based on estimates of the proportion of the population who had ever had a heart attack (3.8% of males and 1.7% of females) published in the *Health Survey for England* in 2003 (Department of Health, 2004a). We only have estimates for a single year, and we therefore assume that the same rate applies across the whole period. This rate, which is for the English population, is applied to UK population estimates published by the Office for National Statistics (2007).

Uptake rates for statins among patients with CHD for 1994–98 were taken from *Key Health Statistics from General Practice 1998* (National Statistics, 2000). The population weighted average estimates of the figures for males and females were 3.6% in 1994, 6.4% in 1995, 10.8% in 1996, 17.0% in 1997 and 23.8% in 1998. The Department of Health (2007) shows that statin use was zero prior to 1990, and that from 1998 onwards it has increased exponentially. We assumed a constant rate of increase from 0% in 1989 to 3.6% in 1994. We then assumed conservatively that the annual increase from 1997 to 1998 (6.8% in absolute terms) applied to each year from 1999 to 2005. These are figures for England and Wales, which were applied to UK population estimates.

We multiplied the numbers of eligible patients by the uptake rates to estimate the numbers of users each year. These range from zero for 1985–89 and then increase up to a maximum of 1.1m in 2005. The numbers of new users each year is the difference between the number of users in that year minus the number of users in the previous year multiplied by a factor 0.99 to account for the assumed 1% mortality rate among users. The estimated total number of new users across the period 1985–2005 was 1,225,451.

Ward *et al*. (2007) accounted for compliance in their estimates of the QALYs gained from statin therapy and therefore we do not make any additional adjustments for this; the estimated number of compliant new users of statin therapy was 1,225,451.

On average, each compliant new user of statin therapy in secondary prevention of CHD achieves a QALY gain of (at least) 0.103 QALYs. Hence the total health gain from statin therapy in the secondary prevention of CHD post-MI is (at least) 126,221 QALYs.

Multiplying this figure by the presumed value of a QALY (£25,000) gives a monetised health gain of £3,155.5m.

Ward *et al*. (2007) also estimated the incremental costs per patient of statin therapy in the selected patient group to be £1,615 in 2004 UK£. As noted above, these costs include private sector returns on research investments. Converting these costs to 2005 UK£ using the NHS pay and prices index gives an incremental cost of £1,680. Multiplying this figure by the number of new users (1,225,451) gives a total incremental cost of £2,058m. In Chapter Seven, the total incremental costs are then deducted from the monetised health gain to calculate net benefits.

Example Two: smoking cessation

Smoking cessation accounted for a relatively large proportion of the monetised total QALYs gained, and because of the nature of the data used it has been treated differently to the other interventions included in the analysis, as explained below.

Wang *et al*. (2008) undertook an economic evaluation of nicotine replacement therapies in smoking cessation. They adopted an NHS/Personal Social Services perspective and they used a lifetime time horizon. Based on previous studies they report QALY gains by smokers who quit at different ages. These range from 0.99 to 2.58 QALYs depending on the age at which the person quits. We used the lowest figure (which applies to patients aged 55–64 years) to give a conservative estimate of 0.99 QALYs gained per person who quits smoking.

To estimate the numbers of quitters we first obtained data for 1985–2005 from the *General Household Survey* (Office for National Statistics, 2008) on the proportion of the population who smoke and applied this to UK population estimates (Office for National Statistics, 2007) to generate figures for the total numbers of smokers each year. We then computed the numbers of quitters each year by subtracting the number of smokers in the previous year from the number in the current year and then from this figure subtracting the numbers of people who died from smoking each year obtained from Peto *et al*. (2006). Since the numbers of smokers generally declined over time we interpret this as the number of quitters each year.

People quit smoking for a variety of reasons, some of which are a result of medical research and some of which are not. We wish to estimate the numbers who quit as a result of medical research. As a crude indicator of this we used data from the *Health Survey for England* on the proportion of smokers who had contact with medical services who told respondents to quit smoking for medical reasons (Department of Health, 2004a). These data were available for 1993–99 and 2003–05 (the range of values reported was 0.22–0.25). We applied the 1993 value to 1985–92 and the 2003 value to 2000–02. We assumed that the proportion of quitters who received advice to stop smoking was the same as the proportion who received this advice who did not quit, and therefore multiplying these proportions by the numbers of quitters provides an estimate of the numbers who quit following the receipt of advice by the medical services to stop smoking. We treat these figures as a crude approximation of the proportion who quit due to medical research. This is probably a conservative assumption because some people may quit smoking of their own accord (rather than due to contacts with medical services) due to the negative impacts of smoking on health (that are known due to medical research). We investigate the impact of this in the sensitivity analysis.

We then accounted for the specific role of cardiovascular disease-related medical research on the decision to quit smoking, as opposed to medical research in other disease areas, most notably cancer. We did this by multiplying our estimates of the proportion who quit smoking due to medical research by published estimates of the proportion of deaths due to cardiovascular disease published by Peto *et al*. (2006). These estimates were available for the year 2000 and were estimated to be 0.27. We applied this proportion to every year of our data. This method assumes that the contribution of cardiovascular disease-related medical research on the decision to quit smoking is proportional to the numbers of smoking deaths due to cardiovascular disease.

Using these assumptions, the estimated total number of people who quit smoking due to CVD medical research over the period 1985–2005 was 265,376. Each quitter is assumed to achieve a QALY gain of 0.99 QALYs. Hence the total QALYs gained from smoking cessation were 262,722. Multiplying this figure by the presumed value of society's willingness to pay for a QALY (£25,000) gives a monetised health gain of £6,568.1m. Smoking

cessation accounts for around 10% of monetised total QALYs gained, and for the reasons outlined above, this is probably an underestimate.

Wang *et al.* (2008) also estimated the incremental costs of various strategies to quit smoking and their success rates over one year. We used the most costly intervention per success at one year, which had a cost of £54.88 and a success rate at one year of 5.86%. Assuming these represent the actual costs of trying to quit smoking and the actual success rate then the 265,376 people who quit represent 5.86% of those who attempted to quit, giving a total number of 4,528,601 people who tried to quit over the period 1985–2005. Assuming that each of these people incurred a cost of £54.88, then the total incremental cost was £248.5m. Smoking cessation accounts for around 2% of the total incremental costs. This is probably an overestimate because we assumed the cost of quitting was equal to the cost of the most expensive intervention and in many cases it will be less than this, possibly even zero. Also, we have not included the cost savings from the reduction in the use of health services after quitting.

Challenges

This bottom-up approach has a clear advantage over a top-down approach starting with overall changes in mortality and morbidity. It is more transparent and considers only gains for which there is clear evidence of their resulting from changes in the use of specific interventions or in specific risk factors. However, the major problem is that this approach is data-hungry, and the overriding difficulty in implementing it, even for cardiovascular disease, is the patchiness of relevant data. Specific problems include, but are not limited to, the following:

- We were unable to find estimates of the QALYs gained for every intervention in each patient group. In some cases we were required to use non-UK studies and in others we used data on the specific intervention in other patient groups. The studies used varied in terms of the time horizons they considered and the discount rates they used.
- We were unable to find data to construct complete time series of the numbers of eligible patients. We modelled the numbers of eligible patients in years with missing data by extrapolating the percentage of the UK population in each patient group in years where data were available.
- We were unable to find comprehensive data on the numbers of overlapping patients between groups. We used the best estimates that were available, which were taken from the IMPACT study.
- We were unable to find data on uptake rates for specific interventions in every patient group for the whole time period. We extrapolated and interpolated estimates where we had missing data, making conservative assumptions where necessary.
- We were unable to find good data on the compliance rates associated with each intervention in every patient group. We used the best estimates that were available, which were taken from the IMPACT study.
- In the absence of data on the use of different combinations of treatment we adjusted for polytreatment in our best estimate by assuming zero polytreatment/maximum polytreatment with additive effects. In the sensitivity analysis we assumed maximum polytreatment with non-additive effects.
- We were unable to find complete estimates of the incremental costs associated with each specific intervention in each patient group. In these cases we were forced to use non-UK studies or different UK studies from those used to obtain the QALYs gained estimates.

In the light of the uncertainty surrounding the analysis we have attempted to be conservative in the estimates we have produced. This is evidenced by the following:

- We assume that the monetised total QALYs gained minus the incremental health care costs of the interventions not included directly in our analysis are equal to zero. This assumes that the net benefits to society from the provision of these interventions are zero.
- When selecting the incremental QALYs where a range of baseline estimates was given we always selected the lowest value.
- Because we focus on new users, all the studies would ideally consider a lifetime time horizon. The studies used varied in terms of the time horizons they considered and not all took a lifetime time horizon. In these cases the QALYs gained are likely to have been underestimated.
- We have probably underestimated the numbers of eligible patients due to the assumptions we made when extrapolating the estimates to account for missing data.
- We have probably underestimated the uptake rates of specific interventions by assuming these are constant in later years when they are likely to have increased.
- We have probably underestimated the all cause mortality rate when computing the numbers of new users each year.
- Smoking cessation accounts for a relatively large proportion of the monetised total QALYs gained and we have probably underestimated the total QALYs gained from smoking and overestimated the incremental costs associated with these.

Chapter Six

R&D spillovers

KEY POINTS

- In addition to health gains, UK publicly and charitably funded medical research generates additional national income.
- Published literature indicates that additional public medical research leads to additional private R&D spending. Both contribute to increasing UK gross domestic product (GDP).
- Relevant empirical literature is sparse but implies that the total social rate of return to public and charitable medical research is in the range 20–67%, with a best estimate of 30%.
- Thus every pound spent on public/charitable medical research yields additional GDP for the UK that is equivalent to a net return of 30p per year in perpetuity (range 20–67p per year).

Conceptual framework

It is extremely important to consider wider economic gains as well as health gains when assessing the economic benefits of medical research. These economic gains are additional to the health gains; they refer to the income for UK residents that is generated by public medical research investment. This is distinct from the monetary value of health (QALY) gains that were estimated in Chapter Five.

Investment in medical research by one organisation, public or private, may benefit not only that organisation but also other organisations in the medical sector, in other sectors, and also in other countries; i.e. there are what the economic literature refers to as 'spillovers'. Spillovers should not be viewed as accidental: they can be, and are, a deliberate policy objective of spending on public research. Our interest lies in spillovers generated by public R&D, as measured in Chapter Three above. Given the link between R&D and knowledge, we do not distinguish here between R&D spillovers and knowledge spillovers but refer to both taken together.

For illustrative purposes, we take a simplified view of the inputs and outputs of the R&D process. Public research refers to R&D carried out or funded by public and charitable organisations, and includes university research. Private R&D is carried out by privately owned enterprises. These inputs, either in isolation or in combination, lead to some 'output': new products, new patents or better performance (measured in a number of ways) by firms. These outputs generate additional GDP, that is to say additional income for the residents of the UK.

As a preliminary step to quantify the spillovers generated by the R&D analysed in this work, we conducted a literature review on the topic of spillovers. This review was originally intended to cover only public medical research. The literature was relatively scarce, so we extended the search to cover public and private R&D in general, without focusing on any industrial sector in particular. The Annex to Chapter Six contains all the details of the methodology used for this review and summarises the findings. Hence, the conceptual framework presented in this chapter applies to R&D in general, as well as to medical/pharmaceutical R&D.

A. Complementarity between public and private R&D

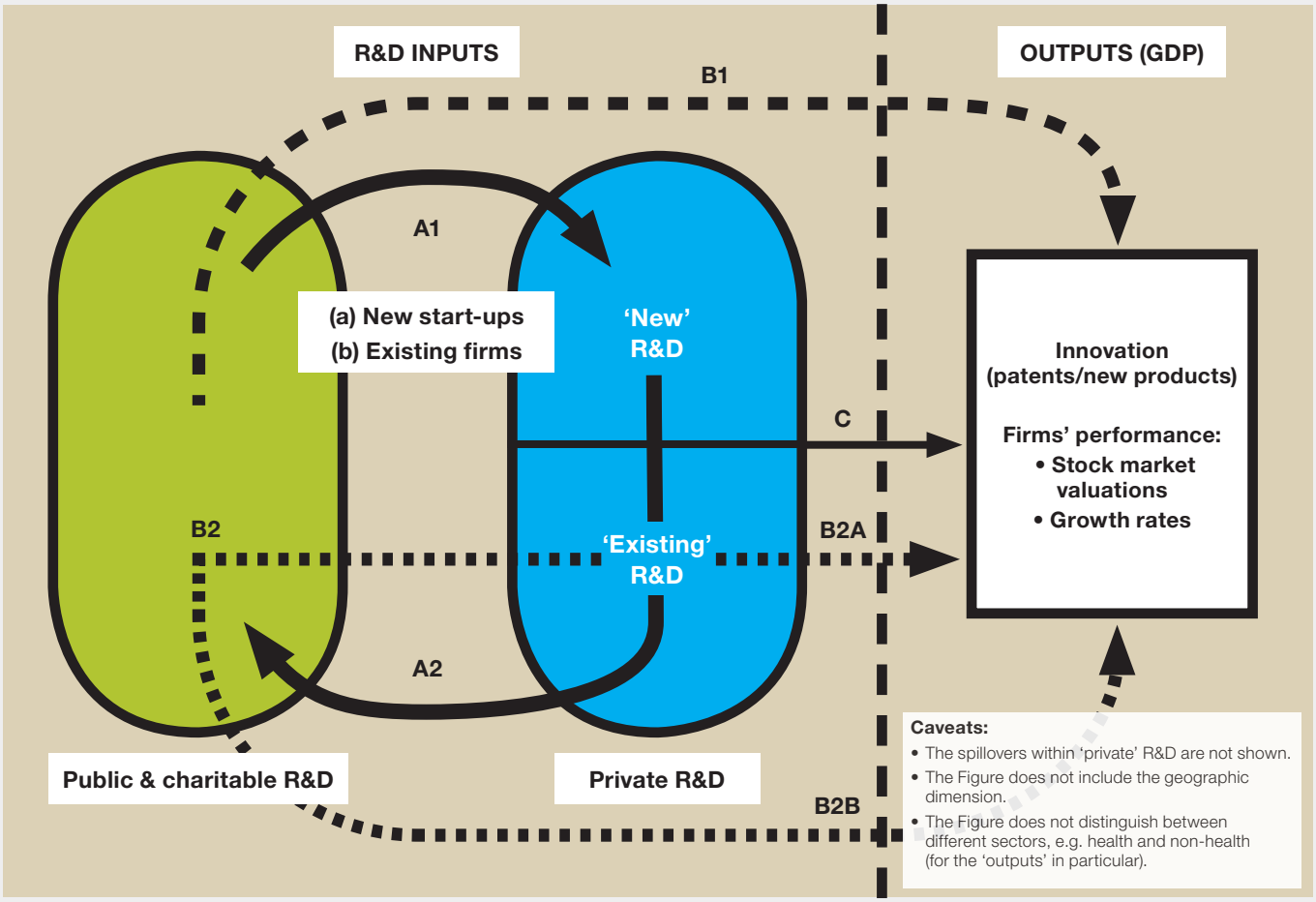
Within the biomedical sector, public research plays an important role in the discovery of new drugs and other health technologies, but the reality of the interaction between the public and private sectors is much more complex than the conventional picture of public research providing a straightforward input of basic knowledge to downstream, applied private research. Thus, the relationship between the public and private sectors in the pharmaceutical industry is not a 'cascade model'.

Figure 6.1 presents our (simplified) overall conceptual framework of how public research generates GDP and economic rent for UK residents. In overview: UK public and charitable research, at the left-hand side of Figure 6.1, leads to increased UK GDP at the right-hand side. Some or all of the effect is mediated via the UK private sector increasing its research (shown in the middle of the diagram). The arrows A1 and A2 illustrate the two-way relationship between public and private R&D. Arrow A1 illustrates the fact that some private R&D, labelled 'new' R&D, takes place in the UK thanks to public R&D in the UK. Some private R&D would take place even if all public R&D activities were to be eliminated, and this is labelled 'existing' R&D. Moreover, as the literature suggests, some public sector R&D is stimulated by the existence of private R&D – arrow A2, which stems from both 'new' and 'existing' private R&D.

The empirical literature, particularly in the medical and biotechnology sectors, has focused primarily on quantifying how much private R&D is generated by publicly-funded R&D. Recent studies by Toole (2000, 2007), based on US data, show that basic medical and applied clinical research funded by public agencies, mainly undertaken in university and not-for-profit laboratories, stimulates and supports private investment on R&D in the pharmaceutical and biotechnology sector. Similar arguments have been presented by the US Congressional Budget Office:

> It is seldom possible to identify particular cases in which the private sector would have performed research if the government had not. Thus, most of the available empirical evidence is based on aggregate studies. On balance, that evidence suggests a positive relationship between public and private pharmaceutical R&D. (CBO, 2006, p. 31)

Figure 6.1 Sources of spillovers: public and charitable R&D and its interaction with private R&D



An earlier paper by Ward and Dranove (1995) also quantified this complementarity.

Another part of the literature looking at the public–private research relationship explores how new firm start-ups and the location decisions of new firms are affected by university and other public research. Several authors argue that the decision by new firm start-ups of where to locate, including in the medical and biotechnology sectors, is influenced by traditional regional characteristics (such as size of cities, population) as well as by the opportunity to access knowledge generated by universities and other public laboratories.

We have found no quantitative evidence on the magnitude of arrow A2 in Figure 6.1, although, as argued by Cockburn and Henderson (1996, 1998, 2000), the private pharmaceutical sector does invest heavily in basic research, viewing it as fundamental to the maintenance of a productive research effort. For instance, their work shows that there is extensive co-authoring of research papers between the public and private sectors. They conclude that the private sector results can have importance for public research.

B. Public research as a source of spillovers

There is wide agreement about the importance of universities and other public laboratories in generating economic growth. They are recognised as generators and repositories of public knowledge. Also, centres of commercial innovation and entrepreneurship are linked to proximity to universities. The literature has identified two potential effects of university research spillovers on: (1) innovation (patents/new product innovations); (2) performance/growth of firms. Referring back to Figure 6.1, arrows B1 and B2A/B correspond to effects (1) and (2) respectively.

The link represented in Figure 6.1 by the arrow B1 is included in the literature on the (modified) 'knowledge production function'. The knowledge production function explores the relationship between knowledge inputs, such as public and/or private R&D, and innovative outputs, such as patents and new products. This strand of the economic literature provides some evidence of the importance of geographically mediated commercial spillovers from public research. Indeed, public research has been found to have a positive and significant effect on both patents and new product innovations.

Arrow B2 in Figure 6.1 is included in the literature that argues that public research has a positive impact on private firms' performance and growth. A number of papers suggest that geographic proximity and university/public laboratory spillovers are complementary determinants of firms' performance. A combination of both factors results in significantly higher stock market performance and productivity for firms. As illustrated in Figure 6.1, arrow B2 shows potentially (at least) two channels for this university spillover. One channel implies that the firm's performance improves because public R&D improves (somehow) the productivity of the existing R&D carried out by existing firms, which in turn leads to better performance (arrow B2A). The other channel by which public research can improve firms' performance is a more direct impact on their productivity, other than via their own private 'existing' R&D (arrow B2B). Unfortunately, the literature leaves relatively undefined the exact mechanism by which this occurs, which is why we show arrow B2 with two 'branches'.

C. Spillovers from private R&D

The literature has identified three types of spillovers generated by private R&D: (1) improving the productivity of other firms' R&D; (2) encouraging entry of potential competitors; (3) reduction of production costs.

For the first effect, the evidence presented in a number of articles suggests that the productivity of a firm's R&D is dependent not only on its own internal R&D, but also on the R&D of other firms. This strand of the literature has explored this type of spillover in the pharmaceutical market in particular. For instance, Cockburn and Henderson (1994) find that competitors' research appears to be a complementary activity to a firm's own R&D: rivals' R&D results are positively correlated with own research productivity. The authors interpret this as evidence of significant spillovers of knowledge across firms.

Existing private R&D has also been shown to affect the entry decision of new firms (effect 2 above). For instance, Aharonson *et al.* (2006) argue that new entrants are influenced systematically by factors promoting the benefits of co-location, and seek locations that would allow them to benefit positively from knowledge spillovers. A number of papers have also explored how knowledge spillovers generated by existing firms shape the locational dynamics of the new entrants to the biotech sector, especially in the USA.

The third type of spillover effect generated by private R&D is reduction in production costs. For instance, it has been estimated that a 1% increase in the R&D spillover can decrease average costs between 0.05% and 0.2% (Levin and Reiss, 1984; Bernstein and Nadiri, 1989).

Arrow C in Figure 6.1 represents these effects taken together. Note the arrow comes out from the private R&D 'bubble', without distinguishing between 'new' and 'existing' R&D, because spillover effects could arise from either or both 'types' of private R&D.

D. Mechanisms transmitting spillovers

The literature highlights a number of mechanisms facilitating the transmission of spillovers.

First, there are the mechanisms facilitated by universities, which include their pool of talented graduates, the ideas generated by faculty, the high-quality libraries and other facilities of research universities, and their publications.

Second, networking and social interactions are also deemed to be important mechanisms, both formal and informal interactions. Formal ways of interaction include technology transfer programmes, such as licensing from universities to firms. Both means of interaction seem to be relatively important for the pharmaceutical and biotech market. It is important to highlight that part of the literature looking at networks concludes that geography might not be a sufficient condition for accessing a local pool of knowledge but rather that it also requires active participation in a network of knowledge exchanges.

The third transmission mechanism discussed in the literature relates to 'absorptive capacity', i.e. the ability of economic agents to recognise, assimilate and apply new scientific knowledge – and thereby to appropriate some of the returns accruing to investments in new knowledge made by others (Cohen and Levinthal, 1989). These authors argue that, whereas the conventional wisdom was that R&D generated only one product, namely new information, R&D also enhances the firm's ability to assimilate and exploit existing information – the firm's 'learning' or 'absorptive' capacity. This second 'face' of R&D is very important, as it represents an important element of a firm's ability to create new knowledge.

Fourth, entrepreneurship has also been identified as an important mechanism to transmit spillovers, in that knowledge spillovers are the source of knowledge creating the entrepreneurial opportunities for new firms.

International trade is usually deemed to be one of the most important mechanisms by which spillovers are transmitted across countries, but these are outside the scope of this work.

E. Measuring spillovers: the geographical dimension

Figure 6.1 abstracts from the geographical dimension. For instance, it does not take into consideration where the public and private R&D actually takes place and how close you have to be to the source of the spillover to access it. This is nevertheless an important dimension, as the evidence gathered in our literature review clearly shows. The empirical evidence suggests that the link between knowledge inputs and innovative outputs becomes stronger when the unit of observation becomes increasingly aggregated (e.g. when the unit of observation is the country or the industry), and that location and proximity clearly matter in exploiting knowledge spillovers. Geographic concentrations of knowledge are likely to create higher levels of innovation than would otherwise be achieved. Not only do product innovations exhibit a pronounced tendency to cluster in regions which contain concentrations of innovative inputs, but also innovative activity tends to cluster more in industries where knowledge spillovers play a decisive role. The propensity for innovative activity to cluster is attributable to the role of knowledge spillovers and not merely to the geographic concentration of production. The literature also suggests that the role of knowledge spillovers is geographically bounded: innovative activity is more likely to occur within close geographic proximity to the source of that knowledge – 'localised knowledge spillovers'.

Approaches to the quantification of spillovers

Three main methodological approaches have been used to assess the value and benefits from R&D: econometric studies, surveys and case studies. The first method relies on the analysis of large databases. Surveys have been conducted of R&D managers drawn from the private sector, while case studies attempt to trace all the antecedents to an innovation. Each method has its own advantages and disadvantages. In this paper we draw upon the evidence generated by all three methods.

The economics literature distinguishes between two types of return to investment:

- 'private' or direct return to R&D investment, meaning the economic benefits generated by a specific R&D programme and accrued by the organisation (whether in the public or private sector) undertaking that research, through royalties and/or sales of a new product or process
- 'social' or total return to investment, which incorporates not only the benefits captured by the organisation undertaking the R&D but also the benefits spilling over for third parties to exploit, e.g. new knowledge and economic conditions that stimulate and enhance innovation and technical progress.

The aim in this section of the report is to estimate the social return to the UK that is generated, in addition to any health gains, by public and charitable sector cardiovascular medical research in the UK, i.e. assessing the contribution of innovative efforts funded by government and charitable institutions to the national economy, excluding the health gains discussed in Chapter Five. The literature does not enable us to distinguish different strengths of effect according to which therapeutic area is invested in initially by the public and charitable sector. We therefore apply average estimates of the impact of medical research in general to the quantity of cardiovascular research spending, in order to estimate the impact of that particular category of research.

The empirical literature provides quantified estimates of the extra GDP created as a result of extra public research expenditure, but not specifically for medical research. Indeed the clearest evidence is from the agricultural sector. However there are empirical estimates of the amount of private medical R&D stimulated by public medical research, and literature quantifying the extra GDP that results from extra private R&D. Hence, we have used two approaches to quantify the social return to public medical research:

1 two-stage approach:

   a) estimating the private R&D stimulated by public research (which is represented by arrow A1 in Figure 6.1)

   b) estimating the social rate of return to the private R&D so stimulated (which is represented by arrow C of Figure 6.1)

2 one-stage approach: a direct estimate of the social rate of return generated, by whatever transmission mechanisms, by public medical research (which is represented by arrows B1, B2A and B2B in Figure 6.1).

The two-stage approach excludes any social benefit that might be achieved by public medical research independently of private R&D and so should in principle be expected to be less than or equal to the estimates produced by the one-stage approach. But because empirical estimates to enable the one-stage approach to be taken come only from non-medical sectors (mainly agriculture), we considered it desirable to provide a check by undertaking the two-stage estimates as well, as described in the following paragraphs.

1a) Private R&D attracted by public/charitable R&D

There are few studies measuring the positive pay-off generated by publicly funded medical research. We found two particularly relevant published empirical studies exploring the relationship between publicly funded and privately funded R&D in the pharmaceutical industry: Ward and Dranove (1995) and Toole (2007). Both studies refer to publicly funded medical research in the USA, funded by the National Institutes of Health (NIH), and to the impact of that on the total of R&D expenditure in the USA by all companies plus R&D expenditure by US-based companies worldwide.

Toole (2007) provides separate estimates of the long-term elasticity of private R&D with respect to publicly funded basic research and publicly funded clinical research (Table 6.1). A 1% increase in NIH expenditure on basic research leads to a 1.69% increase in pharmaceutical industry R&D, after a lag of eight years. In the USA, private pharmaceutical R&D investment spending was 4.96 times the level of public spending on basic biomedical research. Thus an increment of $1 in US public basic research spending is estimated to stimulate $8.38 of private pharmaceutical R&D (1.69 x 4.96 = 8.38).

According to Toole, a 1% increase in public clinical research expenditure leads to a somewhat smaller, but still significant, increase in private pharmaceutical industry spending. The transmission mechanism for this is not made clear but we suppose it might include public–private joint funding of clinical research projects. Toole finds that a 1% increase in NIH expenditure on clinical research leads to a 0.40% increase in private pharmaceutical industry R&D. This is fully achieved after a lag of three years, compared to the eight years it takes for the full extent of increased private R&D to be seen following an increment of public spending on basic research.

We do not have data on the split of public and charitable medical research in the UK between basic and clinical. But the split within the Medical Research Council appears to be around 60:40 and may be similar in the charitable sector. NHS-funded research is likely to be weighted towards clinical rather than basic. Thus we assume as a rough overall approximation that public and charitable medical research in the UK is in total split 50:50 between basic and clinical research. Thus, based on Toole's US estimates, we assume that a 1% increase in public/charitable research produces a ((1.69 + 0.40)/2 =) 1.05% increase in private pharmaceutical R&D in the UK.

Ward and Dranove (1995) do not distinguish between basic and clinical research NIH funding but they do distinguish between the impact of public medical research spend on private R&D spend within the same therapeutic category and the impact on private R&D spend in different therapeutic categories. They estimate that a 1% increase in publicly (NIH) funded basic research expenditure in a particular therapeutic category would, after a lag of seven years, cause a 0.76% increase in private industry R&D spend in that same therapeutic category and a 1.71% increase in private industry R&D spend in other therapeutic categories. Thus a 1% increase in NIH spend across all therapeutic areas leads to a 2.5% increase in the total of private pharma R&D spend in the USA plus worldwide R&D by US-based biopharmaceutical companies, taking seven years to have the full effect. Ward and Dranove do not report their data on the ratio of industry R&D to public R&D.

We estimate the marginal impact relevant to the UK combining the elasticities estimated by Ward and Dranove (1995) and by Toole (2007), and the ratio of pharmaceutical industry to public R&D spend in the UK based on the data we collected for this study, which are presented in Chapter Three. For the latter ratio, in line with Toole's method, we employ the private R&D figure

Table 6.1: Toole's estimates of the impact of NIH-funded R&D on pharmaceutical industry R&D, USA

Type of public research	Basic research	Clinical research
Long-run elasticity of industry R&D relative to publicly funded research	1.69	0.40
Ratio (industry total R&D/publicly funded research of that type)	4.96	5.86
Marginal impact	8.38	2.35

Source: Toole (2007)

Table 6.2: Estimated marginal impact based on Toole (2007) and Ward and Dranove (1995) elasticities

	Toole	Ward and Dranove
Long-run elasticity of industry R&D relative to publicly funded research	1.05	2.50
Ratio (UK industry R&D/public R&D)	2.10	2.04
Marginal impact (estimated)	2.2	5.1

Sources: Ward and Dranove (1995) and Toole (2007)

in the last year of the considered period (2005) relative to the average public research figure for the period 1997–2004 and the period 1998–2004, depending on the reported lag (eight years in Toole and seven years in Ward and Dranove). If we assume that the estimates in Table 6.2 represent the upper and lower ends of the marginal impact of extra public medical research spending in the UK, then a £1 increase leads to an increase in private pharmaceutical industry R&D spending in the range of £2.2 and £5.1.

A great deal of caution must be exercised when considering the relevance of these studies to the question of the impact of UK public and charitable research on UK private sector R&D because:

- the scale of both publicly funded medical research and private sector R&D in the pharmaceutical industry are several times greater in the USA than in the UK; there is thus more scope for public/charitable R&D to have a within-country impact in the USA than in the UK
- estimates of rates of return (the marginal impact) are sensitive to the estimated levels of R&D spend.

It should also be noted that the two source papers do not consider the geographical dimension, that is the extent to which private firms' propensity to raise R&D expenditure (for example opening a new R&D facility or improving an existing one) is linked to the location of key sources of (scientific) knowledge such as universities and publicly funded research institutes. The literature shows that geographic concentrations of knowledge generated by public research are likely to attract R&D investment of private firms and therefore give rise to regional clusters of innovative activities. Evidence provided by Furman *et al.* (2006) shows that this is the case in the biopharmaceutical sector.

1b) Social rate of return to private investment on R&D

The second step of the two-stage calculation is to estimate the impact on the UK economy of the private R&D that is stimulated by the public R&D (arrow C of Figure 6.1).

Table 6.3 summarises the findings of the empirical literature on the total economic returns – i.e. the 'social' returns – to private R&D spending. The rate of total (i.e. social) return to all parts of the economy is typically around 50% and greatly exceeds the rate of 'private' return captured by the firm doing the initial R&D (typically around 20%) in every case. The difference between the social and private returns is the return captured by firms, organisations or individuals other than the firm that made the original investment. A social rate of return of 50%, for example, means that for every pound invested now the economy earns a return that is equivalent to 50 pence per year for every year thereafter, indefinitely. The empirical studies listed in Table 6.3 use various approaches to estimate the productivity growth at the industry and inter-industry level generated by R&D efforts, including cost function approaches (Bernstein and Nadiri, 1988, 1991), total factor productivity (TFP) (Griffith *et al*., 2004a) and production functions using patents as a measure of firms' output (Jaffe, 1986; Scherer, 1982, 1984). Each study considers different sets of industries and data relating to US companies or OECD countries. Some of the references included in Table 6.3 are reviews (Garau and Sussex, 2007; Nadiri, 1993; PICTF, 2001).

We conclude that the total (i.e. social) rate of return to private sector R&D tends to be around 50% but could be significantly higher.

Combining 1a) and 1b)

As illustrated in Table 6.4, £1 extra spent on public medical R&D in the UK leads to an estimated increase of £2.2–£5.1 in R&D by the private pharmaceutical industry in the UK, which in turn yields a 50% rate of return to the national economy as a whole. Overall, for every extra £1 spent in public R&D plus the extra £2.2–£5.1 consequently spent by the private sector, the national economy earns a return equivalent to an extra £1.1–£2.5 per annum, respectively, of GDP thereafter. This represents a social rate of return to the total sum of public and private R&D investment (i.e. £3.2–£6.1 in our example) that is equivalent to 26% using Toole's findings and 34% using Ward and Dranove's findings. Thus the total social rate of return to the marginal 'investment project' that commences with £1 extra of UK public medical research spending is estimated to lie in the range 26–34%, i.e. of the order of 30%.

This rate of return is assumed to apply equally to public cardiovascular research and to any other therapeutic target area of medical research.

Table 6.3: Social return to private R&D

Study	Private rate of return	Social rate of return
Bernstein & Nadiri (1988)	9–27%	10–160%
Bernstein & Nadiri (1991)	14–28%	20–110%
Goto & Suzuki (1989)	26%	80%
Griffith *et al.* (2004a)	N/A	40%
Griliches & Lichtenberg (1984)	N/A	41–62%
Jaffe (1986)	N/A	30%
Mansfield *et al.* (1977)	25%	56%
Nadiri (1993)	20–30%	Approx. 50%
PICTF (2001), Garau & Sussex (2007)	14%	51%
Scherer (1982, 1984)	29–43%	64–147%
Sveikauskas (1981)	10–23%	50%

Note: In this table the 'private' return is that accruing solely to the firm making the R&D investment. The 'social' return is the total return to all organisations and individuals.

These calculations show that for £1 additional public medical research undertaken this year, the future gain to the UK economy would be equivalent to a stream of around £0.30 per year thereafter. But if the resources tied up in this public research, and the consequent private research it stimulates, had been put to other uses instead, then it can reasonably be assumed that these other uses would also have led to some increase in GDP. Nevertheless, there is published evidence (e.g. PICTF, 2001; Garau and Sussex, 2007) to show that medical research yields more extra GDP than would be gained if the same resources were invested in their next best alternative uses: that is to say medical research yields 'economic rent'. Based on Garau and Sussex (2007) that extra amount is equivalent to about one fifth of the extra GDP generated: i.e. four fifths of the extra GDP you could equally well get by investing the same resources in something other than medical research, but one fifth is *only* obtainable if they are invested in medical research and nothing else.

2) One-stage approach: social rate of return generated by publicly funded biomedical R&D

The second approach we explore relies on empirical evidence aimed at measuring the total social rate of return (excluding health gains) to R&D investment by the public and charitable sector, i.e. including the economic benefits spilling over from the party performing R&D to other organisations and bringing about output increase in the form of patents and new products (as represented by arrow B1 of Figure 6.1) and improvement of firms' performance (as represented by arrows B2A/B).

Empirical literature provides estimates of the social return to public investment in agricultural research but not medical research. Table 6.5 summarises the main findings.

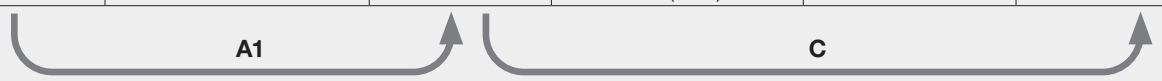
Most of the works estimate the social rate of return to publicly funded research (in the agricultural sector) to be in the range of 20–67%. The implied 26–34% social rate of return to the total of public and private R&D, which we estimated in the two-stage approach above, lies within and towards the bottom end of this overall range, which is consistent with our prior expectation that the two-stage method would yield estimates equal to or less than the one-stage estimate.

As noted by Buxton *et al.* (2004), and based on the review by Salter and Martin (2001), none of the studies measuring the benefits to an economy from publicly funded research provides a simple and comprehensive model. The main limitations of these studies are that they may be biased towards those government R&D programmes that proved successful and that they mainly employ US data which may not translate directly to the situation of the (smaller) national economies of Europe. Nevertheless, they are indicative of the existence of a large and positive economic contribution by public research to the national economy as whole, with a social rate of return of at least 20% and probably significantly higher than that.

More recent contributions on the issue of measuring the rate of return of publicly funded research include the studies conducted by Mansfield, which focus on the contribution of research conducted by academic centres to innovation delivered by commercial sectors (arrow B1). Mansfield (1991) concludes that over 10% of new products and processes marketed by surveyed firms could not have been developed (without substantial delay) in the absence of academic research, and that this proportion is as high as 27–31% in the pharmaceutical sector specifically. Mansfield also provides an estimate of the social rate of return on academic research of 28%. The results of Mansfield's later (1998) study are similar with respect to the impact of academic research on commercial innovation but provide no rate of return estimate.

Table 6.4: Social rate of return generated by increased public medical research

Extra spend in public R&D	Study	Additional private R&D induced	Study	Social rate of return of private R&D	Overall social return due to a £1 increase in public R&D spending
£1	Toole (2007), UK data (see Chapter Three)	£2.2	Nadiri (1993), PICTF (2001), Garau & Sussex (2007), Griffith *et al.* (2004)	50%	£1.1
£1	Ward & Dranove (1995), UK data (see Chapter Three)	£5.1	Nadiri (1993), PICTF (2001), Garau & Sussex (2007), Griffith *et al.* (2004)	50%	£2.5



Summary

Taken together, our two estimation approaches imply that every £1 of extra public/charitable research spending in the cardiovascular (or any other) therapeutic area would yield a total social rate of return of at least 20% and perhaps as much as 67%, based on the, fairly sparse, empirical literature available. The more conservative of our two estimation methods implies a total social rate of return of around 30%. Taking this as our 'best estimate' of the GDP impact of medical research, implies that for an extra £1 invested in cardiovascular research this year, the UK's GDP will be £0.30 higher next year and every year thereafter, than it otherwise would have been. This represents a healthy return on the investment and that is before any account is taken of the value of the health gains produced, as estimated in Chapter Five above.

If all of the £122m (in 2005 price terms) of public and charitable cardiovascular R&D that was invested in 1992 were to yield a 30% rate of return, that would be equivalent to £37m of GDP every year thereafter. A 20% rate of return, the bottom of our range of estimates, would be equivalent to £24m of GDP every year thereafter; and a 67% rate of return, the upper end of our range, would be equivalent to £82m of GDP every year.

Table 6.5: Estimates of social rate of return to public R&D in the agricultural sector

Study	Social rate of return
Griliches (1958)	20–40%
Griliches (1964)	35–40%
Huffman & Evenson (1993)	43–67%
Knutson & Tweeten (1979)	28–47%
Peterson (1967)	21–25%
Schmitz & Seckler (1970)	37–46%

Sources: Griliches (1991), Salter *et al.* (2000)

Chapter Seven

Estimating the rates of economic return from public and charitable CVD research

KEY POINTS

- In this Chapter we bring together the various elements necessary to calculate the return to the estimated investment in public and charitable cardiovascular research (from Chapter Three).
- We consider the health return to be the value of the QALYs gained net of the health service costs to generate them (from Chapter Six).
- We allow for our estimated proportion of this net benefit attributable to UK research (17%) and a time lag between research and health gains of 17 years (Chapter Four).
- We define the internal rate of return (IRR) and use this as our preferred measure.
- Combining our best estimates gives an IRR from net health benefits of 9.2% for CVD research.
- Our one-way sensitivity analyses indicate a range of values for the IRR from 5% to 15%. In our 'pessimistic' scenario the research investment exceeds the value of the net health benefit; in our 'optimistic' scenario the net health benefit gives an IRR of over 25%.
- In addition, we add our best estimate of the return in terms of GDP of 30%.
- Our overall best estimate of the health and GDP gains combined from CVD research is an IRR of 39%.

This Chapter brings together the various estimates and pieces of evidence set out in previous Chapters to provide estimates of the rate of return on the investment in public and charitable funding of cardiovascular related health research.

The value of the research investment

The first main component is our estimates of the research investment. In Chapter Three, drawing on multiple original sources, we produced estimates of the total expenditure on UK publicly and charitably funded research related to CVD for the years 1975–92. Once inflated to constant 2005 price levels, the central estimate showed that expenditure on cardiovascular research in 1975 was £144 million. Spending fell in real terms to £93m in 1981 and then rose fairly steadily again to £121m in 1992. Our alternative estimates, as used in the sensitivity analyses, were: a series of lower estimates of £103m (1975) to £97m (1992), and a series of higher estimates of £186m (1975) to £145m (1992).

The QALYs gained that can be attributed to CVD research

In Chapter Five, drawing on a large number of health technology assessments and economic evaluations, we estimated the QALYS gained (and their value) for all the interventions leading to the main health gains in cardiovascular disease. We calculated the patient-lifetime discounted incremental QALYs from 46 patient category/treatment combinations for interventions instigated in the years 1986–2005. An important element in the estimates of total QALYs gained is the gains from quitting smoking and for the reasons explained in Chapter Five these estimates show substantial variation between years. Our best estimate considers only those quitters whom we estimate did so with some specific intervention or contact with the NHS. This assumption produces estimates of the total QALYs gained per year in the period 1986–2005 ranging from 52,000 to 167,000 QALYs, with an annual average of 138,000.

A more conservative methodology provides a series of somewhat lower estimates with an average of 112,000 QALYs per annum over the same period. Alternatively, taking a view that all those who quit smoking might reasonably be argued to have done so directly, or indirectly, as a result of medical research, gives a considerably higher series of estimates for the QALY benefit with an average of 182,000 QALYs per annum. We use these lower and higher alternatives in our sensitivity analyses. These are valued using the 'opportunity cost' threshold range for the maximum amount NICE is willing/able to pay to obtain a QALY from health care (given the current NHS budget) of £20,000 to £30,000, with a central estimate of £25,000.

Each of these estimates only attributes to CVD research the benefits from a proportion of those who quit smoking equal to the proportion of total deaths avoided from smoking that are related to CVD. (This implies that if we were also estimating the return on R&D in cancer the health benefits from the remaining deaths avoided by quitting smoking would be attributed to cancer research.)

The health service costs of generating these QALYs

In addition in Chapter Five, we estimated the discounted (net) patient lifetime NHS costs of delivering these treatments by the year in which they were instigated (at 2005 prices). These cost estimates 'marry' to the use of interventions that generate the QALYs. These also show annual variability (being influenced by the estimates of the number of interventions instigated in each year). Our best estimate series of these NHS costs per annum in the period 1986–2005 ranges from £415m to £1,355m, with an average of £781m per annum. The average of the lower range is £540m and that of the upper range £824m per annum.

We have already noted that the literature differs in terms of the expenditures to which the health gain is seen as a return. Some studies consider health gains as a return to health care, ignoring the role of R&D (e.g. Luce *et al*., 2006). Others attribute all the returns to R&D, effectively ignoring the health care costs (as in the Australian studies: Access Economics, 2003, 2008). We take the perspective of an initial investment (or stream of investments) in R&D resulting in a subsequent stream of net monetised health benefits; i.e. from the value of the health benefit that we ascribe as attributable to R&D, we deduct the cost of the health care required to generate that benefit. We are of course including the expenditure on all CVD research, not just that which might in principle be related to the interventions we consider, because the return on investment has to allow for not just the major R&D successes but also the research that was less successful, or unsuccessful, in relation to clinically valuable interventions. Effectively our approach assumes that the value of all other CVD interventions just equalled the cost of providing them (that is to say there was no 'net benefit' from these interventions at the prevailing value of a QALY). We believe this is probably a neutral assumption, assuming a degree of economic rationality in the use of NHS resources. The reality is not known: it might be that the net benefit (value of the health gain minus the cost of achieving it) for all other CVD interventions is positive or negative.

The time lag between the research expenditure and health benefits

Combining evidence from our new analysis of citations in UK cardiovascular guidelines with evidence from other sources, we concluded in Chapter Four that our best estimate of the time lag is 17 years. We also consider in our sensitivity analyses the effects of lags of ten and 25 years. Given the time periods for which we have relevant data (which were determined in part by anticipation of likely lags we would use but also heavily by the availability of comparable data), the implication of these lags is that in our best estimate (17 years) we relate the investment in CVD research in the years 1975–88 to health benefits and their costs in 1992–2005. In the alternative ten-year lag estimates we relate investment in 1976–92 to net benefits in 1986–2002, and in the 25-year lag estimate we compare just five years' investment in the period 1975–80 to benefits in 2001–05. (These time lag structures, and those used subsequently for Mental Health in Chapter Eight, are set out in the Annex to this Chapter.)

The proportion attributable to UK research

CVD research is an international endeavour and much research is available rapidly as a public good to potential users anywhere in the world, so not all the UK net benefits can be attributed to UK research. (The corollary of course is that not all the net benefits from UK research accrue in the UK, but as emphasised in Chapter One we are specifically ignoring benefits from UK research that accrue elsewhere). Our analysis of CVD guidelines, combined with existing evidence, led us in Chapter Four to conclude that our best estimate of the proportion of UK net benefits attributable to UK research is 17%, with low and high estimates of 10% and 25%.

Estimating the rate of return on investment

With these various components and assumptions we are able to estimate the internal rate of return (IRR) on the research investment in terms of the net value of the health gains generated. The IRR is a convenient way of representing the return to the original research investment, and has the pragmatic advantage that it is the method used in the published empirical literature on the GDP impact of research discussed in Chapter Six. Expressing health gains as an IRR allows them to be added to the IRR for GDP gains to provide an estimate of the total rate of return achieved by medical research expenditure. For example an IRR of 10% means that the return to an investment of £1 is equivalent to receiving thereafter an income stream of £0.10 per year in perpetuity. Calculating an IRR avoids the need to apply a specific discount rate: the IRR is effectively the interest rate which would yield a zero net present value. However we have additionally presented net present values (NPVs) for these streams of research investments followed by net health benefits, calculated at the current Treasury approved discount rate of 3.5%.

We have generally avoided using the benefit/cost ratio (the sum of the discounted benefits divided by the sum of the discounted costs) or the so-called 'return on investment' (the net sum of the discounted health benefits minus the discounted costs, divided by the discounted costs) because these ratios are susceptible to arbitrary definitions of what is included in the costs and benefits. This problem is particularly important in our analysis where we allow for the health service costs of delivering the health care that yields the benefits attributable to R&D.[1] This problem does not occur in our IRR analysis because the health service costs are subtracted from the monetised health benefits each year.

Table 7.1 summarise our estimated IRRs (and NPVs) for our best estimate and our main tests of sensitivity to alternative key parameter values and assumptions. Our sensitivity analyses consider the separate effect of changing the value of key parameters (the estimate of CVD research expenditure, the estimate of the net health benefit, the value of a QALY, the time lag, and the proportion of benefits attributable to UK research) using our alternative high and low estimates. In addition we present 'pessimistic' and 'optimistic' scenarios in which the values of a combination of parameters are changed together.

The best estimate IRR of 9.2% is a substantial return, given the general conservatism of the methods used. By comparison, an intervention that NICE 'just accepted' as generating QALYs at a cost per incremental QALY of around £25,000 would effectively be yielding a 3.5% return (the required discount rate). The sensitivity analyses suggest rates of return acceptable to the public sector have been achieved under all but the 'pessimistic' scenario.

The sensitivity analyses also appear to behave predictably. They emphasise that the uncertainty around the estimates of research expenditure have a greater effect than uncertainty around the magnitude of the net benefits (the QALYs gained minus the NHS costs involved in producing them), at least within the ranges we have considered, but the value placed on a QALY is important. The results suggest that even more important may be: 1) the assumption concerning the appropriate lag; and 2) the percentage of total health benefits attributable to health research that are attributable to UK research (again within the limits of the ranges we have considered). For both of these assumptions the evidence is relatively weak.

Our analysis in Chapter Six suggests that in addition to these returns in terms of the value of net health benefits, the social return in terms of the impact on GDP is even larger with a best estimate of a rate of return of 30% (with a range from 20% to 67%). Whilst technically our health return represents an average for the total cardiovascular research in the UK, and the social return estimates are for a marginal change in (any) health-related public research, it is not unreasonable to see them as additive: thus spending on past cardiovascular research may well have been delivering a total return of almost 40% (9.2% plus 30%). This effectively means that on average £1.00 invested in research will yield approximately £0.40 worth of benefits every year over an extended period of time.

As will be discussed in the final Chapter, this does not tell us whether the return will be the same in future, or whether the return on a greater level of expenditure would or would not rise proportionately. It does however confirm that even using rather cautious methods and assumptions the return on CVD research is substantial. The final Chapter also attempts to throw light on the comparison of our data with that of the 'exceptional returns' claimed of the US and Australian studies.

Table 7.1: Estimated IRRs (and NPVs) for the health gain from CVD research

Assumptions	IRR	NPV (@ 3.5% discount rate)
Best estimate (central/best estimates as explained in text)	9.2%	£1,847m
Low estimate of research expenditure	13.9%	£3.067m
High estimate of research expenditure	7.7%	£1,536m
Low estimate of net health benefit	8.1%	£1,344m
High estimate of net health benefit	10.8%	£2,757m
QALY value of £20K	7.3%	£1,049m
QALY value of £30K	10.7%	£2,646m
25-year time lag	5.6%	£413m
10-year time lag	13.4%	£2,472m
10% of benefits attributable to UK research	7.2%	£778m
25% of benefits attributable to UK research	14.3%	£3,786m
'Pessimistic scenario': High research investment; low net benefit; QALY = £20K; 25-year lag; 10% attributable to UK research	Inv > net benefit	-£364m
'*Optimistic scenario*': Low research investment; high net benefit; QALY = £30K; 10-year lag; 25% attributable to UK research	25.5%	£9,123m

1 In our CVD base case, the discounted health benefits are £7,165m, the discounted health care costs are £1,646m and the discounted research costs are £1,228m. If the health care costs are netted off the benefits (in the numerator) the B/C ratio is 7.2; if they are added to the R&D costs in the denominator the B/C ratio is 2.5.

Chapter Eight

Applying our methodology to mental health

KEY POINTS

- Total annual public and not-for-profit funding for mental health research in the UK increased from £28m in 1975 to £93m in 1992, representing an annual percentage increase of around 7%. In real terms (2005 prices) this equates to a decrease from £155m in 1975 to £129m in 1992.
- Based principally on the evidence of citations in 12 UK mental health guidelines, we estimate that the proportion of health care benefit that can be attributed to UK mental health research expenditure is 28%, and we test sensitivity to a range from 10% to 60%.
- Based principally on evidence from analysis of the same guidelines, we estimate the time lag between mental health research spending and the health care benefit is around 12 years, ranging from nine to 14 years.
- We estimate the net benefit from six patient group/intervention combinations that arose from research broadly in the relevant period.
- The total value of the QALY gain from these interventions over the whole period of 1985–2005 was £31,435m.
- The total incremental health care cost over the same period was £2,263m.
- Our best estimate of the internal rate of return on UK public and charitable investment in mental health research is 7%. Our sensitivity analyses indicate that under plausible assumptions there is considerable uncertainty in the rate: it might range from around 11% to a situation where the benefits might not have exceeded the costs of research.
- Overall this application suggests that our general methodological approach is equally applicable to mental health but that the greater data problems and uncertainties around the effect of interventions in mental health (as compared to CVD) mean that we can have less confidence in the results.

Earlier chapters have demonstrated that it is possible, though not without difficulty, to estimate the returns in terms of the value of incremental health gains that might reasonably be attributed to UK research in the area of cardiovascular disease. In defining this project we anticipated that to do the same for mental health would be more problematic. In part this reflected the findings in the Australian 'Exceptional Returns' study. The methods used there – building principally on temporal changes in disease specific mortality and morbidity – produced rather implausible estimates that the health gain from research on mental health was negative. (This result was in part masked in their conclusions by combining research – and health gains – on 'nervous system' and 'mental health'.)

In this Chapter, we essentially follow the same steps presented in Chapters Three to Seven in relation to mental health to demonstrate to what extent the same approach as we adopted for CVD research can be applied to mental health research.

Estimated expenditure (public and non-profit) on mental health research

This section summarises our estimation of the UK expenditure on mental health research in the period 1975–92. These estimates are based on similar assumptions to those outlined in Chapter Three, with some important differences:

- For the non-profit sector, we have assumed that mental health research is supported principally by the Wellcome Trust, and identified relevant research using the grants database and the search term 'mental health'. Because of the variations in classification scheme over the period 1975–92, all neuroscience panel grants were also included.
- As for cardiovascular research, the MRC has used a number of systems for classifying grants within the broader field of mental health research over time. To allow for cross-comparison with cardiovascular research, we retained our focus on the years between 1975 and 1992, but the MRC used at least three different classification systems during this period. From 1972 to 1975, all research grants were classified under an 'inclusive' category entitled 'mental disorders'. From 1976 to 1992, the MRC distinguished between research on 'mental handicap and psychiatric disorders' and 'addiction', each of which had 'exclusive' and 'inclusive' definitions (understood in the same way as for cardiovascular research). Since 1992, all grants in this area have been classified as 'neuroscience and mental health'. Our figures for the MRC are based on the 'mental disorders' category for 1972–75, and then totals for inclusive definitions of 'mental handicap and psychiatric disorders' and 'addiction' from 1976–92.
- Based on figures for MRC and Wellcome Trust expenditure, as well as those cited in a one-off report (Dawson *et al.*, 1998), we have assumed mental health research activity to be 10% of total public and charitable health research activity in the UK (and looked at a range from 5% to 20%), where no breakdown by clinical area is available.[1]
- For the for-profit sector, Ward and Dranove (1995) do not show data specifically for a mental health therapeutic category, but rather for 'neuro', which will include neurological conditions outside of mental health. According to their data – for global R&D spend

by US pharmaceutical companies and US R&D spend by non-US pharmaceutical companies – 'neuro' accounted for 22% of total R&D expenditure in 1966 and 17% in 1988. Similarly, CMR International refer to the therapeutic category 'nervous system' which includes, but goes wider than, mental health.[2] From their sample of around 20 multinational pharmaceutical companies, they found that nervous system R&D represented 19% of total global R&D expenditure in 2003, 16% in 2004 and 17% in 2005. Combining these two sources of information, we assume that 'neuro' or 'nervous system' R&D is around 19%, ranging between 16% and 22% for our high and low estimates, of total private sector pharmaceutical R&D spending in the UK. We are unable to estimate within that how much went to mental health specifically rather than neurological conditions.

Figure 8.1 presents our estimates of expenditure on mental health research between 1975 and 1992 by five major sources of funding, from the government and non-profit sectors (see Annex 8A for the data used to construct the figure). We find that, between 1975 and 1992, expenditure on mental health research increased in current prices from £28m to £93m in 1992, representing an annual average increase of around 7%. Total expenditure over the period was £929m. Figure 8.2 provides comparative estimates of research expenditure by the UK pharmaceutical industry on mental health research and indicates that at the end of the period industry spending in this area was approximately three times that of the public/charitable sector. Figure 8.3 provides high and low estimates for the public/charitable expenditure. Figure 8.4 shows the public/charitable spending at constant (2005) prices and shows that in real terms expenditure fell substantially in the first decade and then increased again but did not regain its original value.

Figure 8.1: Total estimated expenditure (public and non-profit) on mental health research, by source of funding, 1975–92, at current prices

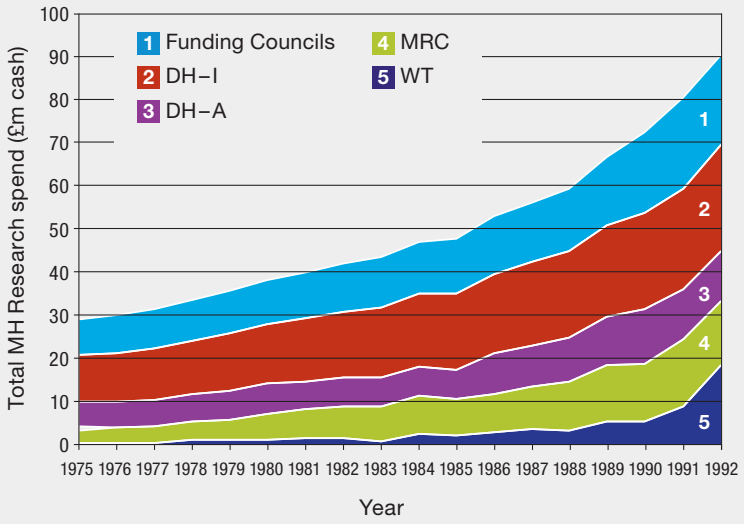
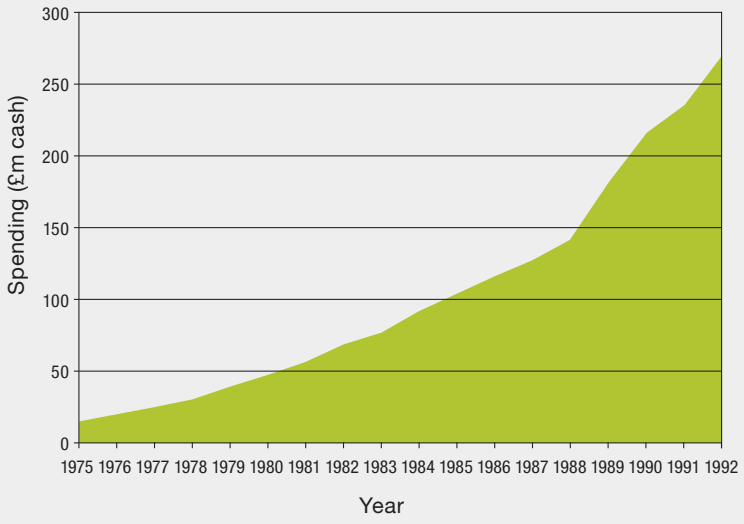


Figure 8.2: Total estimated expenditure by the pharmaceutical industry on mental health research, 1975–92, at current prices



Analysis of UK clinical guidelines in mental health

We reviewed 12 mental health guidelines published by the National Institute for Health and Clinical Excellence plus the Mental Health National Service Framework (NSF) published by the Department of Health (see Annex 8B for a list of the mental health guidelines that were analysed).[3] A total of 3,423 papers from the 13 guidelines that were matched to the CWTS database were analysed.

Key results from the bibliometric analysis were:

- 28% of cited papers were published by UK authors (ranging from 11% for obsessive–compulsive disorder to 58% for the Mental Health NSF). (There is a suggestion that the contribution to health-systems-related guidelines from UK authors may be higher than their contribution to more biological and biomedical guidelines, their contribution to the latter being closer to the general UK contribution to combined international research in clinical medicine.) We use 28% as our best estimate and look at the sensitivity of the results to a range from 10% to 60%.
- The mean knowledge cycle time (the average time between the date of cited publications and the date of publication of the guideline) for all 13 guidelines was around nine years, ranging from nearly six years for the Mental Health NSF to just over 11 years for obsessive–compulsive disorder (OCD). Adding three years as a plausible estimate of the period between funding and publication gives a total time lag of 12 years, ranging between nine and 14 years.

We note, in passing, that the papers cited on mental health clinical guidelines were being cited three times as often as would be expected in the field, consistent with the expectation that the very best (or at least the most cited) papers in the field inform guidelines.

Estimating the number and value of the QALYs gained

We applied essentially the same approach as for CVD to estimate the monetary value of health gains from specific interventions to treat or prevent mental disorders adopted over the period 1985–2005, and estimate the health care costs incurred in delivering these gains. To do this we:

1 identified specific interventions for patients with mental disorders

2 estimated the QALYs gained for each intervention in each patient group

3 computed the numbers of users of each intervention in each patient group

4 adjusted for compliance with treatment

5 computed the total QALYs gained from each intervention

6 valued the total QALYs gained.

From our review of the economic evaluation literature, we also obtained estimates of the incremental costs associated with each intervention and multiplied these by the numbers of users who are compliant with treatment to quantify the health care costs associated with each intervention.

Chapter Five sets out the principles of our approach in more detail. Here we simply summarise the steps, highlighting methodological decisions which were specific to the estimation of health gains and costs of interventions to treat mental disorders. This general account of the methods is followed by an example (in Box 8.1) explaining how these principles were applied in the specific case of SSRIs.

Stage 1: Identifying specific interventions for patients with mental disorders

In the absence of a starting point equivalent to the IMPACT study (Capewell *et al.*, 2007), we selected the patient groups and treatments based on treatment recommendations in the National Service Framework (National Health Service, 1999; Department of Health, 2004b). We focused on a small set of interventions in depressed and schizophrenic patients thought to be most relevant in terms of the additional health gains they have produced since 1985.

In summary, for the treatment of depression, we included:

- Selective serotonin reuptake inhibitors (SSRIs) – on the assumption that patients receiving these would not otherwise have received drug treatments because SSRIs removed the safety concern (particularly relating to drug overdoses) of the existing treatments. We make no assumption that on a per-patient basis SSRIs provide additional QALYs over the tricyclic antidepressants: the QALY gain from SSRIs comes from treatment of patients who would otherwise have remained untreated.
- Cognitive behavioural therapy (CBT) – on the assumption that these patients would otherwise have received usual care in general practice.

For the treatment of schizophrenia, we included:

- Atypical antipsychotics – atypicals are widely perceived as safer, are easier to prescribe than earlier antipsychotics and have been more widely promoted, which has led to much wider use of antipsychotic medications allowing treatment of patients who would otherwise have remained untreated.

Figure 8.3: High and low estimates of total mental health research spend by public and non-profit funders, 1975–92, at current prices

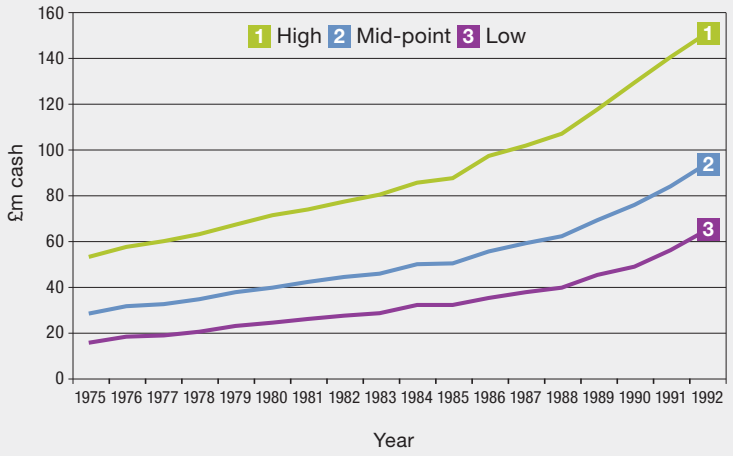
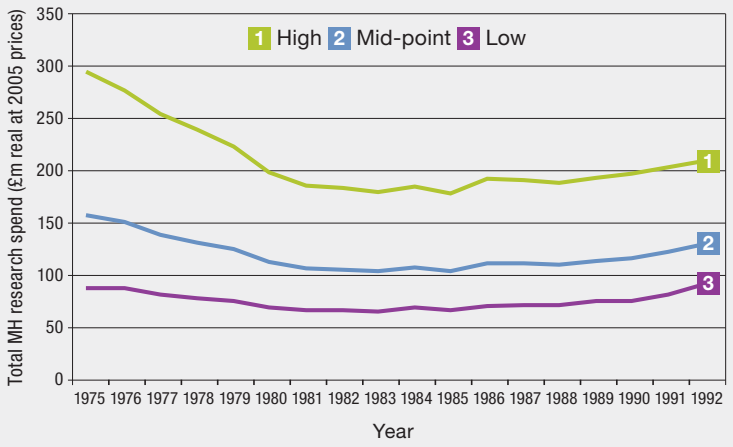


Figure 8.4: Expenditure on mental health research by public and non-profit funders, 1975–92, at 2005 prices



For the treatment of depression, schizophrenia and other mental disorders:

- Community psychiatric nurses (CPNs) – on the assumption that these patients would otherwise have received usual GP care.

The patients groups and interventions are in Table 8.1 column 1.

Stage 2: Estimating the QALYs gained for each intervention in each patient group

Based on a review of the economic evaluation literature, we estimated the QALYs gained from each intervention in each patient group (Table 8.1 column 3). All the estimates of the QALYs gained we obtained from the literature adopted a time horizon between one and 1.5 years. To provide comparable estimates across interventions, we calculated the number of QALYs gained in each of the first 12 months of treatment and then summed the monthly gains up to obtain a QALY estimate for one calendar year. When we did not have data on the quality of life score in each month, we assumed a linear increase in quality of life between baseline and 12-month measurement. In all cases we assumed no continuing benefit (or effect on costs) beyond the period of treatment. See Annex 8C for further details on the studies used to generate these estimates.

Stage 3: The numbers of users of each intervention in each patient group

To calculate the total QALYs gained, we multiplied the QALYs gained for each specific intervention by the numbers of users of that intervention in each year. For SSRIs we could approximate the number of users (strictly 'user years') based on the number of SSRI prescriptions in the UK in each year. A detailed description of how the SSRI users were computed can be found in the example later in this chapter and in Annex 8D. For the community psychiatric nurses we had data on the numbers of initial contacts in each year between 1988 and 2003. For the years 1985–87, we applied the 1988 figure. For 2004–05, we applied the 2003 figure. See Annex 8D for further details on how new contacts with community psychiatric nurses were calculated.

For all other interventions we did not have this information. Analogous to the CVD model, we therefore modelled the numbers of users as a function of the numbers of patients in each patient group and the uptake rate for each specific intervention. The approach is explained in Chapter Five. When we were not able to find complete data on the number of eligible patients or the uptake rates, we modelled the numbers based on the available empirical evidence. Annex 8D gives details how the estimates for the each eligible patient group were generated and Annex 8E gives details on how the estimates for the uptake rates were generated.

Stage 4: Adjusting for compliance with treatment

We searched the economic evaluation studies used to obtain the QALYs estimates for each specific intervention. None of the studies included non-compliance rates in their analysis. We therefore applied a compliance rate of 55% for schizophrenic patients taking atypical antipsychotics, and a compliance rate of 65% for depressed patients taking SSRIs. The figures are based on research by Velligan *et al.* (2003) and Cramer and Rosenheck (1998). We did not adjust for compliance with community psychiatric nurses and cognitive behavioural therapy because we used data on direct contacts for these interventions in our analysis. Accounting for compliance gives an estimate of the numbers of compliant users of each specific intervention in each year. These are reported for each intervention in Table 8.1 column 2.

Stage 5: Estimating total QALYs gained from each intervention

We computed the total QALYs gained from each intervention in each year by multiplying the numbers of users in that year by the QALYs gained from each

Table 8.1: Summary of results by patient group/intervention, 1985–2005

1	2	3	4	5	6	7
		QALYs gained			Incremental costs	
Patient groups/intervention	Compliant user years (000s)	Per user year	Total (000s)	Total monetised (£ million)	Per user year (£)	Total (£ million)
Depression:						
SSRIs	9,160	0.1306	1,197	29,914	102	931
Community psychiatric nurses	356	0.0017	1	15	340	121
Behaviour or cognitive therapy	656	0.0800	52	1,312	736	483
Schizophrenia:						
Atypical antipsychotics	248	0.0212	5	131	892	221
Community psychiatric nurses	576	0.0017	1	24	340	196
Other mental disorders:						
Community psychiatric nurses	917	0.0017	2	39	340	312
Total	**11,914**		**1,257**	**31,435**		**2,263**

SSRI = selective serotonin reuptake inhibitor

intervention. This approach is different from the approach taken to calculate the monetised health gain from CHD research. The estimates of QALYs gained from CHD interventions reflect the health gain over a lifetime so that we had to multiply the QALY gain in each year by the number of *new* users. The QALY estimates for the interventions to treat mental disorders reflect a 12-month gain and could therefore be multiplied by the number of users in each year. Focusing on user years rather than new users is on the one hand likely to be conservative because it assumes that the QALYs gained in the first year of use, when there may be a delay from the start of therapy to the time at which an effect is achieved, apply to subsequent years. On the other hand it may overestimate the QALYs gained because it assumes that the treatment effect does not diminish over time.

We then summed the result for each intervention over the period 1985–2005 to calculate the total QALYs gained. These are reported in Table 8.1 column 4.

Stage 6: Valuing total QALYs gained

We placed a value on the total QALYs gained by multiplying the total QALYs gained by £25,000, which is the central point of the UK's National Institute for Health and Clinical Excellence's threshold range of £20,000 to £30,000 per QALY, giving a value of the total QALYs gained of £31,435m over the period 1985–2005 (Table 8.1 column 5).

Estimating the health care costs from the specific mental health interventions

From our review of the economic evaluation literature, we also obtained estimates of the costs associated with each intervention.

Where UK papers were used to generate the QALY gains estimates we used the same papers to obtain the cost estimates. This was the case except for cognitive behavioural therapy for depressed patients, which was from the Netherlands, and the QALY estimate for atypical antipsychotics for schizophrenic patients, which was from the USA. For cognitive therapy in depressed patients, we used a cost estimate from a UK economic evaluation of cognitive behavioural therapy in patients with depression with an outcome other than QALYs (Scott *et al*., 2003) and for atypical antipsychotics, we used a UK economic evaluation of atypical antipsychotics in schizophrenic patients who are responding poorly to previous therapy (Davies *et al*., 2007). Annex 8F gives further details on the studies used to generate the estimates for costs for each intervention to treat mental disorders. A limitation of our cost estimates is that the major gains in treatment came not just from SSRIs, but from their widespread use and adoption. We have used cost data for prescribing SSRIs but not for any associated medical care such as GP visits. This is consistent with a counterfactual that these patients would have received GP care but would not have received medication for depression. But this will underestimate the costs if without SSRIs these patients would not have received as much GP or other care. A similar issue may also apply to our costs of atypical antipsychotics.

The costs of each intervention per user year are reported in Table 8.1 column 6 and the total cost for users in the period 1985–2005 are reported in Table 8.1 column 7. The total cost over the period was £2,263m.

Upper and lower estimates of QALYs gained and associated health care costs

The overwhelming proportion of the QALY gain is estimated to come from the use of SSRIs. In general, SSRIs (the new medications introduced circa 1987) have largely replaced the older medications (tricyclics) and have been prescribed to a much larger share of the population. The main advance of the SSRIs was their ease of prescription as well as their general safety. This led to much wider use of SSRIs by non-psychiatric specialists and for a much wider range of anxiety-affective conditions than just major depression. A similar concern has been expressed about atypical antipsychotics, as the greater increase in use of these medications has been outside the core indication of schizophrenia (Domino and Swartz, 2008). Unfortunately, we do not have data on the breakdown by the specific conditions for which these drugs are increasingly used in the clinic, or the QALY gains in those precise situations. These are the key factors that we have reflected in our upper and lower estimates of the net health benefit.

On the other hand we have been conservative in our assessment of the QALYs gained for a new patient receiving atypical antipsychotics. Our assessment of the change in utility is based on change from baseline in a recent and robust study (Rosenbeck *et al*., 2006). However, that study obtained QALY estimates in patients switched from a current treatment to an atypical antipsychotic. But many of the patients in that study were already on treatment so their baseline QALY level might have been higher, and hence utility gain from the new medication might have been lower, than for patients who were receiving no treatment and were started on atypical antipsychotics. An older, shorter (eight-week) study in patients not receiving treatment, but using a less appropriate basis for calculating QALYs, indicated a considerably greater utility gain of 0.146 (Chouinard, 1997).

Our lower estimate of the net health gain made three adjustments compared with our best estimate:

- It adjusted downward the quality of life gain from SSRIs, reflecting the suggestion that the QALY gain compared to placebo may be more modest as they are increasingly used in general practice and less severe patients (Kirsch *et al*., 2008). Our lower estimate assumed that each SSRI user gained only half the QALY gain compared to that assumed in the best estimate.

- Rather than simply allowing for the prescription cost of SSRI treatment and assuming that prescribing the drug had no effect on patient contacts with the health care system, our low net benefit case used an estimate of the full cost of patient care, reflecting the alternative assumption that these patients would otherwise not be receiving active health service care (Kendrick *et al*., 2006).
- It used a more conservative estimate of the uptake rate for atypical antipsychotics between 1985 and 2005.

Our upper estimate made two adjustments:

- Our best estimate calculated the QALYs gained per year as a steady increase to observed improvements at one year. This assumption may have underestimated the QALY gain for those patients who are on medication for more than one year. The upper estimate assumed that half the years of use were for new users and the other half for patients continuing on SSRIs and enjoying the full benefit throughout the year.
- Our best estimate of QALYs gained for patients receiving atypical antipsychotics reflected a study in which patients switched from a current treatment to an atypical antipsychotic (Rosenbeck *et al*., 2006). The gain for these patients may have been less than for patients who were not previously treated. For this higher net benefit estimate, we used a higher estimate based on a small earlier study of previously untreated patients (Chouinard, 1997).

Using the adjustments described above, the lower estimate assumptions resulted in total QALYs gained of 656,000 over the whole period, the total monetary value of QALYs gained of £16,408m and total health service costs of £10,585m (see Annex 8G). The upper estimate assumptions resulted in total QALYs gained of 1,500,000 and total value of QALYs gained of £37,490m. The estimated health care costs for the upper estimate were unchanged compared to our best estimate.

Challenges to the estimation of QALYs and costs

The use of this methodology in mental health produced few, if any, distinctive problems but emphasised the need for a strong evidence base relating to the use of interventions and the health gain (in QALYs) and the costs associated with their use. Generally the appropriate evidence was much weaker for mental health, in part reflecting less use, and arguably less applicability, of QALYs as a measure of effect in this disease area. Thus even for the few interventions we considered we were forced to use some non-UK studies and were not able to use any meta-analyses. A further aspect of the weaker data was that there were few studies that considered long-term cost and benefits and most of our analysis is based on one-year studies.

Box 8.1 Example of SSRIs

Kendrick *et al*. (2006) undertook an economic evaluation of SSRIs and tricyclic antidepressants (TCAs) for the primary treatment of depressed male and female patients in the UK. Based on the findings of a randomised controlled trial, they reported the EQ-5D score at baseline and 12 months for the SSRI and TCA group respectively (the SSRI group improved from 0.61 at baseline to 0.78 at 12 months). We calculated the utility gain in each of the 12 months for patients on SSRI as compared to baseline, summed it up and arrived at an estimate of 0.13 QALYs gained per depressed patient per year. This is probably a conservative estimate as we allow for a gradual increase in quality of life for patients receiving SSRI treatment.

The number of patients using SSRIs was based on antidepressant prescription data for the UK between 1975 and 1998 (Middleton *et al*., 2001). For the years following 1998 we linearly extrapolated the prescription data based on the increase in prescriptions between 1997 and 1998. We then translated the number of prescriptions in the number of users for each year (or strictly the number of user years). In the study by Kendrick *et al*. (2006) 931 SSRI prescriptions were given in 81.6 person years of treatment. Consistent with this, we divided the number of prescriptions in each year by a factor of 11.4 to estimate the total number of SSRI user years. The estimated total number of user years for the period 1985 to 2005 was 14,092,497.

Following Cramer and Rosenheck (1998) we assumed that only 65% of all patients will comply with SSRI therapy. The estimated number of compliant user years of SSRI therapy was 9,160,123.

The prescription data show that the use of SSRIs is exponentially increasing after their introduction in 1987, while the number of prescriptions for other antidepressants is effectively constant between 1975 and 1998. We assumed that the steep increase in the total number of SSRI prescriptions between 1987 and 1997 is fully attributable to SSRI users who would not otherwise have received antidepressants medication. Our assumption reflects the general belief that SSRIs are thought to be safer for treating depressions because the drugs themselves cannot be easily used for suicide in contrast to other classes of antidepressants. We consequently attribute the full QALY gain (between baseline and 12 months) of 0.13 to each of the compliant SSRI user years. This gives a total gain from SSRI therapy in depressed patients of 1,196,541 QALYs. (Our analysis is not based on an assumption of superior efficacy of SSRIs over TCAs.)

Multiplying this figure by the opportunity cost of a QALY (£25,000) gives a monetary value of the health gain of £29,914m.

Kendrick *et al*. (2006) estimated the yearly costs per patient on SSRI therapy to be £87. Converting these to 2005 UK£ using the NHS pay and prices index gives an annual cost of £101.7 for SSRI treatment. Multiplying this figure by the number of users gives a total cost of £931m.

Further, we are likely to have been conservative in the inclusion of only six patient indication/intervention combinations. For example, we were unable to find appropriate evidence to include an estimate of the health gain from developments in case management practice. We have however included our estimate of all mental health research as the research investment and some of this may have led to beneficial interventions and to the study of conditions that we were not able to include. As for CVD, the assumption, in the absence of information on other interventions, is that on average the net benefits (in terms of health gains minus costs) from the provision of these non-analysed interventions are zero.

Estimates of the return to mental health research

Applying exactly the same methodology as for CVD we calculated the internal rate of return (IRR) on investment in mental health research. We used the annual estimates of research expenditure shown in Figure 8.4, and the annual estimates of health gains and costs summarised in Table 8.1. Specific estimates for mental health of the time lag between research and health effect of 12 years (range 9–14 years) and of the proportion of health gain attributable to UK research of 28% (range 10–60%) were applied.

This gave a best estimate of the IRR for mental health research of 7.0% and from a series of one-way sensitivity analyses the IRR ranged from a return that was less valuable than the research investment, up to returns of around 11.0%. A 'pessimistic scenario' (inevitably given the one-way sensitivity analyses) showed an even greater excess of the cost of the investment over the value of the net health benefit, whilst an 'optimistic scenario' showed an IRR of over 15%.

These results (see Table 8.2) do not show the same relationship to lag structure as was shown in CVD. This is explained by the fact that the net benefits we have measured were very low at the beginning of the period (1985 and subsequent years) but increased dramatically in the later years (2001–05). The longer time lags omit the earlier years (with small health gains) but include the much larger gains in the later years (see Annex to Chapter Seven). (This problem would be lessened if longer time series were available.) Otherwise the relationships and conclusions are similar to those for CVD. Here again, the results emphasise the importance of the assumptions regarding the proportion of the health benefit attributable to UK research. Our proxy indicator of the proportion of UK guideline citations from UK addresses showed greater variability in mental health and the sensitivity analysis using that range (10–60%) showed considerable variability.

These rates are better than the implicit rates for mental health in the earlier Australian study (Access Economics, 2003) but lower than those for CVD in this study. For mental health as for CVD, a best estimate GDP return of 30% (range between 20% and 67%) should be added to the net health benefit return calculated above to give an overall return to the public/charitable investment in mental health.

Table 8.2: Estimated IRRs (and net present values) for the health gain from mental health research

Assumptions	IRR	NPV (@ 3.5% discount rate)
Best estimate (central/best estimates as explained in text)	7.0%	£1,293m
Low estimate of research expenditure	10.8%	£1,904m
High estimate of research expenditure	3.7%	£74m
Low estimate of net health benefit	INV > net benefit	-£1,006m
High estimate of net health benefit	8.1%	£1,895m
QALY value of £20K	5.6%	£673m
QALY value of £30K	8.2%	£1,915m
14-year lag	7.8%	£1,756m
9-year lag	5.1%	£366m
10% of benefits attributable to UK research	INV > net benefit	-£551m
60% of benefits attributable to UK research	11.5%	£4,574m
'*Pessimistic scenario*': High research investment; low net benefit; QALY = £20K; 9-year lag; 10% attributable to UK research	INV > net benefit	-£2,465m
'*Optimistic scenario*': Low research investment; high net benefit; QALY = £30K; 14-year lag; 60% attributable to UK research	15.6%	£7,260m

So are the methods applicable to clinical areas other than CVD?

This test, applying our methods to mental health, emphasises that our bottom-up approach is data hungry and requires definition of a set of appropriate interventions and detailed evidence relating to the use of, costs of and benefits from them as compared to a counterfactual assumption. Each of these steps was more difficult than for CVD, and because of the less clear evidence base the results may well be more contentious, but the process was possible and the attempt was informative. We see no reason why the approach could not be applied in other areas too, but confidence in the results will depend on the quality of the data and other evidence available.

1 See www.dh.gov.uk/en/Researchanddevelopment/Researchanddevelopmentpublications/informationfromresearch/DH_4078384.

2 M Ogg, personal communication, 28 November 2007.

3 The NICE guidelines are available at www.nice.org.uk/guidance/index.jsp?action=byTopic&o=7281&set=true. 12 of the 14 guidelines that NICE has published in the field of mental health were chosen. The two not selected were Anxiety and Eating disorders as it is was felt these subject areas were too broad to provide useful data in the current context. The mental health NSF is available at www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4009598.

Chapter Nine

Our contribution, our conclusions and main reservations, and a research agenda

KEY POINTS

- The main contribution of this report is to have demonstrated a theoretically sound basis for empirically estimating the two main elements of the economic returns to medical research.
- The more specific original contributions in terms of both data and analysis are summarised.
- We stress that these estimates need to be treated with caution and explain the main caveats.
- We emphasise that our measure of return – the internal rate of return or IRR – is quite different to the benefit/cost ratios used in the Australian studies.
- We reiterate the main characteristics of our methodology (compared with other studies including the Australian studies), namely that it:
  - is based on detailed bottom-up estimates, rather than calculated top-down from temporal differences in mortality and morbidity
  - uses only observed historic data – not projections of what may happen in 20 or more years' time
  - nets off the health care cost necessary to deliver the health gains
  - uses a value of a QALY that reflects the opportunity cost in the NHS rather than a theoretical social willingness to pay.
- Finally we set out a research agenda to improve our understanding of key issues and to enable us in future to make better estimates of the returns to medical research.

The methodological contribution of our report

Overall we have provided a clear demonstration of an approach which provides an improved theoretical basis for empirically estimating the two main elements of the economic returns to medical research – firstly the returns in terms of the value of the health gained and secondly the considerable returns in terms of impact on GDP.

More specifically our main original contributions are to have provided:

- A consistent time series of estimates of UK public/charitable and private pharmaceutical industry expenditure on medical research in cardiovascular disease and mental health from 1975 to 1992, pieced together from a variety of sources.
- A clear conceptual framework to underpin the concept of 'spillovers' from publicly and charitably funded medical research, based on an original broadly scoped literature review.
- Estimates of the magnitude of spillovers in the UK from public and charitable medical research, based on existing literature, but calculated in two different ways: a two-step analysis of the relationship between public (and charitable) and private R&D and then of the relationship between private pharmaceutical R&D and GDP; and based on the economic literature estimating the social rate of return to public R&D, whether medical or not.
- A 'bottom-up' approach to estimating the health gain from research, developed for this study. This represents a significant improvement on earlier attempts to estimate the economic returns from research in that it is measured in terms of QALYs and it is driven by relatively hard evidence on the effects and costs of specific research-derived interventions, not from macro-level, temporal changes in mortality or morbidity.
- A 'successful' test of this approach in two disease areas: the analysis of the gains for cardiovascular disease was built up from evidence on 46 different patient indication/treatment combinations: that for mental health on six such combinations. These two areas had been chosen for the following reasons: cardiovascular disease on the prior assumption that there was more appropriate data and evidence, and mental health as a particularly challenging area to investigate, which was potentially likely to expose methodological and theoretical difficulties of the analysis.
- Analyses of UK clinical guidelines in the areas of cardiovascular disease (five guidelines) and mental health (12 guidelines), to provide indicators to inform the important issues of the lag between research expenditure and health benefits, and the attribution of benefits to UK (rather than worldwide) research.
- Computation of the internal rate of return (IRR) on past expenditures on research investment in the areas of CVD and mental health, allowing explicitly for the estimated time lags involved and the level of attribution to UK research, with sensitivity analysis around key parameters.
- A comparison of the IRRs on research investment from the value of the QALYs gained in these two areas, and with the new estimates of the IRR in terms of the GDP effect (which is not specific to individual disease areas).

Our conclusions on rates of return and our main reservations

All our work emphasises to us that our 'bottom-line' estimates of the rates of return need to be treated with extreme caution.

Nevertheless, our 'bottom-line' best estimate suggests that for CVD the IRR from the value of net health gains alone (ignoring GDP impacts) is around 9%. Most one-way sensitivity analyses place the IRR within the range of 6–14%, but in the 'pessimistic scenario' the value of the net benefit was less than the cost of the investment whilst in the 'optimistic scenario' the IRR was over 25%. For mental health, our best estimate of the IRR from net health gains was around 7%. Most one-way sensitivity analyses place the IRR within the range from a situation where the investment exceeded the net benefits to a positive rate of return of just over 11%. In the 'pessimistic scenario' again the research investment exceeded the net benefits, but in the 'optimistic scenario' we estimated a return of around 16%.

These rates of return are very sensitive to the lags between the research and the health gain. The relationship in these two particular cases is made more complex by the data limitations and artefacts of the differing time periods we were able to consider with different lag structures. However it is clear that in reality, other things being equal, the sooner the benefits can be realised the greater their value relative to the research investment. From a policy point of view this is crucial: a 'guaranteed' way to improve the return is to speed up each or any step in the various stages from basic research to the health gains that it can lead to, and so to reduce the time lag.

It is inevitable that these rates will be compared with the 'exceptional returns' that have featured in the international literature. As previously stated, the 'exceptional returns' for the USA were largely implicit rather than formally estimated as rates of return on a specific past investment, so direct comparisons are not possible (Funding First, 2000; Murphy and Topel, 2003). However, the two analyses from Australia are much more explicit (Access Economics, 2003, 2008). However, not only are the Access Economics methods of estimation different in the two studies and different again from our own, but crucially their method of measuring the return is peculiar, in that they express it as a ratio of the value of health benefits to cost (B/C ratio) or as the ratio of health benefits minus research costs to research costs (so called return on investment). We principally estimate the more meaningful internal rate of return: see Chapter 7 for a fuller explanation of this measure. Using IRR as our standard measure enables us to combine the value of the health gain and GDP returns and it can also be compared, if desired, with returns to other public and private investments.

Therefore, the first point to make is that our estimate of an IRR of 9% for CVD cannot in any way be compared with the estimate of an 'ROI' of 788% for CVD in the 2003 Australian study or of 117% for health R&D overall in the 2008 Australian study. If we take our own (discounted) base-case estimate of CVD benefits and of CVD research investment, the ROI, broadly as measured in the Australian study, would be 484%. But we do not accept that that is a meaningful figure.

So what are the key *substantive* differences in our estimates? The key differences between our methods and those of the Australian studies are:

- The lag structure: the 2003 Australian study compares expenditure and health gain in the same year; the 2008 study uses a 40-year lag. Our CVD best estimate uses 17 years; our mental health best estimate uses 12 years.
- Neither Australian study appears to net off the health service costs involved in achieving the health gain from improved services.
- Both Australian studies use high values for a life year: the first, based on an 'eclectic' calculation underpinned by the US estimates of individuals' 'willingness to pay' for a statistical life used AUS$150,000 per life year gained, and the second, based on a meta-analysis of studies, used AUS$267,000. We valued a QALY at £25,000 (approximately one-fifth of the most recent Australian value), a value that reflects the opportunity cost of the spending on R&D if it were instead to be spent directly on health care.
- Both Australian studies use a 'top-down' approach, starting with overall or disease-specific estimates of national changes in mortality and morbidity over time, and attributed 50% of these changes to health research. Moreover, to cope with the 40-year lag, these were projections of what morbidity/mortality might be in 2033 and later. Our study is 'bottom-up', aggregating health gains from observed changes in the use of specific evidence-based technologies.

We believe that our approach is both more logical and more firmly based in the reality of UK clinical practice and health policy. Nevertheless, we stress that the results should be treated cautiously. Our reservations and cautions relate both to what we have done and to what we have not done:

1 In terms of our analysis, our estimates of the investment and of the health gain both involve a series of assumptions and estimates, about which we have been explicit. Further research and data collation, more systematic reviewing of the evidence, and greater input from clinical specialists could no doubt improve some of these assumptions, and refine these estimates. But it is not self-evident from the lack of

sensitivity of the return to differences in the estimates of the QALY gain, that this effort would be worthwhile at this stage.

2 There are broader concerns that are more conceptual or require new or different lines of research. One example of a key conceptual issue relates to the net benefits of the continued and expanding use of interventions whose 'invention' and initial use clearly predate the period of research investment under consideration. Should these be excluded (as we have aimed to do) from the returns to this investment? Or might it be argued that subsequent research which fails to create, or demonstrate the value of, replacement interventions for these patients is effectively research confirming the continued value and appropriateness of the interventions produced initially by earlier research funding?

3 This leads into the whole issue of time lags and time structure, which needs further consideration and research. Many previous studies have avoided this issue. We have related research over a period of years to health benefits for treatments in (or initiated in) the same number of future years with a specific lag. It is arguable that if we are trying to estimate the impact (net benefits) of research funded during a particular period (for example 1975–85) as compared to a 'counterfactual' that the research funding would not have happened, it may be more appropriate to measure the gains over the lifetime of the use of the interventions that were 'invented' during the period of funding, and these *might* continue to be used for a period much longer than the period of the research investment. But equally one could argue that the research underpinning those interventions may go back many years or decades to key items of past facilitating research, as might be consistent with Comroe and Dripps (1976). Once we consider that it is simply the UK's contribution to research that we are interested in, then one might presume that most of the research would be undertaken by the rest of the world at some point, if it were not done in the UK, and that it is the timing of interventions and of their adoption that is affected by the UK's contribution not the existence of the interventions. Such alternative conceptualisations of the counterfactual will probably have much more impact than changes to specific data or assumptions within a particular conceptualisation.

We have estimated rates of return for cardiovascular disease and mental health that are of similar broad magnitudes, unlike the earlier Australian study for example. Is this error, chance, or can we assume that this is the order of magnitude in other areas? We do not believe it is error, but can certainly see how different assumptions in our analyses in one or both clinical areas could have produced different (and differing) results. But it may be chance that they are similar and we would need to replicate the approach in a number of areas to see whether the results are more broadly applicable: the default assumption should be that they are not.

It is also very important to stress what we have not done. We have estimated average returns in these two areas: we have not estimated marginal returns. This health gain analysis does not tell us what would have been the effect of spending a little more or less in the area. We may have been in the region of increasing or declining returns to marginal investment. Moreover, as the small print at the bottom of the financial investment advertisements reminds us, past performance is not an indication of future performance. Using an estimate of past returns, however accurate, does not, and cannot, provide a reliable indication of future returns. Thus research funders need to use the estimates provided in this volume with considerable care in justifying future returns from research expenditure.

Finally, we have only estimated the benefit, not examined how the benefits of research could be maximised in the future. To do this requires a very different approach, using studies focusing on much more specific research or on specific positive outcomes to research, to understand how research is translated and developed and where the scope for improving this process lies.

A future research and action agenda

Some of the caveats highlighted above are potentially amenable to future research. Starting from those, and our initial thoughts regarding other questions related to the value of UK public and charitable medical research, we propose that a future research agenda should include the following key areas:

Research funders need to use a standardised (and mapped) way of classifying research funding.

Compiling estimates of public and charitable research expenditure for the two disease areas proved to be problematic and consequently involved the use of numerous assumptions. Such estimates are unlikely to be improved by further analysis or research. In the future, if research funders wish to continue with this type of analysis, then it will be important to use a standard system of research classification and – just as importantly – to ensure that subsequent generations of systems can be mapped onto one another. The development of the UKCRC Health Research Classification System (HRCS) provides this opportunity. It would be similarly desirable to initiate collection, e.g. via surveys of companies, of data on private sector medical R&D in the UK using the same classification system.

Further research needs to be undertaken to understand the time lag between research expenditure and health gain.

It is clear from the analysis in Chapter 7 that the internal rate of return to medical research is sensitive to assumptions regarding the time lag before any benefits are realised. The IRR ranges from 9% to 19% for CVD research as the time lag is changed from ten to 25 years. We used a number of indicators to estimate what an appropriate time lag may be, but stress that these are only indicators and they have a number of potentially significant flaws. Given the importance of time lag in the overall IRR calculations, we would recommend that further research efforts are focused on this area.

The 'spillover' effects of public and charitable research expenditure on the national economy are substantial and need further, UK-focused, investigation.

As demonstrated in Chapter 6, public and charitable medical research expenditure does not only lead to health gain. Such investments have a knock-on effect on the investment decisions of the private pharmaceutical and health technology sector which in turn has a positive impact on other industries and the national economy. Much of the evidence base supporting this analysis is either old (from the 1960s and 1970s) or relates specifically to agriculture research. More recent analysis for medical research is largely based on US data. The size of the USA makes it an uncertain comparator for the much smaller UK economy and research community. Future research should be commissioned to understand and provide empirical estimates of the effects of medical research for the UK economy – ideally, at a disease specific level. This has two strands: (1) direct estimation of the magnitude of the relationship in the UK between public/charitable medical research and changes to national income; and (2) estimation of the strength of the stimulus to private R&D that public/charitable research provides in the UK, and of the effect of geographic proximity/distance on the strength of this relationship.

There is a need to improve our understanding of how basic research relates to clinical practice.

We have seen that research funders have used different definitions to map their expenditure at different times, making comparison difficult. An additional problem arising from definitions commonly used, however, is that a great deal of more basic research work can only be linked rather loosely or arbitrarily to specific disease areas, so there may be considerable benefit from basic research to disease areas other than that to which it has been 'allocated'. At present, the relationship between general, basic research work and clinical application is poorly defined, and future studies may benefit from a more nuanced understanding in this area. This might be explored in terms of specific case studies which could also throw light on the time lags involved.

Further research needs to be done to understand the flows of research between fields.

We have assumed that the flows of knowledge and influence are the same into and out of each subject area of research, and from each area of research into the cognate treatment area. There may be research areas that contribute more than they gain from other areas – for example cardiovascular research may contribute more to cancer care than cancer research contributes to cardiovascular care.

We have currently examined the overall rate of return for spending on health research in terms of health gain, not the marginal return.

Any changes in health research spending are likely to take place at the margin, so a deeper understanding of the payback for health research at the margins would be valuable from a policy perspective.

What scale and range of UK medical research would be most efficient?

In order to help public and charitable funders of medical research maximise the benefit per pound spent, research could usefully address the question of the presence and magnitudes of (dis)economies of scale or scope in medical research. Is research better concentrated on a few targets in a few research centres, or spread across a portfolio of either or both?

A deeper understanding of the international flows of knowledge and influence would be valuable.

We have estimated the extent of UK research influence on UK practice using guideline citation rates and UK share of publication production, and this figure is used in the estimate of overall rate of return. However, publication-based measures are only one measure of flows of knowledge and a more nuanced understanding of these knowledge flows could improve the accuracy of our estimate. It is also true that UK research is likely to have significant health benefits beyond the UK, not least in the developing world, so our current figure underestimates the global value of UK R&D.

Further research needs to be done to identify the contribution of UK public and charitable research in informing UK practice.

Currently we have looked only at the proportion of UK publications cited on clinical guidelines. But we need to examine a wider range of policy documents and we need to disentangle the contribution made by publications from public and charitable funders from that made by publications funded by the private sector.

Other disease areas could be examined.

In this study we selected our two examples of clinical areas for pragmatic and design reasons, to demonstrate and test our approach. Further studies could lead to further refinement and codification of the methods, and would indicate whether higher or lower returns prevailed in other areas.

If the approach were to be rolled out it will be important to select other disease areas carefully. One approach would be simply to cover the major clinical areas; an alternative would be to sample clinical areas using different criteria perhaps to test hypotheses about relative rates of return. Where future research is to cover all areas, it would have the advantage that any arbitrariness in allocating research spending to clinical areas, or the impacts of research in one clinical area on treatment of patients in another disease area, would be balanced out.

Research on the relationship between national clinical guidelines and national research investment.

In this study we have placed quite a lot of importance on guidelines as a link between research and practice. It would be interesting and useful to look more deeply in an international study on the extent to which guidelines (and their quality, relevance, acceptance by practitioners and impact) are related to the existence of locally generated research or whether good (local) guidelines simply require access to a good world literature.

The importance of local research in terms of absorptive capacity.

We noted earlier the importance of absorptive capacity in relation to firms undertaking research and in our work we have for some time argued that one of the benefits of having a research capacity in the UK health care system is that it helps the system to absorb health research undertaken anywhere. Apart from one study mentioned in the annotated bibliography this remains an area primarily of speculation and further research to test this would be very valuable, particularly to the health care system and National Institute for Health Research.

What are the *global* health benefits from UK medical research?

In our study we did not attempt to measure the health gains, net of health care costs, achieved in the rest of the world as a result of UK medical research. These are potentially many times the scale of the net health gains achieved for the UK population alone. A study referring to health care practice in other major population centres and its links to UK medical research would address this.

Annex to Chapter Two

Annotated bibliography

Introduction

This selective list of key literature focuses on publications that have key **methodological** points relevant for the assessment of the economic returns from medical research. It is not intended to be a comprehensive review of previous studies of the economic returns from health research as this was contained in the review conducted for the WHO (Buxton *et al.*, 2004: see first publication on the list below).

The bullets below outline some of the main issues covered in this current list, especially ones covered by more than one publication:

- the ways in which we should value the benefits from health research
- the direction of analysis when trying to establish the links between (UK) research and health gain, i.e. should it be backwards from health gain to the research, or forwards from research to health gain (and other possible benefits)
- overlapping with this is the question of how far our aggregate totals should be based on building up from more disaggregated data.

Publications on the issues in general

1 Buxton M, Hanney S, Jones T. Estimating the economic value to societies of the impact of health research: a critical review. Bull WHO 2004;82:733–9.
This paper contains a review of previous literature. It highlights the need to consider three steps: the inputs in terms of resources spent on research; accurately ascribing the impact of the research; and appropriately valuing the impact. Four possible ways of valuing the research are identified: direct cost savings to the health service; the human capital approach of valuing the indirect cost savings that arise when better health leads to the avoidance of lost production; assessing the intrinsic value of health gain by placing a monetary value on a life; and the gains to the economy in terms of product development and consequent employment and sales. The paper forms a starting point for the approach set out in our proposal for this project, but the proposal had some specific emphases. First, the suggested ways of valuing the benefits from health research concentrated just on the third category (the intrinsic value of the health gain) and the final category (product development etc). Second, greater importance was given in the proposal to issues such identifying the costs of the health service.
www.who.int/bulletin/volumes/82/10/733arabic.pdf

2 Sussex J (ed.). Improving Population Health in Industrialised Nations. London: OHE; 2000.
Chapter 4 by Mackenbach provides a concise presentation of three key contributions (by Thomas McKeown in 1976, Johan Mackenbach and John Bunker) that use very different methods (and different directions of analysis) to assess how much of health improvement over the long term can be attributed to health care in total, as opposed to improved hygiene, nutrition, etc. It provides references to the key sources by the original authors and describes how they all come to a figure of less than 20% for the historical contribution made by health care. The same book contains a chapter (1) by Sussex and Yuen, updating the McKeown analysis. This highlights the crucial point about the significant fall in mortality from CVD since McKeown was writing.

3 Sussex J. Estimating Pharmaceutical Companies' Value to the National Economy: Case study of the British pharma group. London: OHE; 2007.
This OHE Briefing describes the economic rent method for valuing the contribution of R&D based pharmaceutical companies.

4 Mushkin S. Biomedical Research: Costs and benefits. Cambridge, Mass: Ballinger Publishing Company; 1979.
Mushkin presented a contemporary challenge to McKeown's analysis claiming his method was "deficient" and she suggested that research-based advances in technology were responsible for about 30% of the improvements in mortality from 1900 to 1975. Using the human capital approach of valuing health gains in terms of the value of production that is no longer lost due to morbidity and premature mortality, Mushkin attempted to calculate the value to the USA of all its health research. She estimated the economic value of the total reductions in mortality and morbidity between 1930 and 1975, estimated the value of the share caused by biomedical research, and after taking away the cost of the research produced a rate of return of 47%.

5 Funding First. Exceptional Returns: The economic value of America's investment in medical research. New York: Lasker Foundation; 2000.
The *Exceptional Returns* report summarises various contributions to show how by producing estimates for the value of a life based on willingness to pay (WTP) experiments in labour economics a very large figure can be produced for the value of the reductions in mortality in the US population, especially in the CVD field ($1.5 trillion annually from 1970 to 1990). The authors suggest that about one third of the total gain is the result of medical research that led to new drugs and treatment protocols and some of the remainder was attributed to changes in public policy and individual behaviour that depended on research. The report draws on various papers

which were subsequently written up as the book below (6) edited by Murphy and Topel.

www.laskerfoundation.org/advocacy/pdf/exceptional.pdf

6 Murphy K, Topel R (eds). Measuring the Gains from Medical Research: An economic approach. Chicago: University of Chicago Press; 2003.
The main book describing the detailed work first presented in the Funding First report, *Exceptional Returns* (see above). Whilst the analysis in each chapter is very rich, it is perhaps unfortunate that the introduction is not very detailed and there is no proper conclusion to pull the various contributions together. It is also noteworthy that the bibliography makes very little, if any, reference to key analyses from the past such as that by Selma Mushkin.

7 Lichtenberg F. Pharmaceutical innovation, mortality reduction and economic growth. In Murphy and Topel (2003; 6 above). pp. 74–109.
This chapter by Lichtenberg estimates the social rate of return on pharmaceutical investment in research (in terms of the value of additional life years generated) is around 67%. Whilst this chapter fits well into Lichtenberg's wider stream of research on related topics it is not particularly well integrated into the rest of Murphy and Topel's book.

8 Access Economics. Exceptional Returns: The value of investing in health R&D in Australia. Canberra; 2003.
This Australian replication of the Funding First study uses the same value for a life to estimate the return on Australian health R&D. It is based on improvements in lifespan which combine reductions in specific mortality and morbidity rates for a range of illnesses. The base-case assumption is that R&D is responsible for 50% of the improvements in healthy lifespan, and that Australian R&D contributes 2.5% of the total gains, this being the percentage of global R&D undertaken in Australia. The study leaves unresolved difficulties. It uses disability-adjusted life years (DALYs) to allow for gains in mortality and morbidity; this leads to the suggestion that because there is a decline in DALYs in the mental health field, there is negative value to the measure of health 'gains' from mental health research.

9 Access Economics. Exceptional Returns: The value of investing in health R&D in Australia II. Canberra; 2008.
This report updates the one above using new figures and a somewhat revised methodology. The value of a statistical life year has been increased to AUS$266,843 (at 2008 prices) based on a new meta-analysis of studies and the Australian contribution to world R&D outputs increased to 3.04% based on more recent bibliometric data on clinical research. Most fundamentally, the analysis now deals with the issue of the lag between R&D spending and the health benefits. Unlike the previous study it does not provide figures for the returns for individual fields.

www.accesseconomics.com.au/publicationsreports/search.php?searchfor=exceptional+returns&from=0&search=Go

10 McGuire A, Raikou M. Inferring the Value of Medical Research to the UK. LSE Health Working Paper 5/2007. London: LSE; 2007.
Broadly replicates the methodology described in Murphy and Topel to the UK. Produces a large figure of £2.6 trillion as the net gain for 1970–2000, but attributes all the improved life expectancy to medical R&D and acknowledges but does not seem to calculate either the contribution from other factors that led to improved life expectancy or the percentage of the R&D impact that comes from UK research.

www.lse.ac.uk/collections/LSEHealth/pdf/LSEHealthworkingpaperseries/LSEHWP5.pdf

11 Johnston SC, Rootenberg JD, Katrak S, Smith WS, Elkins JS. Effects of a US National Institutes of Health programme of clinical trials on public health and costs. Lancet 2006;367:1319–27.
This paper differs from the approaches used in the Funding First and Access Economics work. It adopts a hybrid approach to assess the costs and benefits of phase III randomised trials funded by the US National Institute of Neurological Disorders and Stroke. Yearly total incremental net benefits of the programmes are calculated by combining trial costs and treatment costs with a monetary value for the QALYs gained from the implementation of the trial findings. The study uses a value of a QALY based on the US GDP per capita, suggesting that this reflected "the average yearly economic productivity of a US resident, regardless of employment or age". The study also takes into account any savings made as a result of implementing the trial findings. This work is an advance on many previous approaches but has the weakness of giving insufficient attention to other research that was reporting about the same time.

12 Cutler D, Rosen A, Vijan S. The value of medical spending in the United States, 1960–2000. NEJM 2006;355:920–7.
This attempt to value medical spending in the USA 1960–2000 does not really seem explicitly to discuss the value of research. This is despite Cutler being one of the Funding First team and using somewhat similar approaches to the Funding First work, including using CVD as one of its main examples and the value of a statistical life. They claim that at least 50% of the life expectancy gains since 1950 are due to medical advances, but discuss the increased expenditure on health care and not the role of research.

http://content.nejm.org/cgi/content/abstract/355/9/920

13 Luce B, Mauskopf J, Sloan F, Ostermann J, Paramore LC. The return on investment on health care: 1980–2000. Value in Health 2006;9:146–56. (See also the accompanying editorial: Buxton MJ. Substantial returns to health care spending: but do we spend too little or too much? Value in Health 2006;9:144–5.) The paper concludes that the value of improved health in the US population in 2000 compared with 1980 significantly outweighs the additional healthcare expenditure. (One of the four conditions for which detailed analysis is undertaken is heart attacks.) As Buxton points out in the editorial there is a danger that the returns in the form of health improvements are claimed by those estimating the returns on research and those estimating the returns to healthcare services.

14 Salter A, Martin B. The economic benefits of publicly funded basic research: a critical review. Research Policy 2001;30:509–32.
This review identifies a range of benefits to an economy from publicly funded research (of any kind, not just medical). While finding that none of the included studies provided a simple and comprehensive model, it commends the progress made by Mansfield (see 15 below) in measuring the benefits from basic research.

15 Mansfield E. Academic research and industrial innovation. Research Policy 1991;20:1–12.
Mansfield E. Academic research and industrial innovation: an update of empirical findings. Research Policy 1998;26:773–6.
In these papers Mansfield surveyed large US corporations in seven industries for data concerning the proportion of each firm's new products and processes that could not have been developed, without substantial delay, in the absence of recent academic research. Using figures for the value of sales of research-based products, and knowledge of the level of spending on basic research in the developed countries, he estimated a worldwide social rate of return for research conducted in 1975–78 of 28%. The pharmaceutical industry was the one most dependent on basic academic research.

16 Hanney S, Gonzalez-Block M, Buxton M, Kogan M. The utilisation of health research in policy-making: concepts, examples, and methods of assessment. Health Research Policy & Systems 2003;1:2.
Reviews previous work on how health research can impact on policy, discusses possible ways in which the research contribution to policymaking can be assessed, and shows how research impact on health policy can be a key step towards achieving wider health and economic gains. Depending partly on the type of policy being made, and the type of research involved, various factors can impinge on policymaking in addition to research. These include: interests, values, established positions within institutions and personal ambition. The role that research can play is also influenced by institutional arrangements and capacity to absorb research that can be assessed through the 'receptors and interfaces' model.
www.health-policy-systems.com/content/pdf/1478-4505-1-2.pdf

17 Stoneman P. Government spending on Research and Development in the UK. Fiscal Studies 1999;20:223–59.
Explores the extent of UK government spending on R&D placed in its recent historical context. Also considers patterns of expenditure, the aims behind it and the pay-off. Shows that in real terms in the ten years to 1998 the UK government reduced its expenditure, but this was mostly in defence R&D, and the percentage on health R&D increased.

18 Silverstein S, Garrison H, Heinig S. A few basic economic facts about research in the medical and related life sciences. FASEB Journal 1995;9:833–40.
The authors collated data from many previous studies showing the benefits to the USA from medical research. Inevitably there is considerable inconsistency in the approaches used in the original studies: some concentrate on claimed direct cost savings to the health care system and some include indirect cost savings in the form of reductions in the level of earnings lost (i.e. human capital approach). Of the claimed $69 billion annual savings (discounted to a present level in 1995 of $1.1trn), most came from mental health ($34bn) with CVD second ($12bn).

19 Callon M, Bowker G. Is science a public good? Fifth Mullins Lecture, Virginia Polytechnic Institute, 23 March 1993. Science, Technology, & Human Values 1994;19:395–424.
A complex discussion on the nature of public goods that highlights all the investment and accumulated capabilities (skills, equipment, learning processes etc.) that might be needed by others to be able to make use of knowledge. This raises doubts in practice about viewing knowledge as a pure nonrival good.

20 Belkhodja O, Amara N, Landry R, Ouimet M. The extent and organizational determinants of research utilization in Canadian Health Services Organizations. Science Communication 2007;28:377–417.
Suggests that research experience is one of two factors with the greatest impact on research utilisation, especially in regional health authorities and hospitals. (The relevance of this is that it can be argued that funding research widely within a health care system helps develop the capacity of that system to absorb the findings of research from wherever they may come.)

21 Grant J, Cottrell R, Cluzeau F, Fawcett G. Evaluating "payback" on biomedical research from papers cited in clinical guidelines: applied bibliometric study. BMJ 2000;320:1107–11.
As part of the examination of the papers cited in UK clinical guidelines the team analysed the location of the authors of the cited papers. 25% were based in the UK whereas only about 10% of global biomedical papers (in ISI journals) are from the UK: "the preferential citing of UK papers may provide good evidence for supporting a local science base".

22 Jones T, Hanney S, Buxton M, Burns T. What British psychiatrists read: Questionnaire survey of journal usage among clinicians. British Journal of Psychiatry 2004;185:251–7.
One of a series of studies showing that British clinicians (in this case psychiatrists), not surprisingly, disproportionately read UK-based journals to inform their clinical practice. Similar findings are reported from other countries. The series of papers also shows a natural bias towards UK research being published in UK journals.

23 UK Evaluation Forum. Medical Research: Assessing the benefits to society. London; 2006.
Three bodies (The Academy Medical of Sciences, the Medical Research Council and the Wellcome Trust) came together to support the UK Evaluation Forum and this report led to them funding the current project. The report reviewed previous work and concluded: "We recommend that research funders should support research to assess the economic impact of UK medical research, which should include critiques of existing economic approaches".

Annex to Chapter Three

Breakdown of expenditure on cardiovascular research (in £m), by year, 1970–2005

	UK health expenditure – organisations						Cardiovascular – activity funding					Cardiovascular – support funding			Pharma industry	Grand total exc. pharma.	Grand total exc. pharma. deflated
Date	MRC[1]	Wellcome Trust[2]	BHF	NHS	DH (not NHS)	FC-Health	WT	MRC	BHF	DH–A	Total	DH–I	Funding Councils	Total			
1970							0		0		0						
1971							0		0		0						
1972	29	5	0				0		0		1						
1973	30[3]		0		18[4]		0		0		1						
1974	36	5	0				0		0		1						
1975	**47**	**4[5]**	**1**	**137[6]**	**27[7]**	**84[8]**	**0**	**3[9]**	**1**	**5**	**9**	**10**	**8**	**17**	**12**	**26**	**144**
1976	**52**	**4**	**0**	**144**	**29**	**87**	**0**	**3**	**0**	**5**	**9**	**10**	**8**	**18**	**16[10]**	**27**	**132**
1977	**54**	**6**	**1**	**151**	**30**	**91**	**0**	**3**	**1**	**5**	**9**	**11**	**8**	**19**	**20**	**29**	**121**
1978	**62**	**6**	**1**	**158**	**31**	**95**	**0**	**4**	**1**	**6**	**11**	**11**	**9**	**20**	**24**	**31**	**116**
1979	**74**	**10**	**1**	**166**	**33**	**99**	**0**	**5**	**1**	**6**	**12**	**12**	**9**	**21**	**31[11]**	**33**	**110**
1980	**93**	**10**	**2**	**174**	**34**	**103**	**1**	**6**	**2**	**6**	**15**	**13**	**9**	**22**	**38**	**37**	**102**
1981	**107**	**12**	**2**	**183**	**28[12]**	**107**	**0**	**6**	**2**	**6**	**14**	**13**	**10**	**23**	**44**	**37**	**93**
1982	**113**	**12**	**3**	**191**	**29**	**112**	**1**	**9**	**3**	**6**	**18**	**14**	**10**	**24**	**54**	**42**	**99**
1983	**120**	**17**	**4**	**201**	**27**	**116**	**1**	**10**	**4**	**6**	**21**	**14**	**10**	**25**	**61**	**46**	**103**
1984	**124**	**17**	**4**	**210**	**26**	**121**	**1**	**11**	**4**	**6**	**22**	**15**	**11**	**26**	**72**	**48**	**103**
1985	**129**	**24[13]**	**6**	**221**	**24**	**126**	**1**	**11**	**6**	**6**	**24**	**16**	**11**	**27**	**82**	**51**	**104**
1986	**138**	**29**	**6[14]**	**231**	**49**	**131**	**1**	**11**	**6**	**9**	**26**	**17**	**12**	**28**	**92**	**55**	**108**
1987	**150**	**35**	**7**	**242**	**47**	**137**	**1**	**11**	**7**	**9**	**28**	**17**	**12**	**30**	**100**	**58**	**109**
1988	**163**	**68**	**8**	**254**	**50**	**142**	**2**	**14**	**8**	**9**	**33**	**18**	**13**	**31**	**111**	**65**	**113**
1989	**191**	**43**	**8[15]**	**266**	**58**	**157[16]**	**1**	**14**	**8**	**10**	**33**	**19**	**14**	**33**	**144**	**67**	**109**
1990	**202**	**54**	**10**	**279**	**71**	**187**	**3**	**14**	**10**	**11**	**39**	**20**	**17**	**37**	**171**	**76**	**115**
1991	**228**	**72**	**15**	**293**	**59**	**212**	**5**	**15**	**15**	**11**	**46**	**21**	**19**	**40**	**186**	**86**	**123**
1992	**251**	**92**	**13**	**307**	**55**	**208**	**6**	**17**	**13**	**11**	**47**	**22**	**19**	**41**	**213**	**88**	**121**
1993	288	167[17]	15		61	190[18]	17		15		32						
1994	298	242			59	186	13		0		13						
1995	305	230		347	56	187	11		0		11						
1996	309	168		408	62	186	9		0		9						
1997	321	222		401	59	205	13		0		13						
1998	316	212		403	60	222	18		0		18						
1999	345	354		410	63	243	30		0		30						
2000	368	480		423	55	250	36		0		36						
2001		388		445	59	257	26		0		26						
2002		419		461	53	280	47		0		47						
2003				533	60	306			0		0						
2004				575	54	317			0		0						
2005				586	48	327			0		0						

1 Data provided by the MRC.

2 Data provided by the Wellcome Trust.

3 Maddock (1975) estimates MRC expenditure in 1973/74 to have been £24.8m.

4 Figure taken from Maddock (1975).

5 Data for 1972–84 was provided in two-year bands; we have taken the average for annual estimates.

6 Data for 1975–92 was estimated by back-casting the figures provided for 1995–2005 using an exponential function.

7 Data for 1975–80 based on projecting data for 1973 and 1981–2005 using a linear function.

8 The 1975 to 1989 time series is estimated from a back projection of the 1989 to 1992 UFC data for biomedical subjects for the UK, and the 1993 to 2005 HEFCE QR data for biomedical subjects in England. The latter is then inflated by circa 12% to make a UK-wide estimated.

9 Assumed.

10 Data for 1976 and 1977 interpolated using figures for 1975 and 1978.

11 Taken as the average of the preceding and following points.

12 Data for 1981–85 entered by hand from Annual Review of Government-Funded R&D (Cabinet Office, 1984).

13 Data for 1985–87 was estimated using an exponential function to project funding for the period 1975–84, for which we were provided with data.

14 BHF figures for 1986–88 were estimated by projecting those for 1979–85 using a linear function.

15 BHF grant funding for 1989–92 was provided for a separate project currently being undertaken by RAND Europe.

16 Numbers for these years are taken from UFC figures and are UK-based.

17 Calculated by taking the average of figures for 1992 and 1994.

18 From 1993 onwards, data is provided by HEFCE and is England-based.

Annex to Chapter Four

More detailed, qualitative analysis of the importance of UK research in UK guidelines

We aimed in this report to explore illustrative examples of the quantitative data in a more detailed and qualitative way. This Annex describes such a detailed approach in relation to the quantitative data described in Chapter 4 on the nationality of research referenced in guidelines. In Chapter 4 we used quantitative bibliometric analysis of the research papers in guidelines to inform the estimate of the proportion of the health gain attributable to UK research. This Annex describes a more detailed and qualitative analysis of the references in one of the NICE guidelines for which the proportion of UK references is reported in Chapter 4.

Various ways of undertaking this more detailed analysis were considered. One possible approach would have been to develop a scoring approach drawing on our earlier review of ways of analysing the importance of a citation to the paper in which it was cited (Hanney *et al.*, 2005, 2006). That approach would have combined some judgement about the importance of the specific citation to the guideline and a more detailed quantitative analysis involving how many papers were cited to support a specific point in the guidelines and counting the number of times a paper was cited in the guideline. This approach, however, was rejected as being too mechanistic.

Instead, for this Annex a more wide-ranging and less mechanistic approach was adopted in relation to the hypertension guideline produced for NICE by the Royal College of Physicians – *Hypertension: Management in adults in primary care; pharmacological update* (National Collaborating Centre for Chronic Conditions, 2006). This guideline was selected as the most feasible on which to trial an approach to qualitative analysis. It is probably the most focused of the CVD guidelines listed in Chapter 4 and has the fewest references. It is a 2006 update of a previous 2004 guideline but it concentrates solely on pharmacological interventions.

Of the 79 references in this updated guideline, the first 42 papers describe the 20 trials included in the review of pharmacological interventions. The remaining 36 references (plus one duplicate) cover a range of issues, including: trials that were excluded; and the cost and utility data used in the construction of the guideline. We first analyse the list of 20 trials (42 papers) included in the guideline and then consider the remaining papers. We use the reference numbers used in the guideline.

The papers from the 20 trials drawn on in the guideline

Nine of the 20 trials have been identified as having at least some UK involvement. They are listed on Table A4.1 below in approximate order of level of UK involvement (many of them were international studies).

The dates of the relevant papers are also given. From these 20 trials the team constructing the guideline attempted to make 10 head-to-head drug comparisons, but there was only evidence from these trials for nine of the comparisons. These comparisons are important as they form a key element in the recommendations made in the guideline. Details of the comparisons to which the UK trials contributed are also given in Table A4.1.

The table highlights the complexities. The main non-pharma funding bodies in the UK were probably responsible for just two studies in this guideline that is explicitly on pharmacological interventions. But in total nine out of 20 of the included trials had some UK involvement (as did 14 out of 42 papers in which they are described) but to varying degrees:

- two of the 20 trials (two of the 42 papers) were conducted and funded from the UK
- one trial (two papers) had a UK lead author in an international study funded by the pharmaceutical industry
- one trial (two papers) had a UK co-author in a European study funded by the EU
- one trial (one paper) had more authors from the UK than anywhere else but was led from Sweden and funded by the pharmaceutical industry
- four of the trials (seven papers) had at least one UK co-author in an international study funded by the pharmaceutical industry.

UK research played some part in six out of nine comparisons, but the two solely UK MRC-funded studies together constituted two-thirds of the data for the first head-to-head drug comparison (and the third paper had UK pharma involvement). The UK-led INSIGHT study constituted one of five studies (and less than 20% of the data) for the seventh comparison. It is also worth noting that the two solely UK MRC papers were early papers and therefore perhaps were influential on some subsequent work and of all the papers with at least one UK address; the data from CWTS show that these two were the papers cited most often (1,700 times) and fourth most often (1,154 times) respectively. It is also worth noting that the data from CWTS reported in Chapter 4 suggest that the papers on the hypertension guideline are cited much more often than the average for the field.

The recommendations in the guideline drew on a detailed analysis that incorporated the head-to-head drug comparisons, cost data, utilities data etc. Therefore the recommendations are not directly referenced. It is possible, however, to see that some of the main recommendations seem to have drawn on the evidence from the UK trials. In particular, comparisons one and six seem influential in the first recommendation that "the first choice for initial therapy should be either a calcium-channel blocker or a thiazide-type diuretic" (p. 17).

Table A4.1: The trials included in the hypertension guideline that have some UK involvement, and the comparisons to which they contribute

Trial/papers – refs with some UK involvement	Location of authors, in author order	Main funder	Role of the study in the head-to-head comparisons undertaken in the guideline analysis
MRC (paper 34-1985)	UK	MRC	Constituted one of three trials in the first comparison (between beta blockers [BBs] and thiazide-type diuretics). Meta-analysis showed no significant difference between two drugs in terms of mortality. This trial (but not others) found higher incidence of stoke associated with BBs. This trial and MRC-0 found BBs associated with more withdrawals.
MRC-0 (paper 35-1992)	UK	MRC	Constituted one of three trials in the first comparison (between BBs and thiazide-type diuretics). Meta-analysis showed no significant difference between the two drugs in terms of mortality. This trial (but not others) found higher incidence of MI associated with BBs. This trial and MRC found BBs associated with more withdrawals.
INSIGHT (papers 30-2000, 31-2001)	UK, France, Netherlands, Italy, Israel, Spain	Bayer	Constituted one of five trials in the seventh comparison (between calcium-channel blockers [CCBs] and thiazide-type diuretics). Meta-analysis showed no difference for mortality, MI or stroke. CCBs associated with higher heart failure, but (from this and two other trials) lower diabetes.
ASCOT (paper 22-2005)	Sweden, UK (most authors), Norway, USA, Iceland, Denmark, Finland, Ireland	Pfizer	Constituted one of three trials in the sixth comparison (between CCBs and BBs). Meta-analysis showed no difference in mortality or MI but CCBs reduced incidence of stroke. Was the sole study to show CCBs associated with reduced incidence of diabetes.
SYST-EUR (papers 1-1991, 2-1997) [one other paper (3-1996) was on a sub-group study not including UK]	Belgium, eight other European countries including UK, plus Israel	EU	Constituted one of three trials included in the eighth comparison (between antihypertensive drug and placebo for ISH). Meta-analysis showed antihypertensive drug therapy associated with reduced incidence of stroke and MI but no significant difference in mortality rates.
VALUE (paper 26-2004)	USA, Norway, Switzerland, USA, UK, Italy	Novartis	Only trial (therefore Level 11 evidence) in fourth comparison (between antiotensin-11 receptor antagonists [ARBs] and CCBs). ARBs associated with higher incidence of MI. No significant difference for stroke reduction, mortality or heart failure.
ELSA (paper 28-2002)	Italy, USA, Germany, Sweden, Spain, UK, France	GSK, Italy	Constituted one of three trials in the sixth comparison (between CCBs and BBs). Meta-analysis showed no difference in mortality or MI but CCBs associated with reduced incidence of stroke. Much smaller study than other two in sixth comparison.
LIFE (papers 19-2002, 20-2002 and 21-2002). Paper 16-2004 was a sub-group study. Four other papers (14, 15, 17, 18) had no UK authors	Sweden, USA, UK, Norway, Finland, Denmark	Merck	Constituted the only trial in the third comparison (between ARBs and BBs. No differences in MI, revascularisation procedures, heart failure or angina. But ARBs associated with reduced incidence of stroke and diabetes, and fewer study drug withdrawals.
HAPPHY (paper 29-1987) [but only UK address is ICI not academic]	Sweden, UK, Germany, Finland	AB Astra and ICI	Constituted one of three trials in the first comparison (between BBs and thiazide-type diuretics). Meta-analysis showed no significant difference between the two drugs in terms of mortality.

The remaining papers in the guideline

Moving on from the 42 papers in the 20 included trials, a further nine papers (43–51) relate to five excluded trials (most of which had been included in the previous 2004 version of the guideline). One of these trials (papers 43, 44) was led from the USA but had one UK author and was funded by the pharmaceutical industry.

Two papers (52, 53) describe sub-studies of the LIFE trial; both had one UK co-author on this US-led, Merck-funded study.

Eight further papers (54–61) consider the evidence for patients' age and ethnicity. Six were entirely UK papers (55, 56, 58–61) and another paper (57) had an incomplete reference but is linked to the ASCOT trial, which involved more UK authors even though it was led from Sweden. Funding, from a pharmaceutical company, was acknowledged on just one of these papers (56), but presumably the others were most likely to have relied on some element of funding from UK public sources such as the authors' hospitals or universities. Paper 60 was a review and paper 61 was itself a guideline from the British Hypertension Society published as a journal article (it appears twice, as references 61 and 63).

In the Appendices four papers (62, 64–66) describe the cost data used by the Guideline Development Group to conduct their economic analysis. The NICE reference case for NICE guideline development states that "costs should be measured from an NHS and personal social services perspective". Not surprisingly all four papers

were from the UK, with two being funded by the Health Technology Assessment Programme, which is part of the Department of Health NHS R&D Programme.

Eight papers (67–74) were noted that had estimated drug-related adverse events and quality of life but none included data in a form suitable for estimation of utilities. Of these just two had UK addresses. Paper 67 was a UK-led international study funded by Hoffmann-La Roche. Paper 74 was a Belgium-led study funded by Menarini International.

Finally, five further papers (75–79) provide some utility data but just one (79) was a UK study, with entirely UK addresses and funding from the MRC and the NHS.

Comparisons with the quantitative data from CWTS

As reported in Chapter 4, the quantitative data from CWTS show that 88% of the papers cited on the hypertension guideline were analysed and the proportion of UK addresses of all the authors was neither the highest nor lowest among our sample of guidelines. More detailed analysis of the data reveals that at 14.3% the proportion of UK addresses on this guideline was the second lowest. It also shows that the proportion of UK addresses, most unusually, was third rather than second, with Sweden being second to the USA with 18.5% of the addresses.

Some conclusions and implications for our analysis of the contribution made by UK research

The more detailed resource-intensive analysis in this Annex is inevitably richer than the bibliometric analysis described in Chapter 4. For example, the bibliometric analysis cannot distinguish between trials included in the guideline and those trials that are listed as being excluded but nevertheless appear in the reference list. But the key question is what we can learn from this greater detail about the nature of the contribution made by UK research.

- The detailed analysis highlights the complexity beneath the seemingly straightforward issue of the proportion of papers with authors with UK addresses. There are varying degrees of UK involvement in the research. A few studies are clearly fully funded by traditional UK funders and conducted solely in the UK. But more of the trials cited on this guideline, which unusually was exclusively on pharmacological interventions, are international with varying degrees of UK involvement and often funded by the pharmaceutical industry.
- Chapter 4 provides various possible figures that could be used for the contribution from UK research, including: 10% (UK contribution to global research) and 17% (average proportion of UK papers on the guidelines). For this hypertension guideline UK research probably constitutes well over 10% of the research in the key trials (i.e. two out of 20 trials were solely UK, and they were described in important papers, and there was some contribution to another seven out of the 20). One of the nine head-to-head drug comparisons relied heavily on UK research and there was some contribution to five others. UK research on costs is the only research evidence used in this field and is of major importance because it provides the most relevant data for the context within which the guideline will be applied.

Annexes to Chapter Five

Annex 5A: Studies used to generate QALYs gained for each intervention in each patient group

Table A5A: Summary of studies used to generate QALYs gained for each intervention in each patient group

Patient groups/interventions	QALYs gained	Patients	Comparator	Country	Time horizon	Source	Notes
Treatment of acute MI:							
Community resuscitation	0.220	Patients with cardiac arrest of cardiac origin	No resuscitation	Norway	Up to 24 years	Naess and Steen (2004)	Assume HRQOL of 0.6 from study based on lowest value in Ward *et al.* (2007). 1,066 of 2,831 cardiac arrest patients survived from ROSC until hospital admission for a mean time of 532 days. Assume all would have died without resuscitation.
Hospital resuscitation	0.619	Patients with cardiac arrest of cardiac origin alive at arrival at hospital	No resuscitation	Norway	Up to 24 years	Naess and Steen (2004)	Assume HRQOL of 0.6 from study based on lowest value in Ward *et al.* (2007). 269 of 1,066 cardiac arrest patients alive at admission survived for a mean time of 6.13 years. Assume all would have died without resuscitation.
Thrombolysis	0.058	Patients with chest pain with electrocardiographic signs that were typical of myocardial infarction	No thrombolytic therapy	The Netherlands	1 year	Vermeer *et al.* (1988)	Table 3, 'Quality adjusted data' for 'All patients'.
Aspirin	0.213						Cannot find studies comparing aspirin versus usual care; use same estimates as for Secondary prevention of CHD post-MI (this was also assumed in the IMPACT study).
Clopidogrel	0.077	Patients with acute coronary syndromes	Standard therapy	UK	Lifetime	Main *et al.* (2004)	Table 29, p. 43.
Primary angioplasty	0.084	Patients with acute myocardial infarction	Thrombolysis	UK	6 months	Hartwell *et al.* (2005)	Table 18, p. 38.
Secondary prevention of CHD post-MI:							
Aspirin	0.213	Patients aged 35–84 years with coronary disease and who survived the first month with it	No treatment	USA	Up to 25 years	Gaspoz *et al.* (2002)	Table 2. QALYs gained = 121,768,000 ('current use of aspirin') minus 115,535,000 ('zero utilisation') in a population of 'about 6.8 million people' are estimated to have CHD, and each year about 700,000 to 900,000 new cases are estimated to occur.
Clopidogrel	0.038	Patients with prior occlusive vascular events	Aspirin	UK	Lifetime	Karnon *et al.* (2005)	Table 4, 'Baseline' analysis.
Beta blockers	0.142	Patients discharged following MI, without absolute contraindications for beta blocker use	No treatment	USA	20 years	Phillips *et al.* (2000)	Table 3, QALYs gained = 42,000 ('Current' minus 'Zero' beta blocker use) (Size of single cohort = 296,613, online technical appendix 8)
ACE inhibitors	0.180	Survivors of myocardial infarction with an ejection fraction <=40%	Placebo	USA	4 years	Tsevat *et al.* (1995)	Table 4, 'Limited benefit model' for patients age 60.
Statins	0.103	Patients who have had coronary events	No statin therapy	UK	Lifetime	Ward *et al.* (2007)	Table 63, p. 101, figures for men aged 85.
Warfarin	0.006						Cannot find studies investigating warfarin for secondary prevention of CHD; use same estimates as for stroke.
Rehabilitation	0.009	Patients who had had an acute coronary syndrome	Conventional care	Australia	1 year	Briffa *et al.* (2005)	p. 453, final column, third paragraph.

Revascularisation:							
CABG surgery	0.400	Patients appropriate for CABG only	Medical management	UK	6 years	Griffin *et al.* (2007)	Table 3, 'Adjusted MD' values in those 'Appropriate for CABG' only.
Angioplasty	0.060	Patients appropriate for PCI only	Medical management	UK	6 years	Griffin *et al.* (2007)	Table 3, 'Adjusted MD' values in those 'Appropriate for PCI' only.
Treatment of unstable angina:							
Aspirin	0.213						Cannot find studies comparing aspirin versus usual care; use same estimates as for secondary prevention of CHD post-MI (this was also assumed in the IMPACT study).
Clopidogrel	0.077	Patients with acute coronary syndromes	Standard therapy	UK	Lifetime	Main *et al.* (2004)	Table 29, p. 43.
Glycoprotein IIB/IIIA antagonists	0.099	Patients with non-ST-elevation acute coronary syndromes	No use of GPAs	UK	Lifetime	Palmer *et al.* (2005)	Table 2. Strategy 1 versus strategy 4.
Treatment of chronic stable angina:							
Aspirin	0.213	Patients aged 35–84 years with coronary disease and who survived the first month with it	No treatment	USA	Up to 25 years	Gaspoz *et al.* (2002)	Table 2. QALYs gained = 121,768,000 ('current use of aspirin') minus 115,535,000 ('zero utilisation') in a population of 'about 6.8 million people' are estimated to have CHD, and each year about 700,000 to 900,000 new cases are estimated to occur.
Clopidogrel	0.038	Patients with prior occlusive vascular events	Aspirin	UK	Lifetime	Karnon *et al.* (2005)	Table 4, 'Baseline' analysis.
Statins	0.103	Patients with CHD	No statin therapy	UK	Lifetime	Ward *et al.* (2007)	Table 63, p.101, figures for men aged 85
Treatment of arrhythmia:							
ICD	1.060	Patients with arrhythmia	Amiodarone treatment	UK	20 years	Buxton *et al.* (2006)	Table 85, p.106, 'UK average patient'
Treatment of heart failure:							
ACE inhibitors	0.110	Persons with symptomatic heart failure and left ventricular ejection fractions <=35%	Placebo	Belgium, Canada and the USA	4 years	Glick *et al.* (1995)	Table 1, Within-trial model, Total.
Beta blockers	0.137	Patients with chronic heart failure	Placebo	UK	5 years	Varney (2001)	Assume HRQOL of 0.6 from study based on lowest value in Ward *et al.* (2007). This is multiplied by LYG under the 'Limited benefits' scenario (0.228 years; p. 368 section 3.1). Note that this assumes no morbidity benefit.
Diuretics	0.130	Patients with severe heart failure and a left ventricular ejection fraction of <=35%	Standard therapy + placebo	16 countries	35 months	Glick *et al.* (2002)	Table 1, Total.
Aspirin	0.213						Cannot find studies comparing aspirin versus usual care; use same estimates as for secondary prevention of CHD post-MI (this was also assumed in the IMPACT study).
Statins	0.103						Cannot find studies for statins in this patient group; use same estimates as for secondary prevention of CHD post-MI (this was also assumed in the IMPACT study).
CRT-P	0.700	Patients with heart failure with a marker for cardiac dyssynchrony and left ventricular systolic dysfunction	Optimal pharmaceutical therapy	UK	Lifetime	Fox *et al.* (2007)	Table 58, p. 67, 'Mixed'
CRT-D	0.990	Patients with heart failure with a marker for cardiac dyssynchrony and left ventricular systolic dysfunction	Optimal pharmaceutical therapy	UK	Lifetime	Fox *et al.* (2007)	Table 64, p. 83, 'Mixed'.

Heart transplant:							
Heart transplant	1.475	Patients with end-stage heart failure	Death	UK	5 years	Clegg *et al*. (2005)	Cannot find specific figures for heart transplant; see Table 52, p. 104 and use figures for Medical group, assuming 7.2 months pre-transplant life expectancy for no transplant.
Treatment of acute stroke:							
Aspirin	0.013						Cannot find studies comparing aspirin versus usual care; use same estimates as for secondary prevention of stroke.
Anticoagulants	0.090	Patients aged 18 years and above with acute stroke	Placebo	USA and Canada	Lifetime	Samsa *et al*. (2002)	Table 3, 'Trial+long term'.
tr-PA	0.036	Patients with acute ischaemic stroke	Standard care	UK	Lifetime	Sandercock *et al*. (2002)	Table 10, p. 76, 'Base case'.
Stroke unit	0.190	Patients with acute stroke	Contemporary conventional care	UK	5 years	Chambers *et al*. (1998)	
Early diagnosis and treatment	0.078	Patients with acute stroke (but not subarachnoid haemorrhage)	Do not scan anyone	UK	5 years	Wardlaw *et al*. (2004)	Table 3, Comparator minus S12.
Secondary prevention of stroke:							
Rehabilitation therapy	0.009						Cannot find studies for rehabilitation in this patient group; use same estimates as for Secondary prevention of CHD post-MI
Aspirin	0.013	Patients aged 70 who had survived an initial stroke and who were suitable for treatment with an antiplatelet therapy	No treatment strategy	UK	5 years	Beard *et al*. (2004)	
Clopidogrel	0.038	Patients with prior occlusive vascular events	Aspirin	UK	Lifetime	Karnon *et al*. (2005)	Table 4, 'Baseline' analysis.
Statins	0.103						Cannot find studies for statins in this patient group; use same estimates as for secondary prevention of CHD post-MI.
Warfarin	0.006	40–80 year old men and women after their first idiopathic venous thromboembolic event or pulmonary embolism	3 month conventional therapy with warfarin (standard therapy after stroke)	USA	Lifetime	Aujesky *et al*. (2005)	Figures for men aged 40 years, 6 months conventional therapy versus 3 month conventional therapy (standard therapy after stroke).
Antihypertensive drugs	0.142						Cannot find studies in this patient group; use same estimates as for beta blockers for secondary prevention of CHD post-MI.
Primary prevention of CVD:							
Treatment of hypertension	0.060	65 year old women with an annual CVD risk of 2%, HF risk of 1% and diabetes risk of 1.1%	Thiazide-type diuretics	UK	Lifetime	National Collaborating Centre for Chronic Conditions (2006)	Table 3, p. 13, figures for women, C versus D.
Treatment of hypercholesterolaemia	0.310	Patients aged 55 years without CHD	No treatment	UK	20 years	Davies *et al*. (2007)	Figures for women receiving PRA (least effective).
Primary prevention of stroke:							
Warfarin	0.810	70 yr old patients with AF at moderate risk of stroke	Aspirin	USA	20 years	O'Brien *et al*. (2005)	Table 2, base case.
Aspirin	0.020	Patients aged 50–60 years with no known CVD	No treatment	UK	10 years	Annemans *et al*. (2006)	Table 5, risk level = 5%.
Smoking cessation:							
Quitting smoking	0.990	55–64 year old	Not quitting smoking	UK	Lifetime	Wang *et al*. (2008)	Table 14, p. 38, use 0.99 value (most conservative).

CHD = coronary heart disease, MI = myocardial infarction, ICD = implantable cardioverter defibrillator, CRT-P = cardiac resynchronisation therapy device, CRT-D = CRT device plus ICD, CVD = cardiovascular disease.

Annex 5B: Estimating the numbers of eligible patients in each patient group

Table A5B delineates the data sources and assumptions used to generate the numbers of eligible patients in each patient group over the period 1985–2005.

Table A5B: Data and assumptions used to generate the numbers of eligible patients

Patient groups/interventions	Data and assumptions
Treatment of acute MI	Data for 1998–2005 obtained from *Hospital Episodes Statistics* website (www.hesonline.nhs.uk/Ease/servlet/ContentServer?siteID=1937&categoryID=192) based on the total number of emergency admissions for primary diagnosis I21 (acute myocardial infarction). These are figures for England; UK figures are computed by multiplying the numbers of admissions in England by the ratio of UK population to the English population. Figures for 1985–87 were computed by applying the ratio of admissions to UK population size to the population size in 1985–97. This applies to all treatments of acute MI except for community resuscitation, hospital resuscitation and primary angioplasty.
Community resuscitation and hospital resuscitation	As for treatment of acute MI, except the analysis is based on the numbers of emergency admissions for primary diagnosis I46 (cardiac arrest).
Primary angioplasty	Data on numbers receiving surgery for 2005 obtained from the Myocardial Infarction National Audit Project (MINAP Steering Group, 2007). Prior to 2001 the numbers receiving surgery was zero. We assumed a constant rate of increase between 2001 and 2005.
Secondary prevention of CHD post-MI	Data for 2003 obtained from the *Health Survey for England* (www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsStatistics/DH_4098712), based on the proportion who reported having ever had a heart attack. This proportion was then applied to UK population figures. In earlier and later years the same proportion was applied to the UK population figures in each year.
Revascularisation	
CABG surgery	Data on numbers receiving surgery for 1985–99 obtained from Society of Cardiothoracic Surgery in Great Britain and Northern Ireland website (www.scts.org/). From 2000 to 2005 the number each year was held constant at the 1999 value.
Angioplasty	Data on numbers receiving surgery for 1991 to 2005 obtained from British Cardiovascular Intervention Society website (www.bcis.org.uk/). Assume increase from 1991 to 1992 applies to each preceding year.
Treatment of unstable angina	As for treatment of acute MI, except the analysis is based on the numbers of emergency admissions for primary diagnosis I20 (angina pectoris).
Treatment of chronic stable angina	As for secondary prevention of CHD post-MI, except the analysis is based on the proportion who reported having ever had angina.
Treatment of arrhythmia	
ICD	Data on total numbers of ICDs for 1985–2005 obtained from report for European Heart Rhythm Association. (www.ic.nhs.uk/webfiles/Services/NCASP/audits%20and%20reports/ReportforEuropeanHeartRhythmAssociation-AnnualReport2005.pdf)
Treatment of heart failure	Data for 1994–98 obtained from *Key Health Statistics from General Practice* (National Statistics, 2000). These are figures for England; UK figures are computed by multiplying the prevalence in England by the UK population. For 1985–93 we assume the rate is the same as in 1994. For 1999–2005 we assume the rate is the same as in 1998. This applies to all treatments for heart failure except for CRT-P and CRT-D.
CRT-P and CRT-D	Data on total numbers of CRT-Ps and CRT-Ds for 1985–2005 obtained from *Report for European Heart Rhythm Association*.
Heart transplant	As for treatment of acute MI, except the analysis is based on the numbers of emergency admissions for main procedure K02 (other transplantation of heart).
Treatment of acute stroke	As for treatment of acute MI, except the analysis is based on the numbers of emergency admissions for primary diagnoses I60–I69.
Secondary prevention of stroke	As for secondary prevention of CHD post-MI, except the analysis is based on the proportion who reported having ever had stroke.
Primary prevention of CVD	Data for 1985–2005 based on the UK population (Office for National Statistics, 2007).
Primary prevention of stroke	As for heart failure, except the analysis is based on the numbers of people with atrial fibrillation.
Smoking cessation	Data for 1985–2005 from the *General Household Survey* (www.statistics.gov.uk/ssd/surveys/general_household_survey.asp) on the number of smokers. Data on the numbers of people who died from smoking each year were taken from Peto *et al.* (2006). The numbers of quitters in year x+1 was calculated as the number of smokers in year x minus the number of smokers in year x+1 minus the number of people who died from smoking in year x+1.

CHD = coronary heart disease, MI = myocardial infarction, ICD = implantable cardioverter defibrillator, CRT-P = cardiac resynchronisation therapy device, CRT-D = CRT device plus ICD, CVD = cardiovascular disease.

Annex 5C: Adjusting for overlapping patient groups

We calculate the numbers of patients in each patient group who are eligible for treatment. It is likely that in some cases patients feature in more than one patient group, in which case the total number of eligible patients will be overestimated. To account for this we adjusted for overlapping patent groups using the assumptions outlined in Table A5C, which are based on the IMPACT study.

Table A5C: Assumptions used to adjust for overlapping users

Patient group	Adjustment
Revascularisation	1. Assume that 20% of angioplasty patients go on to have CABG surgery; hence multiply angioplasty patients by a factor of 0.80. 2. Subtract numbers of primary angioplasty patients from numbers receiving angioplasty.
Treatment of chronic stable angina	1. Subtract numbers of patients being treated for unstable angina. 2. Subtract 50% of patients receiving CABG surgery. 3. Subtract 50% of patients receiving secondary prevention of CHD post-MI.
Treatment of heart failure	1. Subtract 50% of cases (since assume these are due to CHD and are considered elsewhere). 2. Subtract heart transplant patients.
Primary prevention of CVD	1. Subtract those receiving antihypertensive drugs elsewhere in the model from those receiving antihypertensive drugs as primary prevention of CVD. 2. Subtract those receiving lipid-lowering drugs elsewhere in the model from those receiving lipid-lowering drugs as primary prevention of CVD.

Annex 5D: Estimating the uptake rates for specific interventions in each patient group

Table A5D: Data and assumptions used to generate uptake rates

Patient groups/interventions	Data and assumptions
Treatment of acute MI:	
Community resuscitation	Figures for 1994–95 from Norris (1998), Table 2. Assume constant after 1995. According to Tunstall-Pedoe *et al*. (1992) cardiopulmonary resuscitation was "largely neglected" before 1982. Assume zero in 1985 and linearly interpolate to ` 1994 value.
Hospital resuscitation	Figures for 1994–95 from UKHAS (1998), p. 117 column 1. Assume constant after 1995. According to Tunstall-Pedoe *et al*. (1992) cardiopulmonary resuscitation was "largely neglected" before 1982. Assume zero in 1985 and linearly interpolate to 1994 values.
Thrombolysis	Figures for 2001 and 2005 from MINAP Steering Group (2007), Table 1. Linearly interpolate for 2002–04. Thrombolysis used since 1950s; assume constant rate at 2001 value.
Aspirin	Figures for 1994–98 from *Key Health Statistics from General Practice*. Aspirin introduced for reducing MI in 1988 by FDA (www.bayeraspirin.com/pain/asp_history.htm); assume zero up to this point and linearly interpolate after this point. Assume constant after 1998.
Clopidogrel	According to UKMI (2002) clopidogrel use is predicted to be 30–50% of acute coronary syndrome cases within five years of introduction in this indication (in 2002). Assume 0% use in 2001.
Primary angioplasty	Have actual numbers of cases – see data for eligible patients (assume all cases are new cases).
Secondary prevention of CHD post-MI:	
Aspirin	Figures for 1994–98 from *Key Health Statistics from General Practice*. Figures for 2000 from EUROASPIRE II (2001), Table 9. Figures for 2001 and 2005 from MINAP Steering Group (2007). Aspirin introduced for reducing MI in 1988 by FDA (www.bayeraspirin.com/pain/asp_history.htm); assume zero up to this point and linearly interpolate up to 1994. Linearly interpolate in 1999.
Clopidogrel	According to Main *et al*. (2004), p. 6 in 2001 aspirin = 91% of antiplatelet prescriptions and clopidogrel = 4%. According to UKMI (2002) clopidogrel use in 2001 was double the value in 2000. Assume zero use before 2000 and constant 4% use relative to aspirin's 91% use after 2001.
Beta blockers	Figures for 2000 from EUROASPIRE II (2001), Table 9. Beta blockers first introduced in 1984 (www.medscape.com/viewarticle/542689_2) hence assume zero for 1985 and linearly interpolate to 2000. Assume constant rate after 2000.
ACE inhibitors	Figures for 2000 from EUROASPIRE II (2001), Table 9. Landmark clinical study published in 1988 (Swedberg and Kjekshus) hence assume zero uptake before then and linearly interpolate to 2000. Assume constant rate after 2000.
Statins	Figures for 1994–98 from *Key Health Statistics from General Practice*. Assume no use prior to 1990 (Department of Health, 2007) and linearly interpolate to 1994. From Department of Health (2007) assume constant increase after 1998.
Warfarin	Figures for 2000 from EUROASPIRE II (2001), Table 9. Anticoagulants used since 1950s; assume constant rate at 2000 value.
Rehabilitation	Figures for 2000 from EUROASPIRE II (2001), Table 5. Landmark clinical study published in 1983 hence assume zero uptake at 1985 and linearly interpolate to 2000. After 2000 assume constant rate at 2000 value.
Revascularisation:	
CABG surgery	Have actual numbers of cases – see data for eligible patients (assume all cases are new cases)
Angioplasty	Have actual numbers of cases – see data for eligible patients (assume all cases are new cases)

Treatment of unstable angina:	
Aspirin	Figures for 1994–98 from *Key Health Statistics from General Practice*. Aspirin introduced for reducing MI in 1988 by FDA (www.bayeraspirin.com/pain/asp_history.htm); assume zero up to this point and linearly interpolate after this point. Assume constant after 1998.
Clopidogrel	According to UKMI (2002) clopidogrel use is predicted to be 30–50% of acute coronary syndrome cases within five years of introduction in this indication (in 2002). Assume 0% use in 2001.
Glycoprotein IIB/IIIA antagonists	Figures for 2000 from Capewell *et al*. (2006), Table 1. Landmark clinical study published in hence assume zero uptake before then and linearly interpolate to 2000. After 2000 assume constant rate at 2000 value.
Treatment of chronic stable angina:	
Aspirin	Figures for 1994–98 from *Key Health Statistics from General Practice*. Aspirin introduced for reducing MI in 1988 by FDA (www.bayeraspirin.com/pain/asp_history.htm); assume zero up to this point and linearly interpolate after this point. Assume constant after 1998.
Clopidogrel	According to Main *et al*. (2004), p. 6 in 2001 aspirin = 91% of antiplatelet prescriptions and clopidogrel = 4%. According to UKMI (2002) clopidogrel use in 2001 was double the value in 2000. Assume zero use before 2000 and constant 4% use relative to aspirin's 91% use after 2001.
Statins	Figures for 1994–98 from *Key Health Statistics from General Practice*. Assume no use prior to 1990 (Department of Health, 2007) and linearly interpolate 1994. From Department of Health (2007) assume constant increase after 1998.
Treatment of arrhythmia:	
ICD	Have actual numbers of cases – see data for eligible patients (assume all cases are new cases).
Treatment of heart failure:	
ACE inhibitors	Figures for 1994–98 from *Key Health Statistics from General Practice*. Landmark clinical study published in 1988 (Swedberg and Kjekshus) hence assume zero uptake before then and linearly interpolate to 1994. Assume constant rate after 1998.
Beta blockers	Figures for 1994–98 from *Key Health Statistics from General Practice*. Beta blockers first introduced in 1984 (www.medscape.com/viewarticle/542689_2) hence assume zero for 1985 and linearly interpolate to 1994. Assume constant after 1998.
Diuretics	Figures for 1994–98 from *Key Health Statistics from General Practice*. Diuretics first introduced in 1984 (www.medscape.com/viewarticle/542689_2) hence assume zero for 1985 and linearly interpolate to 1994. Assume constant after 1998.
Aspirin	Assume same as for CHD, but constant after 1998.
Statins	Assume same as for CHD, but constant after 1998.
CRT-P	Have actual numbers of cases – see data for eligible patients (assume all cases are new cases).
CRT-D	Have actual numbers of cases – see data for eligible patients (assume all cases are new cases).
Heart transplant:	
Heart transplant	Have actual numbers of cases – see data for eligible patients (assume all cases are new cases).
Treatment of acute stroke:	
Aspirin	Figures for 1994–98 from *Key Health Statistics from General Practice* based on use in patients with atrial fibrillation. Aspirin introduced for reducing MI in 1988 by FDA (www.bayeraspirin.com/pain/asp_history.htm); assume zero up to this point and linearly interpolate after this point. Assume constant after 1998.
Anticoagulants	Figures for 1994–98 from *Key Health Statistics from General Practice* based on use in patients with atrial fibrillation. Anticoagulants used since 1950s; assume constant rate prior to 1994 at 1994 value and after 1998 use constant 1998 value.
tr-PA	Figures for 2001 and 2004 from CEEU (2007), p. 79. Landmark clinical study published in 1993 hence assume zero uptake before then and linearly interpolate to 2001. Linearly interpolate between 2001 and 2004. Assume 2004 value in 2005.
Stroke unit	Figures for 2001 and 2004 from CEEU (2007), p. 79. Landmark clinical study published in 1984 hence assume zero uptake in 1985 and linearly interpolate to 2001. Linearly interpolate between 2001 and 2004. Assume 2004 value in 2005.
Early diagnosis and treatment	Figures for 2001 and 2004 from CEEU (2007), p. 79. Landmark clinical study published in 1978 hence assume zero uptake in 1985 and linearly interpolate to 2001. Linearly interpolate between 2001 and 2004. Assume 2004 value in 2005.
Secondary prevention of stroke:	
Rehabilitation therapy	Figures for 2001 and 2004 from CEEU (2007), p. 79. Landmark clinical study published in 1983 hence assume zero uptake in 1985 and linearly interpolate to 2001. Linearly interpolate between 2001 and 2004. Assume 2004 value in 2005.
Aspirin	Figures for 1994–98 from *Key Health Statistics from General Practice* based on use in patients with atrial fibrillation. Aspirin introduced for reducing MI in 1988 by FDA (www.bayeraspirin.com/pain/asp_history.htm); assume zero up to this point and linearly interpolate after this point. Assume constant after 1998.
Clopidogrel	According to Main *et al*. (2004), p. 6 in 2001 aspirin = 91% of antiplatelet prescriptions and clopidogrel = 4%. According to UKMI (2002) clopidogrel use in 2001 was double the value in 2000. Assume zero use before 2000 and constant 4% use relative to aspirin's 91% use after 2001.
Statins	Assume same as for CHD, but constant after 1998.
Warfarin	Figures for 1994–98 from *Key Health Statistics from General Practice* based on use in patients with atrial fibrillation. Warfarin used since 1950s; assume constant rate prior to 1994 at 1994 value and after 1998 use constant 1998 value.
Antihypertensive drugs	CEEU (2007) p. 19: in 2006, on discharge, 70% of patients were on antihypertensive medication (assume for 2005). Beta blockers first introduced in 1984 – assume zero for 1985. www.medscape.com/viewarticle/542689_2
Primary prevention of CVD:	
Treatment of hypertension	Figures for whole population for 1994–98 from *Key Health Statistics from General Practice*. Beta blockers first introduced in 1984 (www.medscape.com/viewarticle/542689_2) hence assume zero for 1985 and linearly interpolate to 1994. Assume constant after 1998. Assume constant rate of increase after 1998.
Treatment of hypercholesterolaemia	Figures for whole population for 1994–98 from *Key Health Statistics from General Practice*. As for statins assume no use prior to 1990 (Department of Health, 2007) and linearly interpolate 1994. From Department of Health (2007) assume constant increase after 1998.

Primary prevention of stroke:	
Warfarin	Figures for 1994–98 from *Key Health Statistics from General Practice* based on use in patients with atrial fibrillation. Warfarin used since 1950s; assume constant rate prior to 1994 at 1994 value and after 1998 use constant 1998 value.
Aspirin	Figures for 1994–98 from *Key Health Statistics from General Practice* based on use in patients with atrial fibrillation. Aspirin introduced for reducing MI in 1988 by FDA (www.bayeraspirin.com/pain/asp_history.htm); assume zero up to this point and linearly interpolate after this point. Assume constant after 1998.
Smoking cessation:	
Smoking cessation	Adjust actual numbers of smokers by proportion who had contact with medical services who told respondents to quit smoking for medical reasons, obtained from Health Survey for England (www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsStatistics/DH_4098712; variable name: drsmoke); this variable is available for 1993–99 and 2003–05 (range of values: 0.22–0.25). Applied 1993 value to 1985–92 and applied 2003 value to 2000–02. Then, multiply the result by the proportion of deaths due to cardiovascular disease published by Peto *et al.* (2006). These estimates were available for the year 2000 and were estimated to be 0.27 (we applied this proportion to every year).

CHD = coronary heart disease, MI = myocardial infarction, ICD = implantable cardioverter defibrillator, CRT-P = cardiac resynchronisation therapy device, CRT-D = CRT device plus ICD, CVD = cardiovascular disease.

Annex 5E: Adjusting for compliance

We searched the economic evaluation studies used to obtain the QALYs gained estimates to ascertain whether or not non-compliance had already been accounted for in the estimates generated by the cost-effectiveness models used. In some of these non-compliance was accounted for in which case it was not considered further because its effects were already included in the estimates of the QALYs gained. Also, for some interventions we were able to find data directly on numbers of users, thereby already accounting for compliance. Where it was not accounted for we applied compliance rates used in the IMPACT study. These were:

- 100% in hospital patients
- 50% in asymptomatic community patients
- 75% in symptomatic community.

We assumed that compliance rates were constant over time. Table A5E summarises the assumptions used.

Table A5E: Compliance rates used in the analysis

Patient groups/interventions	Compliance rate (%)	Notes
Treatment of acute MI:		
Community resuscitation	100	Assumed to be 100% based on IMPACT study
Hospital resuscitation	100	Assumed to be 100% based on IMPACT study
Thrombolysis	100	Assumed to be 100% based on IMPACT study
Aspirin	100	Assumed to be 100% based on IMPACT study
Clopidogrel	100	Assumed to be 100% based on IMPACT study
Primary angioplasty	100	Assumed to be 100% based on IMPACT study
Secondary prevention of CHD post-MI:		
Aspirin	100	Compliance included in QALY estimates; rate set to 100%
Clopidogrel	100	Compliance included in QALY estimates; rate set to 100%
Beta blockers	75	Assumed to be 75% based on IMPACT study
ACE inhibitors	75	Assumed to be 75% based on IMPACT study
Statins	100	Compliance included in QALY estimates; rate set to 100%
Warfarin	75	Assumed to be 75% based on IMPACT study
Rehabilitation	100	Compliance included in QALY estimates; rate set to 100%
Revascularisation:		
CABG surgery	100	Have numbers of new users directly; rate set to 100%
Angioplasty	100	Have numbers of new users directly; rate set to 100%
Treatment of unstable angina:		
Aspirin	100	Compliance included in QALY estimates; rate set to 100%
Clopidogrel	100	Assumed to be 100% based on IMPACT study
Glycoprotein IIB/IIIA antagonists	100	Assumed to be 100% based on IMPACT study

Treatment of chronic stable angina:		
Aspirin	100	Compliance included in QALY estimates; rate set to 100%
Clopidogrel	100	Compliance included in QALY estimates; rate set to 100%
Statins	100	Compliance included in QALY estimates; rate set to 100%
Treatment of arrhythmia:		
ICD	100	Have numbers of new users directly; rate set to 100%
Treatment of heart failure:		
ACE inhibitors	75	Assumed to be 75% based on IMPACT study
Beta blockers	75	Assumed to be 75% based on IMPACT study
Diuretics	75	Assumed to be 75% based on IMPACT study
Aspirin	100	Compliance included in QALY estimates; rate set to 100%
Statins	100	Compliance included in QALY estimates; rate set to 100%
CRT-P	100	Have numbers of new users directly; rate set to 100%
CRT-D	100	Have numbers of new users directly; rate set to 100%
Heart transplant:		
Heart transplant	100	Have numbers of new users directly; rate set to 100%
Treatment of acute stroke:		
Aspirin	100	Assumed to be 100% based on IMPACT study
Anticoagulants	100	Assumed to be 100% based on IMPACT study
tr-PA	100	Assumed to be 100% based on IMPACT study
Stroke unit	100	Assumed to be 100% based on IMPACT study
Early diagnosis and treatment	100	Assumed to be 100% based on IMPACT study
Secondary prevention of stroke:		
Rehabilitation therapy	100	Compliance included QALY estimates; rate set to 100%
Aspirin	75	Assumed to be 75% based on IMPACT study
Clopidogrel	100	Compliance included QALY estimates; rate set to 100%
Statins	100	Compliance included QALY estimates; rate set to 100%
Warfarin	75	Assumed to be 75% based on IMPACT study
Antihypertensive drugs	75	Assumed to be 75% based on IMPACT study
Primary prevention of CVD:		
Treatment of hypertension	100	Compliance included QALY estimates; rate set to 100%
Treatment of hypercholesterolaemia	50	Assumed to be 50% based on IMPACT study
Primary prevention of stroke:		
Warfarin	50	Assumed to be 50% based on IMPACT study
Aspirin	50	Assumed to be 50% based on IMPACT study
Smoking cessation:		
Smoking cessation	100	Have numbers of quitters directly; rate set to 100%

CHD = coronary heart disease, MI = myocardial infarction, ICD = implantable cardioverter defibrillator, CRT-P = cardiac resynchronisation therapy device, CRT-D = CRT device plus ICD, CVD = cardiovascular disease.

Annex 5F: Adjusting for polytreatment

We adjust for polytreatment because patients in a particular patient group may receive more than one intervention and this is not reflected in the numbers of new users. Ideally we would have data on the numbers of patients receiving every combination of the interventions for each patient group, but invariably we do not have these data. Hence, we need to account for the use of multiple interventions or we may overestimate the QALYs gained.

We adjust for polytreatment in three ways:

1 we assume there is no polytreatment

2 we assume there is maximum polytreatment and that the QALYs gained from each intervention are additive

3 we assume there is maximum polytreatment and that the QALYs gained from each intervention are not at all additive.

Suppose that according to our calculations there are 1,225,500 patients in the secondary prevention of CHD post-MI group who are new users of statins over the period 1985–2005 and 1,737,500 new users of aspirin. With no polytreatment (option 1) we assume that the two sets of new users do not overlap and none of the new users receiving statins is a new user of aspirin, and vice versa. With maximum polytreatment (options 2 and 3) we assume that the 1,225,500 new users of statins are a subset of the total new users of aspirin and that there are no new users of statins who are not new users of aspirin. With option 2 we assume that the QALYs gained from each intervention are additive. Therefore the 1,225,500 new users of statins (who are also new users of aspirin) receive the QALYs gained from statins plus the QALYs gained from aspirin. The 512,000 new users of aspirin who are not new users of statins receive only the QALY gains associated with aspirin. Note that options 1 and 2 yield the same estimates of the total QALYs gained because in each case these are computed by multiplying the QALYs gained for each intervention by the numbers of new users and summing the totals for each specific intervention to generate a total for the patient group. This is method is used to generate the central estimates in our analysis.

With option 3 we assume as with option 2 that there is maximum polytreatment, but the effects of the different interventions are not additive. In this case we allocate the highest QALY gains to each patient from the different treatments they receive. We calculate the total QALYs gained as follows:

1 in each year, we order the specific interventions for each patient group in increasing order of the numbers of new users

2 moving down the ordered list of specific interventions we identify the intervention with the highest QALYs gained and allocate these to all those who received that intervention (plus, assuming maximum polytreatment, all other new users falling above in the ordering)

3 we then move down the list and identify the intervention with the next highest QALYs gained and allocate this to the new users who did not receive the intervention with the highest QALYs gained identified in the previous step

4 we repeat this process until all new users have been allocated a QALY gain

5 the above process is then repeated for every year.

This option is used to generate the lower estimates in our analysis.

In order to ensure that the total incremental costs are commensurate with the total QALYs gained for all three options, the total incremental costs are allocated on the same basis as the total QALYs gained. Hence, the above approaches are used to generate the central and lower estimates of the total incremental costs.

Annex 5G: Estimates of total QALYs gained by year used to generate Figure 5.1

Table A5G: Total QALYs gained by year

	QALYs gained (000s)
1986	52.1
1987	70.9
1988	72.4
1989	113.8
1990	127.7
1991	151.1
1992	157.7
1993	146.7
1994	153.8
1995	128.1
1996	142.6
1997	147.3
1998	163.4
1999	190.5
2000	197.8
2001	132.5
2002	153.0
2003	126.0
2004	160.3
2005	167.5

Annex 5H: Studies used to generate incremental costs for each intervention in each patient group

Table A5H: Summary of studies used to generate incremental costs for each intervention in each patient group

Patient groups/interventions	Raw incremental costs	Country	Time horizon	Cost base year	Source	Incremental costs (2005 UK£)	Notes
Treatment of acute MI:							
Community resuscitation	1,165	UK	Discharge	1999	Gage *et al.* (2002)	1,491	Not the same study used to obtain QALYs gained; UK study
Hospital resuscitation	1,165	UK	Discharge	1999	Gage *et al.* (2002)	1,491	Not the same study used to obtain QALYs gained; UK study
Thrombolysis	110					141	Cannot find studies for thrombolysis in this patient group; use same estimates as for tPA in acute stroke
Aspirin	-247					-289	Cannot find studies for aspirin in this patient group; use same estimates as for secondary prevention of stroke
Clopidogrel	467	UK	Lifetime	2001	Main *et al.* (2004)	546	Table 29, p. 43
Primary angioplasty	543	UK	6 months	2003	Hartwell *et al.* (2005)	543	Table 18, p. 38
Secondary prevention of CHD post-MI:							
Aspirin	-247					-289	Cannot find studies for aspirin in this patient group; use same estimates as for secondary prevention of stroke
Clopidogrel	819	UK	Lifetime	2002	Karnon *et al.* (2005)	925	Table 4, 'Baseline' analysis
Beta blockers	630					773	Cannot find studies for beta blockers in this patient group; use same estimates as for treatment of heart failure
ACE inhibitors	1,679	USA (US$)	4 years	1991	Tsevat *et al.* (1995)	1,919	Table 4, 'Limited benefit model' for patients age 60
Statins	1,615	UK	Lifetime	2004	Ward *et al.* (2007)	1,680	Table 63, p. 101, figures for men aged 85
Warfarin	76					56	Cannot find studies for warfarin in this patient group; use same estimates as for secondary prevention of stroke
Rehabilitation	486	UK	1 year	2000	Jolly *et al.* (2007)	597	Not the same study used to obtain QALYs gained; UK study, Appendix 2
Revascularisation:							
CABG surgery	5,870	UK	6 years	2003	Griffin *et al.* (2007)	6,301	Table 3, 'Adjusted MD' values in those 'Appropriate for CABG' only
Angioplasty	2,847	UK	6 years	2003	Griffin *et al.* (2007)	3,056	Table 3, 'Adjusted MD' values in those 'Appropriate for PCI' only
Treatment of unstable angina:							
Aspirin	-247					-289	Cannot find studies for Aspirin in this patient group; use same estimates as for Secondary prevention of stroke
Clopidogrel	467	UK	Lifetime	2001	Main *et al.* (2004)	546	Table 29, p. 43
Glycoprotein IIB/IIIA antagonists	569	UK	Lifetime	2000	Palmer *et al.* (2005)	699	Table 2, strategy 1 versus strategy 4
Treatment of chronic stable angina:							
Aspirin	-247					-289	Cannot find studies for Aspirin in this patient group; use same estimates as for Secondary prevention of stroke
Clopidogrel	819	UK	Lifetime	2002	Karnon *et al.* (2005)	925	Table 4, 'Baseline' analysis
Statins	1,615	UK	Lifetime	2004	Ward *et al.* (2007)	1,680	Table 63, p.101, figures for men aged 85
Treatment of arrhythmia:							
ICD	68,805	UK	20 years	2005	Buxton *et al.* (2006)	68,805	Table 85, p. 106, 'UK average patient'

Treatment of heart failure:							
ACE inhibitors	1,679					1,919	Cannot find studies for ACE inhibitors in this patient group; use same estimates as for secondary prevention of CHD post-MI
Beta blockers	630	UK	5 years	2000	Varney (2001)	773	
Diuretics	-713	16 countries (US$)	35 months	1999	Glick *et al.* (2002)	-592	Table 2
Aspirin	-247					-289	Cannot find studies for aspirin in this patient group; use same estimates as for secondary prevention of stroke
Statins	1,615					1,680	Cannot find studies for statins in this patient group; use same estimates as for secondary prevention of CHD post-MI
CRT-P	11,630	UK	Lifetime	2005	Fox *et al.* (2007)	11,630	Table 58, p. 67, 'Mixed'
CRT-D	23,320	UK	Lifetime	2005	Fox *et al.* (2007)	23,320	Table 64, p. 83, 'Mixed'
Heart transplant:							
Heart transplant	34,306	UK	5 years	2003	Clegg *et al.* (2005)	36,824	Cannot find specific figures for heart transplant; see Table 52, p.104 and use figures for Medical group, assuming £1806 pre-transplant costs for no transplant.
Treatment of acute stroke:							
Aspirin	-247					-289	Cannot find studies for aspirin in this patient group; use same estimates as for secondary prevention of stroke
Anticoagulants	-194	USA and Canada (US$)	Lifetime	1996	Samsa *et al.* (2002)	-178	Table 3, 'Trial+long term'
tr-PA	110	UK	1 year	1999	Sandercock *et al.* (2002)	141	Table 9, p. 70, 'Base case'. Note that costs are measured over 1 year – this is conservative since lifetime costs are more negative
Stroke unit	228	UK	5 years	1998	Chambers *et al.* (1998)	305	
Early diagnosis and treatment	-274	UK	5 years	2000	Wardlaw *et al.* (2004)	-337	Table 3, Comparator minus S12
Secondary prevention of stroke:							
Rehabilitation therapy	486					597	Cannot find studies for rehabilitation in this patient group; use same estimates as for secondary prevention of CHD post-MI
Aspirin	-247	UK	5 years	2001	Beard *et al.* (2004)	-289	
Clopidogrel	819	UK	Lifetime	2002	Karnon *et al.* (2005)	925	Table 4, 'Baseline' analysis
Statins	1,615					1,680	Cannot find studies for statins in this patient group; use same estimates as for secondary prevention of CHD post-MI
Warfarin	76	USA (US$)	Lifetime	2002	Aujesky *et al.* (2005)	56	Figures for men aged 40 years, 6 months conventional therapy versus 3 months conventional therapy (standard therapy after stroke)
Antihypertensive drugs	630					773	Cannot find studies in this patient group; use same estimates as for beta blockers treatment of heart failure

Primary prevention of CVD:							
Treatment of hypertension	760	UK	Lifetime	2005	National Collaborating Centre for Chronic Conditions (2006)	760	Table 3, p. 13, figures for women, C versus D
Treatment of hypercholesterolaemia	243	UK	20 years	2004	Davies *et al.* (2007)	253	Figures for women receiving PRA (least effective)
Primary prevention of stroke:							
Warfarin	2,000	USA (US$)	20 years	2003	O'Brien *et al.* (2005)	1,393	Table 2, base case
Aspirin	-247					-289	Cannot find studies for aspirin in this patient group; use same estimates as for secondary prevention of stroke
Smoking cessation:							
Smoking cessation	55	UK	Lifetime	2005	Wang *et al.* (2008)	55	Table 16, p. 39, use 54.88 value; this is associated with a success rate at 12 months of 5.86% and produces highest cost overall given success rate at 12 months; therefore compute total costs as 54.88*New users*1/0.0586

CHD = coronary heart disease, MI = myocardial infarction, ICD = Implantable cardioverter defibrillator, CRT-P = Cardiac Resynchronisation Therapy device, CRT-D = CRT device plus ICD, CVD = cardiovascular disease.

Annex 5I: Estimates of total incremental costs by year used to generate Figure 5.2

Table A5I: Total incremental costs by year

	Incremental costs (£ million)
1986	415.3
1987	445.6
1988	453.7
1989	409.5
1990	488.2
1991	524.0
1992	553.1
1993	551.2
1994	570.3
1995	647.6
1996	811.6
1997	954.1
1998	1,042.0
1999	854.6
2000	973.1
2001	1,051.3
2002	1,103.3
2003	1,155.7
2004	1,268.6
2005	1,354.5

Annex 5J: Sensitivity analysis

We undertook a sensitivity analysis to generate upper and lower estimates of the total QALYs gained and incremental costs around our central estimates. These were calculated as follows:

- Upper estimate: smoking cessation is a relatively important component of the total QALYs gained. We assumed in the central estimate that 22–25% of people who quit smoking did so as a result of medical research, based on the numbers of quitters who were told by medical services to quit smoking for medical reasons. This may underestimate the contribution of medical research because some people may quit smoking for medical reasons without being told to do so by the medical services. Hence, to generate an upper estimate of the total QALYs gained we assumed that 100% of people who quit smoking did so as a result of medical research.
- Lower estimate: we calculated the lower estimate of the total QALYs gained by assuming there was maximum polytreatment and that the QALYs gained from each specific intervention are not at all additive (see Annex 5F for a more detailed description of the method).

The same approach was used to generate upper and lower estimates around the central estimates of the total incremental costs.

Table A5J: Results of sensitivity analysis, 1985–2005

	Total QALYs gained (000s)	Total monetised QALYs gained (£ million)	Total incremental cost (£ million)
Central estimate:			
Non-smoking related activities	2,492.5	62,312.5	15,378.9
Smoking cessation	262.7	6,568.1	248.5
Total	**2,755.2**	**68,880.6**	**15,627.4**
Upper estimate:			
Non-smoking related activities	2,492.5	62,312.5	15,378.9
Smoking cessation	1,155.8	28,895.7	1,093.4
Total	**3,648.3**	**91,208.3**	**16,472.3**
Lower estimate:			
Patient groups/interventions			
Treatment of acute MI:	**149.8**	**3,744.5**	**-74.7**
Community resuscitation	2.8	69.1	6.7
Hospital resuscitation	1.2	30.2	2.9
Thrombolysis	11.6	289.7	27.9
Aspirin	14.3	357.1	-2.8
Clopidogrel	95.5	2,386.9	-128.8
Primary angioplasty	24.5	611.4	19.4
Secondary prevention of CHD post-MI:	**439.9**	**10,997.6**	**462.1**
Aspirin	1.4	34.0	-1.8
Clopidogrel	8.8	220.6	-12.0
Beta blockers	42.8	1,070.1	-58.1
ACE inhibitors	42.2	1,055.2	-57.3
Statins	30.1	753.7	-38.0
Warfarin	82.4	2,060.0	-7.8
Rehabilitation	232.2	5,804.0	637.2
Revascularisation:	**186.5**	**4,662.3**	**3,748.8**
CABG surgery	68.4	1,709.5	1,394.4
Angioplasty	118.1	2,952.8	2,354.4
Treatment of unstable angina:	**177.5**	**4,438.7**	**-241.0**
Aspirin	15.5	387.5	-21.0
Clopidogrel	54.6	1,363.9	-74.1
Glycoprotein IIB/IIIA antagonists	107.5	2,687.3	-145.9
Treatment of chronic stable angina:	**286.3**	**7,157.1**	**981.5**
Aspirin	6.7	166.4	-9.0
Clopidogrel	77.5	1,936.9	-88.7
Statins	202.2	5,053.8	1,079.2
Treatment of arrhythmia:	**21.0**	**525.2**	**1,363.5**
ICD	21.0	525.2	1,363.5
Treatment of heart failure:	**79.0**	**1,975.8**	**-37.1**
ACE inhibitors	2.0	48.8	46.0
Beta blockers	1.1	28.1	25.3
Diuretics	5.4	134.2	24.0
Aspirin	3.6	89.5	12.4
Statins	28.9	721.4	-10.1
CRT-P	22.4	560.0	-5.1
CRT-D	15.8	393.8	-129.5
Heart transplant:	**5.1**	**128.0**	**127.9**
Heart transplant	5.1	128.0	127.9
Treatment of acute stroke:	**118.6**	**2,965.2**	**89.2**
Aspirin	58.5	1,463.4	94.0
Anticoagulants	19.6	489.3	31.4
tr-PA	12.3	307.6	7.4
Stroke unit	14.0	348.8	-54.6
Early diagnosis and treatment	14.2	356.0	11.1
Secondary prevention of stroke:	**126.9**	**3,171.7**	**918.5**
Rehabilitation therapy	1.3	33.1	7.2
Aspirin	19.5	486.5	106.2
Clopidogrel	10.8	269.5	58.9
Statins	30.0	750.8	164.2
Warfarin	52.0	1,300.7	332.8
Antihypertensive drugs	13.2	331.0	249.2
Primary prevention of CVD:	**282.4**	**7,061.2**	**3,128.3**
Treatment of hypertension	37.9	947.9	30.9
Treatment of hypercholesterolaemia	244.5	6,113.3	3,097.4
Primary prevention of stroke:	**59.9**	**1,498.0**	**76.4**
Warfarin	53.0	1,323.8	91.1
Aspirin	7.0	174.3	-14.7
Smoking cessation:	**262.7**	**6,568.1**	**248.5**
Quitting smoking	262.7	6,568.1	248.5
Total	**2,195.7**	**54,893.3**	**10,792.0**

CHD = coronary heart disease, MI = myocardial infarction, ICD = implantable cardioverter defibrillator, CRT-P = cardiac resynchronisation therapy device, CRT-D = CRT device plus ICD, CVD = cardiovascular disease.

Annex to Chapter Six

Literature review on R&D spillovers

1. Introduction

In this Annex we focus solely on the non-health benefits of medical research and development (R&D). It is extremely important to consider non-health as well as health gains. Returns to investment in medical research by one organisation may benefit not only that organisation but also other organisations in the medical sector, in other sectors, and also in other countries (although this last is outside the scope of the current research project). That is, there are spillovers. In this paper, we present the findings of our review of the research spillovers literature in general and as applied specifically to medical research.

The structure of this Annex is as follows. In Section 2 we outline the methodology used for the literature review. Section 3 describes the concepts of knowledge and information and goes on to discuss the differences between private and social rates of return to R&D, to introduce the concept of spillovers. Section 4 summarises the literature analysing the sources of spillovers. Section 5 discusses the main transmission mechanisms for spillovers identified by the literature. In Section 6 we comment on the literature on the economics of the geography of innovation, highlighting how spillovers have helped develop this strand of work. Section 7 summarises the main results.

2. Methodology

We have adopted a selective approach for the literature search, mainly driven by:

- our accumulated knowledge and experience on the topic
- core references from past reviews of the value of the pharmaceutical industry, which have also helped us in identifying key authors in the fields.

This is a strategy suitable for methodological reviews where conventional keyword based search strategy (such as R&D) may result in a very large number of references – too large to be handled within the time constraints of this project.

Nevertheless, we searched the following databases: British Library Integrated Catalogue – search on Serials/ Periodicals; economic working papers database – EconPapers; EconLit; and PubMed. We looked for papers that combined the following keywords (or nearest equivalents): 'medical'; 'research' (or 'R&D' or 'research and development' or 'medical research'); 'spillovers' (or 'externalities' or 'synergies'); 'social rate of return' (or 'rate of return'). Part of the remit was to explore the factors attracting private R&D to the UK, including public medical research, so we also carried out a literature review combining the following keywords: 'location'; 'research' (or 'R&D' or 'research and development' or 'medical research'); 'companies' (or 'firms' or 'enterprises' or 'business' or 'economic activity' or 'manufacturing' or 'clinical trials'); 'productivity'; 'competitiveness'; 'nations' (or 'countries' or 'regions'). As an illustration of the large number of hits obtained with the different databases, the search criteria ('medical' and 'research' and 'spillovers' or 'externalities' or 'synergies') yielded 100, 829 and 345 hits in the economic working papers database (EconPapers), PubMed and the British Library Integrated Catalogue respectively.

The references listed in previously known and identified literature also provided an additional indirect route to the 'grey literature', which is information produced at all levels of government, academia, business and industry in formats not controlled by formal publishing, monographs and books.

Overall, we have identified and reviewed 139 papers/ reports.

3. Measuring rates of return from R&D

Our starting point is defining the basic characteristics of 'knowledge'.

3.1 Knowledge: basic characteristics

Arrow (1962) suggests that knowledge is inherently a public good. He also argues that knowledge differs from the typical factors of production (labour, capital) in two ways. First, it is non-excludable, non-rivalrous or non-exhaustible. Thus, knowledge developed for any particular application can easily spill over and have economic value in very different applications. This leads to what has become known as the appropriability problem for any organisation generating new information. This problem may diminish firms' incentives to invest in R&D. Second, compared with other factors of production knowledge has a greater degree of uncertainty, a higher extent of asymmetries and a greater cost of transacting new ideas.

It is also useful to distinguish between tacit and codified knowledge. Tacit knowledge can be difficult to write down in such a way that is meaningful and readily understood. It needs face-to-face and even nonverbal communication as well as reciprocity, all of which may be ineffective or infeasible over longer distances. It has also been referred to as "sticky knowledge" (von Hipple, 1984). Codified knowledge, on the other hand, can be written down – it is more akin to information than to tacit knowledge. It is better structured and less ambiguous. The cost of transfer of codifiable knowledge is lower than for tacit knowledge and is not bounded by close proximity of the source of knowledge. This distinction is critical in giving rise to the concept of 'localised knowledge spillovers', as discussed later.

3.2 Private versus social rate of return from R&D

Early attempts to identify the link between national R&D spending and economic performance employ macroeconomic models of growth which integrate R&D stock into the traditional production function as an input – treated as a residual factor accounting for growth in earlier works (Solow, 1957) and as a source of endogenous growth in more recent models (Romer, 1986; Lucas, 1988).

Empirical estimation of the impact of R&D stock on economic performance has proved to be problematic due to difficulties in:

- measuring R&D stock and economic output
- developing reliable econometric models using aggregate data which do not allow for variations across sectors and firms.

In general, the main limitation of these models is that they work as a 'black box' producing financial measures of social return to R&D investment, but unable to explain how R&D spending and innovation generate economic development.

Three main methodological approaches have been used to assess the value and benefits from research: econometric studies, surveys and case studies. The first method relies on the analysis of large databases; surveys have been conducted of R&D managers; while case studies attempt to trace all the antecedents to an innovation. Each method has its own advantages and disadvantages. In this Annex we draw upon the evidence generated by all three methods.

At the more general level, it is possible to distinguish between two types of return:

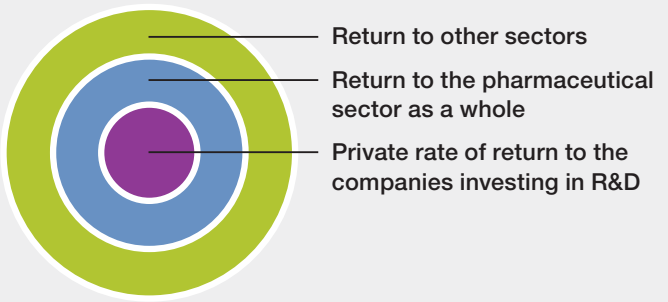
- private or direct return to investment, meaning the economic benefits generated by a specific R&D project and accrued by the organisation originally involved, through royalties and/or sales of a new product or process
- social or indirect return to investment, meaning economic and non-economic benefits spilling over for third parties to exploit, e.g. new knowledge and economic conditions that stimulate and enhance innovation and technical progress.

The difference between the social and the private rate of return represents R&D spillovers arising from innovative initiatives or projects undertaken by a public or private organisation and not captured by the originator.

The starting point for our work on estimating the magnitude of the impact of R&D spillovers from public and charitable medical research in the UK is Garau and Sussex (2007), who calculated the value of two major British based, research intensive, pharmaceutical companies to the UK's economy. The estimation is a practical application of an economic methodology based on the 'economic rent' that the companies earn for the UK. Specifically, they estimate the net additional income brought to the UK by these companies' activities in excess of the income they would be expected to generate in the next best alternative use(s) to which labour and capital would be diverted, if, hypothetically, these companies ceased to operate in the UK. One of the key elements generating the economic rent is the spillovers generated by the R&D investment carried out by these companies in the UK.

The underlying framework behind these authors' methodology for estimating the value of R&D spillovers in particular is illustrated in Figure A6.1. Here it is applied to pharmaceutical R&D in particular – but it could be applied to R&D carried out in any sector.

Figure A6.1 Spillovers from private pharmaceutical R&D



As shown in Figure A6.1, R&D investment undertaken in one company not only generates benefits to itself (the 'private' return – shown in purple above) but also could bring about economic benefits to other companies and organisations operating in the same industry (shown in blue), and to organisations in other sectors altogether (shown in green). The sum of all three 'rings' represents the total social return to the investment.

Garau and Sussex (2007) estimate, among other things, the spillovers generated by the (private) pharmaceutical R&D carried out by two companies in the UK. The range of estimates is based on empirical economic literature looking at the rate of return to private R&D. The total social rate of return is found to be around 51%, of which only 14% is captured by the investing firm, 26% is captured by other firms in the same sector, and 11% is captured in other (non-pharmaceutical) sectors of the UK economy. As highlighted by the authors, this estimate is highly uncertain, however, owing to the wide range of values attributed to the social rate of return to R&D in different studies.

The work carried out in Garau and Sussex (2007) is based on the methodology described in the joint Association of the British Pharmaceutical Industry (ABPI), Department of Health, Department of Trade and Industry (DTI) and HM Treasury study undertaken for the UK's Prime Minister's Pharmaceutical Industry

Competitiveness Task Force (PICTF) in 2000 and published in the December 2001 PICTF report *Value of the Pharmaceutical Industry to the UK Economy* (PICTF, 2001). The PICTF report presented an estimate of the economic value added by the pharmaceutical industry as a whole to the UK economy.

4. Sources of spillovers

Before discussing in detail the sources of R&D spillovers identified by the literature, we present the conceptual framework that forms the basis for the qualitative and quantitative analysis carried out on this topic.

4.1 Conceptual framework

It is extremely important to consider wider economic gains as well as health gains when assessing the economic benefits of medical research. These economic gains are additional to the health gains: they refer to the income for UK residents that is generated by public medical research investment. This is distinct from the monetary value of health (QALY) gains that were estimated in Chapter 5.

Investment in medical research by one organisation, public or private, may benefit not only that organisation but also other organisations in the medical sector, in other sectors, and also in other countries: i.e. 'spillovers'. Spillovers should not be viewed as accidental: they can be, and are, a deliberate policy objective of spending on public research. Our interest lies in spillovers generated by public medical R&D. Given the link between R&D and knowledge, we do not distinguish here between R&D spillovers and knowledge spillovers but refer to both taken together.

For illustrative purposes, we take a simplified view of the inputs and outputs of the R&D process. 'Public research' refers to R&D carried out or funded by public and charitable organisations, and includes university research. Private R&D is carried out by privately owned enterprises. These inputs, either in isolation or in combination, lead to some 'output': new products, new patents or better performance (measured in a number of ways) by firms. These outputs generate additional GDP, i.e. income, and economic rent for the residents of the UK.

As a preliminary step to quantify the spillovers generated by the R&D analysed in this work (see Chapter 6 of this report), we conducted a literature review on the topic of spillovers. The review was originally intended to cover only public medical research. That literature was relatively scarce, however, so we extended the search to cover public and private R&D in general, without focusing on medical research in particular.

The literature on R&D spillovers, as a general concept, is relatively abundant. However, the literature is not clear about defining and outlining the conceptual framework within which spillovers exist and transmit. The aim of this section is to combine and synthesise the existing literature to present a (simplified) conceptual framework that will help the reader understand better what spillovers are and how they work in practice.

This section has been divided into three main elements, each discussing in turn the three sources of spillovers described below (sections 4.2, 4.3 and 4.4 of this Annex respectively). We distinguish between public and private R&D as sources of spillovers.

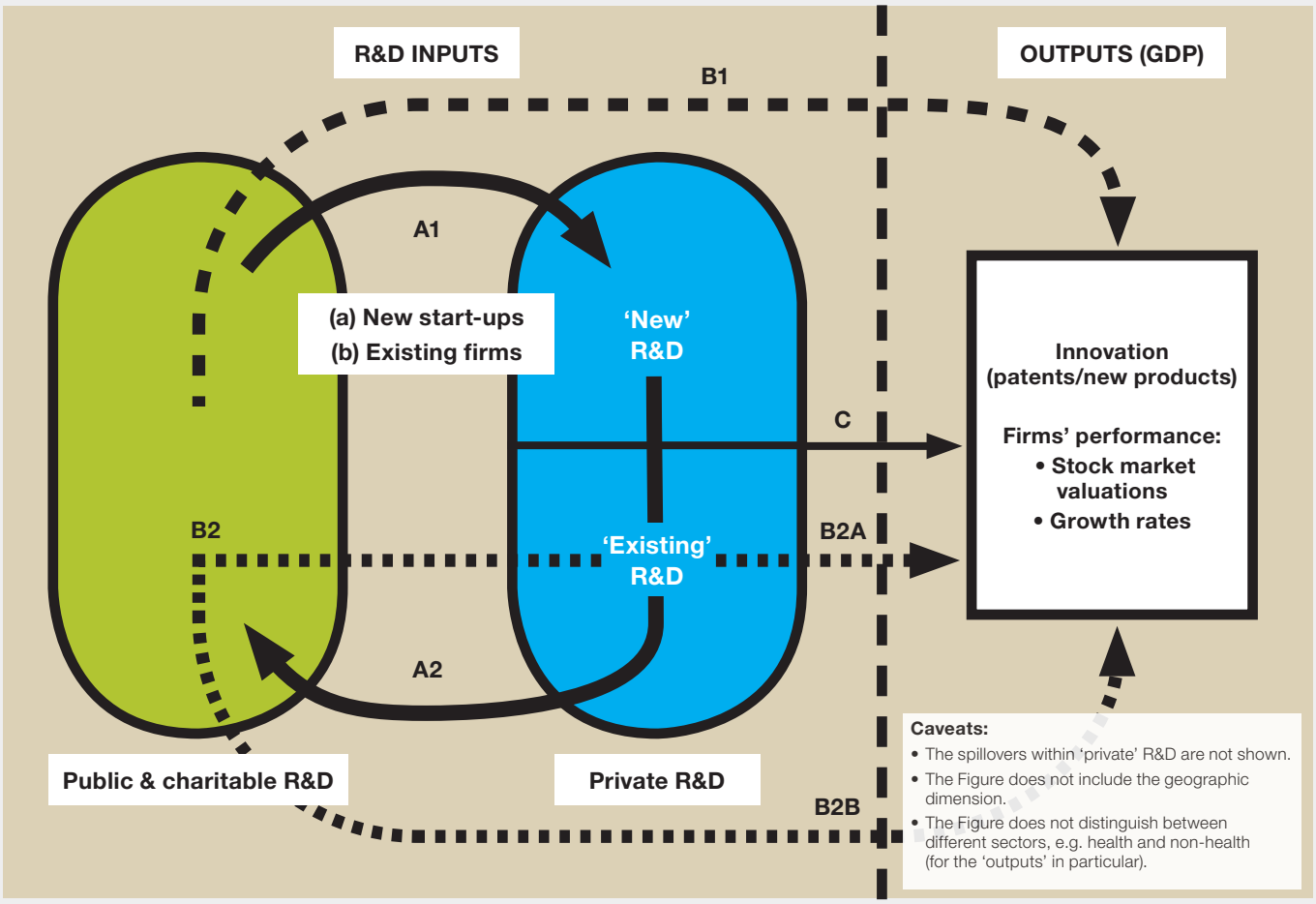
The first 'source' refers to the degree of complementarity between public and private R&D, and, in particular, whether and how much private R&D is generated as a result of public R&D. Section 4.2 of this Annex relies mainly on the literature on biomedical R&D, given the distinct nature of the R&D process for pharmaceuticals. An additional interesting result identified from this literature is that the relationship between public and private pharmaceutical R&D is bi-directional, i.e. private R&D helps generate public R&D, as well as the other way around, and it is the interaction between the public and private research sectors that helps to generate and develop new technologies. However, and as discussed in more detail later, the quantitative evidence available looks primarily at the first effect, i.e. how much private R&D is done thanks to public R&D. This strand of the literature looks at the relationship at an aggregate level, rather than looking at individual organisations.

Another part of the literature looking at the public–private research relationship explores how new firm start-ups and the location decisions of new firms are affected by university and other public research. This literature looks at other sectors other than the biomedical sector. Several authors argue that the decision of new firm start-ups where to locate is influenced by traditional regional characteristics (such as size and concentration of population) as well as by the opportunity to access knowledge generated by universities and other public laboratories.

The main differences between these two strands of the literature (other than the sectors analysed) is that the former literature is more aggregated in that it does not explore how individual firms/agents respond. The latter literature looks at decisions taken by individual organisations (in this case, firms) as a result of public R&D. In addition, the latter can be described as the stimulation of creating capacity to do R&D (via new firms), while the former is more of a stimulus of R&D itself.

The second source of spillovers is public research (see Section 4.3 of this Annex). The literature here primarily focuses on university research, which we take as 'public' R&D. The literature for this section focuses on a micro level, in that it explores the reactions and decisions taken by individual organisations, such as individual firms, in response to public research.

Figure A6.2 Sources of spillovers: public and charitable R&D and its interaction with private R&D



Private R&D is the third source of spillovers identified by the literature (see Section 4.4). Figure A6.2 represents graphically public research as a source of spillovers and its complementarity with private R&D. Sections 4.2 to 4.4 in effect describe Figure A6.2 in more detail, referring back to the three sources of spillovers mentioned above.

4.2 Complementarity between public and private R&D

From our literature review we have grouped a selection of papers into two broad approaches to the analysis of the relationship between public and private R&D. On the one hand, we have grouped together the literature looking at the biomedical sector. Then there is another strand of the literature that explores the links between public research (in particular, university research) and the decision to locate new firm start-ups in all sectors, not just the biomedical sector. We take these two strands of the literature in turn.

4.2.1 The biomedical sector

Within the biomedical sector, public sector research plays an important role in the discovery of new drugs and other health care technologies, but the reality of the interaction between the public and private sectors is much more complex than a simple basic/applied dichotomy would suggest. As some authors have argued, the conventional picture of public research as providing a straightforward input of basic knowledge to downstream, applied private research may be quite misleading. Thus, the relationship between the public and private sectors in the pharmaceutical industry is not well described as a 'cascade model'.

Referring to Figure A6.2, the arrows headed 'A1' and 'A2' illustrate the two-way relationship between public and private R&D. Arrow 'A1' illustrates the fact that some private R&D takes place in the UK thanks to public R&D in the UK. However, some private R&D would take place even if all public R&D activities were to be eliminated. Moreover, and as the literature suggests, we need to take into account the public sector R&D generated due to the private R&D – the arrow labelled 'A2'. Note that arrow 'A2' stems from both 'new' and 'existing' private

R&D; i.e. there might be a feedback loop back to public R&D from the private R&D that has been generated in the first place from public R&D. The literature has focused primarily on estimating quantitatively how much private R&D is generated by publicly funded R&D.

We found two particularly relevant published empirical studies of the relationship between publicly funded and privately funded R&D in the pharmaceutical industry: Ward and Dranove (1995) and Toole (2007). Both studies refer to publicly funded medical research in the USA, by the National Institutes of Health (NIH), and to the impact on the sum of R&D expenditure in the USA by all pharmaceutical companies and R&D expenditure by US-based pharmaceutical companies worldwide. A great deal of caution must be exercised when considering the relevance of these studies to the question of the impact of UK public and charitable medical research on UK private sector R&D. The scales of both publicly funded medical research and private sector R&D activity in the pharmaceutical and other health industries are several times greater in the USA than in the UK. The opportunities for interactions between the two are therefore much greater in the USA than in the UK. However we were unable to find empirical data on the public/private R&D linkages for the UK or for an economy closer to it in scale.

Ward and Dranove (1995) used annual data for the period 1966–88. Over that period NIH-funded R&D grew at an average rate in money of the day terms by 8–11% p.a. depending on therapeutic category. Pharmaceutical industry R&D (in money of the day) grew over the same period at an average rate of 11–19% p.a. depending on therapeutic category. From these data Ward and Dranove estimated that a 1% increase in publicly (NIH) funded basic research expenditure in the USA in a particular therapeutic category would, after a lag of seven years, cause a 0.76% increase in private industry R&D spend in that same therapeutic category and a 1.71% increase in private industry R&D spend in other therapeutic categories. Thus a 1% increase in NIH spend across all therapeutic areas leads to a 2.5% increase in total private pharmaceutical R&D spend by members of the US trade association, Pharmaceutical Manufacturers of America. Industry data cover "both domestic and overseas R&D by US manufacturers" but "only US-based R&D for foreign manufacturers" (p. 76). Ward and Dranove did not attempt to estimate whether there was any impact of public medical research on non-pharmaceutical sector private R&D.

The recent studies published by Toole, based on US data, show that basic research supported by government and public agencies, mainly undertaken in university and non-profit laboratories, stimulates and supports private investment on R&D in the pharmaceutical and biotech sector. Toole (2007) concluded that public medical research complements, rather than crowds out, private pharmaceutical industry R&D investment. Unlike Ward and Dranove, Toole distinguishes different strengths of impact for NIH funded basic laboratory research and for the clinical human research they fund. But, unlike Ward and Dranove, Toole does not distinguish the impact of public research spend on private R&D spend within the same therapeutic category from that on private R&D spend in different therapeutic categories. Like Ward and Dranove, Toole also did not attempt to estimate the impact of public medical research on non-pharmaceutical sector private R&D.

Toole used data for the period 1981–96 for NIH spend disaggregated into seven therapeutic categories, and for 1981–97 for US pharmaceutical industry R&D spend defined as US and worldwide spending by US companies and spending in the USA by non-US companies (i.e. the same definition used by Ward and Dranove, and again from the trade association of the pharmaceutical industry in the US, now named Pharmaceutical Research and Manufacturers of America, PhRMA). Over the 1981–96 period, NIH expenditure was growing at an average rate of around 3% p.a. in real terms, and pharmaceutical industry R&D grew faster than NIH in most therapeutic categories. The study is based on an empirical model where the level of private investment is a function, among other things, of basic scientific knowledge generated by public research. Toole found that a 1% increase in NIH expenditure on basic research leads to a 1.69% increase in pharmaceutical industry R&D after a lag of eight years. Toole also found a U-shaped pattern of response: with private R&D increasing in years 1, 2, 7 and 8 after the increase in NIH spend, but with no great response in years 3–6. The response to public clinical research is shown to be smaller than for basic research but achieved sooner. Toole estimates that a 1% increase in NIH expenditure on clinical research leads to a 0.40% increase in pharmaceutical R&D, and that this is achieved within three years. Moreover, Toole's results indicate that "a dollar increase in public basic research stimulates an additional $8.38 in pharmaceutical investment after eight years" (Toole, 2007).

Similar arguments have been presented by the US Congressional Budget Office (CBO, 2006): "It is seldom possible to identify particular cases in which the private sector would have performed research if the government had not. Thus, most of the available empirical evidence is based on aggregate studies. On balance, that evidence suggests a positive relationship between public and private pharmaceutical R&D" (p. 31).

For the UK in particular, recent data published by the Association of the British Pharmaceutical Industry (ABPI) shows the extensive collaborative research links between the pharmaceutical industry and the UK university science base. The ABPI figures, gained from a survey of 11 major pharmaceutical companies operating in the UK, show that 606 PhD studentships and 327 postdoctoral grants were conducted in collaboration with 78 British universities in 2007 (ABPI, 2008). However, the figures are down from 2003 – by

nearly 14% on PhD studentships and almost 25% for postdoctoral grants. According to the ABPI, there are three main types of collaboration between industry and universities: PhD studentships, where students carry out research projects jointly between a university and a company; postdoctoral grants, where jointly funded research programmes are undertaken between companies and universities, including exchanges of personnel; and industrial placements, where undergraduate students work within companies for usually one year as part of their degree studies.

Crespi and Geuna (2004) focus on the impact of higher education sector R&D spending on science productivity (not specifically on the pharmaceutical sector) and attempt to estimate any crowding-in or crowding-out effect of different sources of funding. Because of the need for more robust country level data, however, they do not find any significant evidence of this phenomenon.

4.2.2 New firm start-ups

As mentioned above, the second strand of the literature looking at the public–private R&D relationship explores how new firm start-ups and the location decisions of new firms are affected by the presence of university research. Several authors argue that the decision of new firm start-ups where to locate is influenced by traditional regional characteristics (such as size and concentration of population) as well as by the opportunity to access knowledge generated by universities. For instance, Audretsch and Lehmann (2004a) and Audretsch *et al*. (2003) show, based on German data, that university spillovers play an important role and have a strong influence in shaping strategic locational decisions of firms.

Two main results can be highlighted from this work. First, the number of entrepreneurial start-ups is greater in those regions with a greater presence of knowledge inputs. Second, the 'type' of knowledge generated and the mechanism by which the knowledge is transmitted are important. The authors make a distinction at two levels – between research carried out in the social sciences and natural sciences areas, and between human capital and publications – which relates back to whether the knowledge is tacit or codifiable. For those university outputs and spillover mechanisms that are more tacit in nature (social sciences and human capital), geographic proximity plays a greater role in accessing and absorbing university spillovers. As a conclusion, the authors argue that new firm start-ups' decisions to locate are influenced by traditional regional characteristics as well as by the opportunity to access knowledge generated by universities. But the impact of university output on new firm location depends on both the type of knowledge and mechanism used to access that knowledge.

Mansfield (1995) distinguishes between basic and applied research, and argues that firms tend to trade off faculty quality for geographical proximity, particularly in the case of applied research. For basic research, firms seem to pay less attention to location in choosing universities to work with and support, perhaps because in many kinds of applied R&D it is very useful for academics and firm personnel to interact and work together face-to-face, whereas in basic research ties may be weaker and more sporadic. This relates back to the distinction between tacit and codified knowledge – the former being probably more akin to applied research and the latter to basic research.

4.2.3 The impact of proximity on innovative activity

A recent article explores the links between university research and business innovation in the UK in particular for a number of sectors, including pharmaceuticals. Abramovski *et al*. (2007) examine whether firms are locating R&D facilities close to top university departments in the UK, and conclude that there is a positive correlation between the location of R&D-performing establishments and the presence of high quality relevant university research departments. They also claim that in some industries, private-sector R&D labs are disproportionately clustered around highly rated university research departments. These authors also found that the clustering of R&D facilities close to university departments is particularly strong in the pharmaceuticals and chemicals sector. For example, their results suggest that a postcode area with a university chemistry department rated 5 or 5* for its research is likely to have around twice as many labs doing R&D in pharmaceuticals and around three times as many foreign-owned pharmaceuticals R&D labs compared with a postcode area with no 5 or 5* rated chemistry departments. Interestingly, the authors also suggest that their results do not provide direct evidence on how firms indeed connect and link with universities – which is what they plan to examine in more detail in their future research.

Martin and Tang (2007) reinforce the previous results in that researchers and students can spin out from universities to exploit new ideas and technologies, by establishing start-up companies. This in turn transfers skills, tacit knowledge and the other benefits of university know-how mentioned above into the commercial environment. These authors cite three examples illustrating how universities can stimulate regional and firm growth: Route 128 in Boston (MIT), Silicon Valley in California (Stanford), and the development of new 'high technology' firms around Cambridge University in the UK. The references found therein again reinforce the relation between new firms and their interactions with universities – with a particular focus on the biotechnology sector.

According to a UK report by the then Minister for Science (Department of Trade and Industry, 1999), the biotech sector in the UK (broadly defined as the sector focusing on new technologies, including pharmaceuticals) offers an example of the development of clusters and factors encouraging them. The UK has a strong research base spread across a number of

regions supported by the presence of world leading research institutes such as the Sanger Institute and the Roslin Institute. To these areas of research strength correspond areas of concentration of biotechnology companies in East Anglia (Cambridge), South East England (Oxfordshire and Surrey) and Central Scotland.

The quantitative analysis presented in Furman (2003) is based on panel data reflecting activities of more than 30 pharmaceutical firms over the period 1984–94. The analysis suggests that lab-level scientific orientation does indeed vary by region and is positively related to the strength of scientific and technical bases in the region geographically proximate to the focal laboratory. Furman proposes that the extent to which firms incorporate science in their drug discovery efforts is correlated with the strength of the scientific base in the local geographic regions in which they operate. The hypothesis is that regions that offer extensive scientific resources, such as universities, government laboratories, or a collection of private, science-oriented firms, will be more likely to generate science-oriented firms than will those with more limited scientific assets.

4.2.4 Why are public and private research complements?

The large majority of the literature and empirical evidence we found supports the view that public/charitable medical research, overall, stimulates additional private R&D rather than crowding it out. There is a much smaller and empirically less well supported literature that takes a contrary view – see David and Hall (2000), and Kealey and Al-Ubaydl (2000).

Beyond the empirical estimates, it is important to understand why an increase in public expenditure on research might have a positive effect on private R&D in the biopharmaceutical sector. In other words, what are the key characteristics of R&D for health care technologies that make it so important for the public sector to intervene though specific policy mechanisms? What is the role of public funding supporting biomedical basic research?

The development of innovative technology in the pharmaceutical and biotech sector is characterised by:

- a high level of uncertainty due to a significant scientific challenge at early stage (basic research and pre-clinical) and recurrent risk of failure at clinical phases
- large investment required compared to other sectors – the average out-of-pocket costs of a new product approval is $400 million (DiMasi *et al*., 2003), whilst in other highly innovative sectors, such as IT and communications technologies, an investment of £4 million allows companies to bring new products to the market (Cooksey, 2006).

Investors in the pharmaceutical and biotech sectors (shareholders and venture capitalists, respectively) need to assess the expected returns on their investments, which is particularly problematic at the basic research stage where the outcomes of research efforts are very uncertain, and are keen to generate returns as quickly as possible. Venture capitalists are key funders of early-stage biotech firms but have a time horizon of three years for a particular investment, compared to 10–12 years required by companies to develop and market successful health care products (Pisano, 2006).

Against this background, various reports commissioned by government authorities have attempted to illustrate and explain why publicly funded medical research can stimulate and complement private investment on R&D in the pharmaceutical and biotech sectors. Factors cited as important to private companies include:

- Potential collaborations with research centres and universities supported by government funding. These are associated with "cost-sharing and risk reduction opportunities" (NERA, 2007; CRA, 2004). For example, public resources can be used to finance fixed capital costs (e.g. laboratories and other infrastructures) and private funds can cover variable costs of research projects (Crespi and Geuna, 2004).
- Returns may be subsidised by public investment on research and clinical trials. The NIH in the USA is often cited as an example of government funds effectively complementing venture capitalists' investments in the biotech sector.

We have found no quantitative evidence on the magnitude of arrow A2 in Figure A6.2, although as argued by Cockburn and Henderson (1996, 1998, 2000) the private sector also invests heavily in basic research, viewing it as fundamental to the maintenance of a productive research effort. As argued by these authors, public and private sector scientists meet as scientific equals, solve problems together and regard each other as scientific peers, which is reflected in extensive co-authoring of research papers between the public and private sectors. For instance, Cockburn and Henderson (1998) show there is extensive co-authoring of research papers between the public and private sectors, and that there is some evidence that this co-authoring activity is correlated with private sector productivity. They conclude that the private sector results can have importance for public sector work.

4.3 Public research as a source of spillovers

4.3.1 Literature review: social rate of return to public research

Empirical literature provides estimates of the social return to public investment in agricultural research but not medical research. Table A6.1 summarises the main findings.

Table A6.1: Estimates of social rate of return to public R&D in the agricultural sector

Study	Social rate of return
Griliches (1958)	20–40%
Griliches (1964)	35–40%
Huffman & Evenson (1993)	43–67%
Knutson & Tweeten (1976)	28–47%
Peterson (1967)	21–25%
Schmitz & Seckler (1970)	37–46%

Sources: Griliches (1991), Salter *et al.* (2000).

Most of the works estimate the rate of return to publicly funded research (in the agricultural sector) to be in the range of 20–67%. The main limitations of these studies are that they may be biased towards those government R&D programmes that proved successful, and the preponderance of US data which may not translate directly to the situation of the UK. Nevertheless, they are indicative of the existence of a large and positive economic contribution of public research to the national economy as a whole with a social rate of return of at least 20% and probably higher. As noted by Buxton *et al*. (2004), and based on the review by Salter and Martin (2001), none of the studies measuring the benefits to an economy from publicly funded research provides a simple and comprehensive model.

More recent contributions on the issue of measuring the rate of return of publicly funded research include the studies conducted by Mansfield, which focus on the contribution of research conducted by academic centres to innovation delivered by commercial sectors (arrow B2 in Figure A6.2). Mansfield (1991) concludes that over 10% of new products and processes marketed by surveyed firms could not have been developed (without substantial delay) in the absence of academic research, and that this proportion is as high as 27–31% in the pharmaceutical sector specifically. Mansfield provides an estimate of the social rate of return on academic research of 28%. The results of Mansfield's later (1998) study are similar with respect to the impact of academic research on commercial innovation but provide no rate of return estimate.

There is wide agreement about the importance of universities in generating economic growth. As argued by Nelson (1986), universities are recognised generators and repositories of public knowledge. Also, centres of commercial innovation and entrepreneurship are linked to proximity to universities. Hughes (2006) identifies four kinds of interaction that work at the university–industry interface: (1) basic university role of educating people, including providing suitably qualified human capital for the business sector; (2) research activity and the role it plays in increasing the stock of codified knowledge which may have useful or commercial elements; (3) problem-solving in relation to specifically articulated business needs; (4) 'public space' functions. The last of these includes a wide range of interaction mechanisms between university staff and the business community: informal social interactions, specially convened meetings, conferences, centres to promote entrepreneurship and entrepreneurship activities, and the exchange of personnel including the role of internships. These may lead to the transfer of both codified and tacit knowledge and the establishment of relationships which may feed back into the other three kinds of interactions.

Martin and Tang (2007) refer to many studies which, they argue, suggest that the recruitment of skilled graduates represents the most important mechanism through which firms derive economic benefits from basic research.

4.3.2 Public research spillovers: effects on innovation

The literature identifies two potential effects of university research spillovers on respectively: (1) innovation (patents/new product innovations); (2) performance/ growth of firms. Arrow B1 in Figure A6.2 represents the results of the literature that examines the use of the (modified) 'knowledge production function'. The knowledge production function explores the relationship between knowledge inputs, such as public and/or private R&D, and (innovative) outputs, such as patents and new products. This strand of economic literature provides some evidence of the importance of geographically mediated commercial spillovers from university research, highlighting the positive effects from locating close to the sources of public research, in this case, universities. Indeed, university research has been found to have a positive and significant effect on both patents and new product innovations. Arrow B1 thus represents one 'direct' spillover effect of public R&D that is not generated via the private sector.

Arrow B2 represents the literature that argues that public R&D, in the form of university research, has a positive impact on firms' performance and growth. A number of papers suggest that geographic proximity and university spillovers are complementary determinants of firm performance. A combination of both factors (but not alone) results in significantly higher stock market performance. This effect depends on the type of university output. As illustrated in Figure A6.2, arrow B2 shows potentially (at least) two channels for this university spillover. One channel implies that the firm's performance improves because public R&D improves (somehow) the productivity of the existing R&D carried out by existing firms, which in turn leads to better performance (B2A). The other channel by which public R&D can improve firms' performance is more direct, without influencing 'existing' R&D (B2B). Unfortunately, the literature leaves relatively undefined

the exact mechanism by which this occurs, which is why arrow B2 has two 'branches'. The difference between arrows B1 and B2B (both go directly from 'public and charitable research' to 'outputs' without going through 'private R&D') is the 'effect' of the public research: while the literature that gives rise to arrow B1 focuses on the relationship between public research and innovation (measured as new patents or new products), the literature underlying arrow B2B explores the link between public research and firms' performance.

For the first effect, as illustrated by arrow B1, Jaffe (1989a) uses a modified 'knowledge production function', where the dependent variable is state-level (US) corporate patents (a proxy for useful knowledge). The two inputs are private R&D and university research. The results provide some evidence of the importance of geographically mediated commercial spillovers from university research, which turns out to be strongest for the subsegment classified as 'drugs'. The overall elasticity of corporate patents with respect to university R&D is around 0.1, meaning that a 1% increase in university R&D expenditure is associated with a 0.1% increase in corporate patents. Jaffe also models simultaneously industry R&D and university research. He finds an indirect or inducement effect, via increasing private R&D; and this effect is even larger. While we have included this result within the literature that supports the existence of B1 (direct effect of public research), this result could also be used to corroborate arrow A1. Indeed, given Jaffe's elasticity of industry R&D with respect to total university research (0.704) and the elasticity of corporate patents with respect to corporate research (0.814), the implied elasticity of induced corporate patents with respect to university research is almost 0.6 (0.704 × 0.814). This author also finds evidence, albeit weak, of the impact of co-location of universities and research labs. Acs *et al*. (1992) replicate this analysis using actual product innovations from the USA, and find even higher elasticities and stronger support for co-location. Based on a survey of companies, Nelson (1986) also supports these results, as he claims university research is positively and significantly related to the R&D intensity of the industry in question.

Arundel and Geuna (2001) use the PACE survey of Europe's largest industrial firms to test, among other things, the importance of proximity in the transfer of knowledge from publicly funded research organisations (PROs), which includes universities, to firms. Their descriptive results show that PROs are the most important external source of knowledge for firms' innovation. Also, their results show firms use a variety of methods to acquire different types of knowledge from PROs, including some that provide access to codified knowledge (e.g. reading publications or attending conferences), and methods that provide the opportunity to access non-codified knowledge, such as informal personal contacts, joint research, and hiring trained scientists and engineers.

Link and Rees (1990) compare university-based research relationships between small and large firms in an effort to identify one factor that might explain the noted difference in innovativeness between firms of different sizes. The underlying hypothesis of this work is that there are diseconomies of scale in large firms owing to the fact that bureaucratisation in the innovation decision making process inhibits not only inventiveness but also slows the pace at which new inventions move through the corporate system towards the market. Link and Rees argue that although large firms are more active in university-based research per se, small firms appear better able than large firms to utilise their university-based associations to leverage their internal R&D.

Gambardella (1992) offers empirical evidence for the pharmaceutical sector that in-house scientific research raises the ability of firms to take advantage of public science. Using evidence from case studies, he argues that firms with better in-house scientific research programmes have more effectively exploited outside scientific information. He also finds, based on data from the then 14 largest US-based pharmaceutical companies, that company patents are positively correlated with the scientific publications of the firms even after controlling for the scale of R&D.

For new medicines in particular, Toole (2000) examines the impact of public research on pharmaceutical innovation using a production function approach, linking new molecular entities (NMEs) approved by the US Food and Drugs Administration (FDA) with the stock of public basic research (number of awards granted by the NIH) and private pharmaceutical R&D. Public research has a positive and significant impact on discovery of NMEs: elasticity estimates are in the range of 2–2.4 implying that a 1% increase in the stock of basic research leads to an average 2–2.4% increase in the number of approved NMEs. The results also show there is a lag of 17 to 19 years between investment on public research and new products approval.

4.3.3 Public research spillovers: effects on firms' performance and growth

For the impact on firms' performance and growth (arrow B2), and based on the German dataset used in Audretsch and Lehmann (2004a) and Audretsch *et al*. (2003), the empirical evidence in Audretsch *et al*. (2003) and Audretsch and Lehmann (2004b, 2006) suggests geographic proximity and university spillovers are complementary determinants of firm performance. A combination of both factors (but not alone) results in significantly higher stock market performance. This effect, as with the decisions to locate and start a new firm, also depends on university output. If the spillover involves knowledge in the natural sciences, geographic

proximity is less important; if in the social sciences, geographic proximity is seen to be a necessary condition for generating abnormal profits. Moreover, the smaller the distance from the nearest university and the higher the number of academic papers published, the higher the growth rate of firms. The Audretsch papers, however, leave unclear the mechanism by which university research ultimately improves firm performance. However, as highlighted by Jaffe (1989), public research has an indirect effect on corporate (i.e. private) patents, by increasing private R&D. Thus, this evidence might support more the existence of arrow B2A rather than B2B.

4.4 Spillovers from private R&D

4.4.1 Literature review: social versus private rate of return to private R&D

Table A6.2 summarises the findings of the empirical literature on the total economic returns – i.e. the 'social returns' – to private R&D spending. The social return is typically around 50% and greatly exceeds the private return captured by the investing organisation (typically around 20%) in every case. The difference between the social and private returns is the return captured by firms, organisations or individuals other than the firm that made the original investment. The empirical studies listed in Table A6.2 use various approaches to estimate the productivity growth at the industry and inter-industry level generated by R&D efforts, including cost function approaches (Bernstein and Nadiri, 1988; Bernstein and Nadiri, 1991), total factor productivity (TFP) (Griffith *et al*., 2004a) and production functions using patents as a measure of firms' output (Jaffe, 1986; Scherer, 1982, 1984). Each study considers different sets of industries and data relating to US companies or OECD countries. Some of the references included in Table A6.2 are reviews (Garau and Sussex, 2007; Nadiri, 1993; PICTF, 2001).

We conclude that the social rate of return to private sector R&D tends to be around 50% but could be significantly higher. The variability of the figures is partly due to the lack of a widely accepted theoretical model explaining accurately the complexity of the innovative process and to a paucity of reliable data providing robust support to the research question. In particular, some studies measure benefits induced by R&D spending in terms of output of new products and process, not taking into account that investment on R&D also contributes significantly to building absorptive capacity and accumulating capability to solve complex problems. With regard to the available data, one of the main limitations is related to a high degree of aggregation not accounting for inter-industry or interfirm differences.

In terms of the literature measuring the spillovers from private R&D in particular, we have identified three potential effects of private R&D spillovers: (1) productivity of other firms' R&D; (2) entry decisions of potential competitors; (3) reduction of production costs.

Table A6.2: Social return to private R&D

Study	Private rate of return	Social rate of return
Bernstein & Nadiri (1988)	9–27%	10–160%
Bernstein & Nadiri (1991)	14–28%	20–110%
Goto & Suzuki (1989)	26%	80%
Griffith *et al*. (2004a)	NA	40%
Griliches & Lichtenberg (1984)	NA	41–62%
Jaffe (1986)	NA	30%
Mansfield *et al.* (1977)	25%	56%
Nadiri (1993)	20–30%	Approx. 50%
PICTF (2001), Garau & Sussex (2007)	14%	51%
Scherer (1982, 1984)	29–43%	64–147%
Sveikauskas (1981)	10–23%	50%

4.4.2 Productivity of other firms' R&D

Jaffe (1989b) carries out an analysis of firms' patents over patent classes. He defines classes or technological groups, and measures a pool of spillovers. This pool is the sum of all other firms' R&D, weighted by technological proximities. He finds that a firm's R&D productivity is increased by the R&D of technological neighbours, though neighbours' R&D lowers profits and market value of low R&D intensity firms. Moreover, if everyone increased their R&D by 10%, total patents would increase by 20%, with more than half the increase coming from the spillover effect; and if everyone increased their R&D by 10%, then aggregate profits would increase by about 3%, with about one third of the net increase coming from the spillovers.

Frantzen (2000) performs a cointegration analysis on annual panel data with respect to a set of manufacturing industries in a series of OECD countries over the period 1972–91. Results show that not only own R&D capital, but also domestic and international R&D knowledge spillovers, as well as human capital, play an important role in explaining the evolution of manufacturing productivity in OECD countries. The spillover effects were shown to be both intersectoral and intrasectoral in nature and there was evidence that they are especially strong in research intensive industries. Similar results, based on the same data, are obtained in Frantzen (2002a, 2002b).

Guellac and de la Potterie (2001) investigate the long-term effects of various types of R&D on multifactor productivity growth (MFP), which is argued by the authors to be the spillover effect of R&D. Econometric estimates are conducted on a panel of 16 OECD

countries, over the period 1980–98. These authors argue that business R&D has a positive and significant impact on MFP, indicating that there are substantial spillovers from business R&D – the return to the economy as a whole is larger than the private return. Also, the impact of business R&D on MFP is larger in countries where R&D intensity is higher, and the effect of government and university performed research on productivity is positive and significant.

Park (2004), based on pooled time-series data from 14 OECD economies and three East Asian economies for the period 1980–95, allows for the simultaneous presence of international and intersectoral (manufacturing to non-manufacturing) R&D spillovers. He finds an asymmetry in intersectoral R&D spillovers: while manufacturing R&D has a strong intersectoral R&D spillover effect on non-manufacturing TFP, the reverse is not true. Park argues that this is because the manufacturing sector provides relatively more technology-embodied intermediate goods for the non-manufacturing sector.

Cassiman and Veugelers (2002), based on Belgian data in the 1993 Community Innovation Survey (CIS), show that incoming spillovers have a positive and significant effect on the probability of firms cooperating. Cooperating firms, because of the improved technological competence of the partners, better tap the existing base of know-how. Firms with better appropriability have a higher probability of cooperating in R&D. Moreover, firms that find the publicly available pool of knowledge more important for their innovation process are more likely to benefit from cooperative agreements with other research institutes.

A number of articles analyse the spillover effects specifically in pharmaceutical R&D. Cockburn and Henderson (1994) use detailed data on R&D investments and outcomes at the level of individual research programmes conducted within ten pharmaceutical firms over a period of 17 years. They find that competitors' research appears to be a complementary activity to own R&D: rivals' R&D results are positively correlated with own research productivity. The authors interpret this as evidence of significant spillovers of knowledge across firms, rather than the depletion externality implied by 'winner takes all' models. Henderson and Cockburn (1996) focus on the 'knowledge production function'. Knowledge is measured as grants of 'important' patents, and the explanatory variables include two measures of 'spillovers': (1) count of competitors' output in the same narrow research area; (2) count of competitors' output in all the other programmes in the wider therapeutic class. Results, based again on programme-level data, show that at the mean, programmes whose competitors' programmes are in the same or related fields that are roughly 10% more productive, will be approximately 2% more productive themselves.

Henderson and Cockburn (1996) argue that the pharmaceutical industry is characterised by high rates of publication in the open scientific literature. They carried out an extensive interview programme with scientists and researchers. They note that many of the scientists interviewed stressed the importance of keeping in touch with the science conducted both within the public sector and by their competitors. Nearly all of the interviewees, according to the authors, had a quite accurate idea of the nature of the research currently being conducted by competitors, and they often described ways in which their rivals' discoveries had been instrumental in shaping their own research.

Moreover, these authors suggest that there may have been a concomitant change in the role of spillovers in shaping research productivity in the pharmaceutical industry. Some decades ago, when research in the pharmaceutical industry was done via screening compounds, there was little to be learned from others unless they found a particularly promising molecule. Now, however, pharmaceutical companies actively invest in the generation of new physiological and biochemical knowledge, so even knowledge of others' false starts and failures may help to shape one's own research programme. Thus, the impact of interfirm spillovers on research productivity in the pharmaceutical industry may have increased over time. Henderson and Cockburn argue that before 1978 the benefits of spillovers were realised primarily within narrow therapeutic areas, while after 1979 the opposite appears to be true. The authors argue that after 1979 programmes benefited primarily from work conducted by their competitors in related therapeutic areas, rather than research focused on the same disease targets. As the authors conclude, "modern theory ascribes a central role to interfirm spillovers as drivers of economic growth, so it is reassuring to find them present in research intensive industry such as pharmaceuticals" (p. 56).

A more recent paper explores the relationship between R&D productivity and the potential for spillovers provided by local research to distributed research laboratories, drawing on a sample of multinational pharmaceutical firms in the 1980s (Furman *et al*., 2006). The authors first analyse the productivity of a firm's research effort at therapeutic class level, rather than looking at the whole firm's research efforts. This allows for more direct comparisons between firms' research programmes as well as within-firm productivity differences across therapeutic areas that may be driven by local spillovers. Furman and colleagues also test for the importance of local spillovers by constructing local measures of knowledge generation directly, rather than inferring their impact. Furthermore, they distinguish between privately and publicly generated spillovers. The authors find that spillovers exist and are significant. Patent output at the therapeutic class level is positively correlated with a firm's 'exposure' to papers related to that therapeutic

class authored by scientists based within 35 miles of where the firm conducts research.

One of the novelties of Furman *et al*. (2006) is that the authors distinguish between privately and publicly authored papers (by institutional affiliation of the author). This distinction yields a striking result: patent output is positively and significantly correlated with publicly authored work, but negatively and significantly correlated with private sector work. Thus, this work somewhat contradicts the previous analyses suggesting that private R&D was a source of spillovers for other firms not directly carrying out that R&D. The authors do argue, however, that it is a reduced form result, so probably the result summarises a mix of factors. For instance, it may be that extensive rival publication in a particular area reduces the opportunity for any single firm to make novel discoveries that are a prerequisite to patent generation. Alternatively, extensive rival publication may signal significant future competition in a particular market, thus reducing the attractiveness of dedicating effort in the area and the incentive to generate patents after research efforts have already been expended. As suggested by the authors, these hypotheses are just a handful of many credible explanations that merit further research.

4.4.3 Entry decisions of potential competitors

In terms of the second spillover from private R&D, entry decisions of potential competitors, Aharonson *et al*. (2006) use detailed data on Canadian biotechnology entrants in the 1990s to explain the dichotomous variable of whether or not to enter in a postcode area in a given year. One of the explanatory variables is the intensity of incumbents' inventive activity, measured as R&D spending and number of R&D employees. The authors argue that new entrants are influenced systematically by factors promoting the benefits of co-location, and seek locations that would allow them to benefit positively from knowledge spillovers.

Stuart and Sorenson (2003) look for an explanation for firm co-location in high-tech industries. Their results suggest that areas with large populations of biotech and venture capitalist firms do enjoy a 'regional advantage' and that such areas experience the highest rates of biotechnology entrepreneurship. Feldman (2003) also looks at the locational dynamics of the US biotech industry. This author argues that the biotech industry is becoming more geographically concentrated and highly specialised in certain locations. There might be several reasons for this, but one put forward by the author is that "existing firms serve as anchors that attract skilled labour pools, specialised intermediate industries and provide knowledge spillovers that benefit new technology intensive firms in the region" (p. 312).

4.4.4 Reduction of production costs

For the third spillover effect of private R&D on reduction of costs, Levin and Reiss (1984) estimate that a 1% increase in the R&D spillover causes average cost to decline by 0.05%. Bernstein and Nadiri (1989) show that average cost declines (on average) by 0.2% in response to a 1% growth in R&D spillovers. However, there are differences in the impact on cost reduction across the different industries analysed (chemicals, petroleum, machinery and instruments) and in the short run and long run. For instance, in the long run, a 1% increase in the intra-industry spillover caused average cost to decline by around 0.1% for instruments and machinery and by approximately 0.2% for chemicals and petroleum (estimates twice as large as in the short run). Spillover-receiving firms gained a 0.27%, 0.22%, 0.15% and 0.14% variable cost reduction in the petroleum, chemical, machinery, and instruments industries respectively as a result of a 1% increase in the intra-industry spillover.

Arrow C in Figure A6.2 summarise these effects. Note the arrow stems from the private R&D 'bubble' without distinguishing between 'new' and 'existing' R&D. This is because spillover effects could arise from either or both 'types' of private R&D.

5. Mechanisms transmitting spillovers

As we have seen, the literature is unambiguous in accepting that R&D/knowledge spillovers exist and are important. However, the literature is less clear about the mechanisms by which spillovers are transmitted. Krugman (1991) argues that knowledge flows are invisible, as they leave no paper trail, making spillovers difficult to measure. Jaffe *et al*. (1993) argue that on the contrary there is a visible paper trail in the form of patented inventions and new product introductions.

Probably, most researchers involved in this area will agree with the assertion about the difficulty of measuring spillovers. There have been several attempts. Before going into the details of how spillovers are measured, we briefly discuss some of the mechanisms identified in the literature as facilitating spillovers' transmission.

First, there are the mechanisms facilitated by universities, which include their pool of talented graduates, the ideas generated by faculty, their high quality libraries and other facilities of research universities and their publications.

Second, networking and social interactions are also deemed to be important mechanisms – and these include both the informal and formal ways of interaction. Formal means of interaction include technology transfer programmes, such as licensing from universities to firms. Both means of interaction seem to be relatively important for the pharmaceutical and biotech market.

Powell (1990) argues that social networks offer a highly feasible means of utilising and enhancing such intangible assets as tacit knowledge and technological innovation. Powell also argues that the exchange of distinctive competencies – be it knowledge or skills – is more likely to occur in networks. Breschi and Lissoni (2006) carry out a reassessment of the arguments and tests in support of exercise and magnitude of local knowledge spillovers proposed by Jaffe *et al*. (1993). They add both new data (Italian patents) and new measurable variables (social proximity between inventors, and inventors' mobility across firms). Breschi and Lissoni interpret their results as an indication that localisation effects tend to vanish where citing and cited patents are not linked to each other by any network relationship. On the contrary, knowledge flows, as evidenced by patent citations, are strongly localised to the extent that labour mobility and network ties also are. These authors conclude that geography is not a sufficient condition for accessing a local pool of knowledge, which also requires active participation in a network of knowledge exchanges. Results found in Agrawal *et al*. (2006) are also consistent with the conjecture that social relationships facilitate knowledge spillovers.

Gambardella (1992) argued that for the pharmaceutical market in particular, information exchange, rather than retaining it within one's own organisational boundaries, is a major determinant of successful innovation. He claimed that this requires companies to be prepared to diffuse research findings in exchange for the knowledge produced by others. Thus, to become part of a network, and to be able to effectively exploit the information that circulates in the network, has become even more valuable than being able to generate new knowledge autonomously.

Owen-Smith and Powell (2004) highlight the importance of knowledge networks in the biotech sector. These authors claim that within regional economies, contractual linkages among physically proximate organisations represent relatively transparent channels for information transfer. Also, they argue that spillovers that result from proprietary alliances (i.e. formal networks) are a function of institutional commitments and practices of members of the network.

Feldman and Kelley (2006) argue that successful strategies for learning abut technical advances outside a company's internal R&D efforts may depend on the breadth of collaborative links with other enterprises, connections to universities and the adoption of university norms of publishing research; and, probably more important, that knowledge flows both ways along these pathways. Along the same lines, Martin and Tang (2007) cite a number of papers highlighting how "through these networks, scientists can quickly and effectively contact acknowledged experts on a particular issue to obtain from them information or advice" (p. 11).

Feldman (2000) also defends the importance of social interactions, although she argues that we do not know exactly how economically useful knowledge is created as a result. Breschi and Malerba (2005) reinforce the importance of social networks and argue that one of the key issues raised by all of the approaches in the literature is that learning through networking and by interacting is seen as the crucial force pulling firms into clusters and the essential ingredient for the ongoing success of an innovative cluster.

The third mechanism discussed in the literature relates to the possibility of 'absorptive capacity', which refers to the ability of economic agents to recognise, assimilate and apply new scientific knowledge – and then to appropriate some of the returns accruing to investments in new knowledge made externally (Cohen and Levinthal, 1989). Indeed, as these authors argue, the conventional wisdom was that R&D generated only one product: new information. They argue, however, that R&D also enhances the firm's ability to assimilate and exploit existing information – the firm's 'learning' or 'absorptive' capacity. This second 'face' of R&D is very important, as it represents an important element of a firm's ability to create new knowledge. Griffith *et al*. (2004a) find strong evidence that R&D has this second face: industries lagging behind the productivity frontier catch up particularly fast if they invest heavily in R&D. Griffith *et al*. identify human capital as having a role in stimulating innovation and absorptive capacity.

Fourth, entrepreneurship has been also identified as an important mechanism to transmit spillovers, in that knowledge spillovers are the source of knowledge creating the entrepreneurial opportunities for new firms. Partly due to the emergence of the literature identifying entrepreneurship as a mechanism to facilitate spillovers, the so-called Knowledge Spillover Theory of Entrepreneurship (KSTE) has been developed. It identifies one source of entrepreneurial opportunity: new ideas and knowledge. Under this theory, the implementation of new knowledge and new ideas created in one source but left uncommercialised or not fully pursued generates entrepreneurial opportunities to start up new firms. Thus, the creation of a new firm in a localised context is an important mechanism by which knowledge spills over. By serving as a conduit for knowledge spillovers, entrepreneurship is the missing link between investments in new knowledge and economic growth (Audretsch *et al*., 2006).

Related to the fourth mechanism, Audretsch and Stephan (1999) try to answer the question: 'how does knowledge spill over?' They argue that the answer lies in the incentives confronting scientists to appropriate the expected value of their knowledge, considered in the context of their path-dependent career trajectories. In particular, Audretsch and Stephan focus on the ability of scientists to appropriate the value of the

knowledge embedded in their human capital along with the incentive structure influencing whether and how scientists choose to commercialise their knowledge. They conclude that the spillover of knowledge from the source creating it, such as a university, research institute or industrial corporation, to a new firm start-up facilitates the appropriation of knowledge for the individual scientist(s) but not necessarily for the organisation creating the knowledge in the first place.

International trade is usually deemed to be one of the most important mechanisms by which spillovers are transmitted across countries, but international spillovers are outside the scope of this paper. The interested reader is referred to Coe and Helpman (1995), Keller (1998, 2002a, 2002b, 2004) and Griffith *et al.* (2004b).

6. The rise of the economics of geography of innovation

Figure A6.2 (deliberately) ignores the geographical dimension. For instance, it does not take into consideration where the public and private R&D takes place and how close you have to be to the source of the spillover to access it. This is nevertheless an important dimension, as the evidence gathered in our literature review shows.

Griliches' (1979) seminal paper offered for the first time a tool to measure spillovers, by suggesting the production function approach to the estimation of the return to R&D. He argued that the level of productivity achieved by one firm or industry depends not only on its own research efforts but also on the size of the pool of general knowledge accessible to it. Moreover, the productivity of own research may be affected by the size of the pool or pools it can draw upon. A simple model of such a within-industry spillover effect is given by:

$$Y_i = B\, X_i^{1-\gamma}\, K_i^{\gamma}\, Ka^{\mu}$$

where Y_i = output of ith firm, which depends on an index of conventional inputs, X_i, its specific knowledge capital, K_i, and the state of aggregate knowledge in this industry, Ka. Griliches assumed that the aggregate level of knowledge capital was the sum of all specific firm R&D capital levels. Aggregating the individual production functions, the coefficient of aggregate knowledge capital ($\gamma + \mu$) is higher than at the micro level (γ), since the aggregate level reflects not only the private but also the social returns to R&D.

This production function approach is aspatial or insensitive to issues involving location and geography. As argued by Audretsch (1998), there is considerable empirical evidence supporting the model of the knowledge production function. The empirical link between knowledge inputs and innovative output becomes stronger when the unit of observation becomes increasingly aggregated, e.g. when the unit of observation is the country or the industry. However, at the level of the firm the link between knowledge inputs and innovative output becomes tenuous and only weakly positive in some studies, and even non-existent or negative in others. This is not surprising, as formal R&D is concentrated among the largest corporations and small firms account disproportionately more for new product innovations. Several economists (see references below) have therefore modified the model of the knowledge production function to include an explicit specification for both spatial and product dimensions. The modified knowledge production function becomes:

$$I_{si} = IRD^{\beta_1} * (UR_{si})^{\beta_2} * [UR_{si} * (GC_{si})^{\beta_3}] * \varepsilon_{si}$$

where I = innovative output, IRD is private corporate expenditures on R&D, UR is research expenditures undertaken by universities, and GC measures geographic coincidence between university and corporate research. This co-location variable was added later. The unit of observation is at the spatial level, s, a state, and industry level, i.

The estimation of this new equation shifts the model of the knowledge production function from the unit of observation being a firm to being a geographic unit: state, region or metropolitan area. This work has led to the notion of 'localised knowledge spillovers'. The breakthrough paper on the topic is probably that by Jaffe (1989a), who argued that transport mechanisms for spillovers at the time were still not understood. As a first approach to analyse these issues, he examined (for the US) production of patents assigned to corporations by state over time, and related this to industry R&D and university research. Jaffe interprets the influence of university research on these patents at the state level (after controlling for industry R&D) as evidence of geographically mediated spillovers. Several papers have followed a similar methodology: see for instance Feldman (1993), Acs *et al.* (1994a), Feldman (1994), Audretsch and Feldman (1996), Audretsch (1998), Feldman and Audretsch (1999), Feldman (2000), Arundel and Geuna (2001), Audretsch *et al.* (2003), Baum and Sorenson (2003), Audretsch and Feldman (2004), Audretsch and Lehmann (2006). The authors of these papers, to a greater or lesser extent, argue that the empirical evidence they present suggests that location and proximity clearly matter in exploiting knowledge spillovers. They argue that one of greatest developments in the literature of the economics of innovation is that geography, the spatial context, does matter.

This strand of the literature has gone one step further to analyse the different 'elasticities' according to firm size. Empirical results from the USA suggest that small firms are the recipients of R&D spillovers from knowledge generated in the R&D centres of their larger counterparts and in universities (Acs *et al.*, 1994b). Such spillovers are apparently more decisive in promoting the innovative

activity of small firms than of large corporations. Audretsch and Vivarelli (1996) replicated the analysis for 20 Italian regions over nine years and found similar results. They show that while firm R&D expenditures contribute to the generation of innovative output for all firms, the spillovers from university research are apparently more important for small-firm innovation.

Jaffe *et al*. (1993) provide an alternative analysis for looking at the importance of geography. They show, based on US data, that patent citations are highly localised. These authors also argue that it is probable that knowledge spillovers are not confined to closely related regions of technology space – in their study, approximately 40% of citations do not come from the same primary patent class. This is consistent with Jaffe (1986) who found that a significant fraction of the total flow of spillovers affecting firms' own research productivity comes from firms outside the receiving firm's immediate technological neighbourhood.

Botazzi and Peri (2003) use the total number of patents granted to inventors residing in a European region as a measure of that region's innovative output in order to investigate R&D externalities, identified as the effect of R&D intensity in one region on the innovative output of another region. These authors find evidence that spillovers are important. However, they find the effects of R&D in generating innovation quite localised – most of the benefits accrue to the region that employs the R&D resources and small positive externalities accrue to regions within 300 km of it. Quantitatively, they find that doubling R&D in a region would increase by 2–3% the patenting activity in another region within 300 km of distance. Closer to its border (within 100 km) and for regions of the same country the effect could be as large as 5–6%. They offer a tentative explanation for the small size and the short range: spillovers are the result of the diffusion of non-codified knowledge between people who have frequent (weekly or monthly) interactions. In Europe, the authors argue, people probably commute and interact much more within countries than across borders.

In summary, results from the literature reviewed here suggest that one of the greatest developments in the study of the economics of innovation is to demonstrate that location and proximity do matter in exploiting knowledge spillovers. Geographic concentrations of knowledge are likely to create higher levels of innovation than would otherwise be achieved. Not only do product innovations exhibit a pronounced tendency to cluster in regions which contain concentrations of innovative inputs, but also innovative activity tends to cluster more in industries where knowledge spillovers play a decisive role. The propensity for innovative activity to cluster is more attributable to the role of knowledge spillovers than merely to the geographic concentration of production. The literature suggests that the role of knowledge spillovers is geographically bounded: innovative activity is more likely to occur within close geographic proximity to the source of that knowledge – 'localised knowledge spillovers'.

Breschi and Lissoni (2001a, 2001b) have criticised this literature. They recognise that there is hardly any doubt that innovation networks are often localised. However, in their view the rationale for co-localisation may have less to do with knowledge spillovers mediated by physical proximity, than with the need to access a pool of skilled workers and to establish transaction-intensive relationships with suppliers and customers. Thus, in their critique, they argue that the notion of localised knowledge spillovers has been abused, generating great conceptual confusion. These authors do not deny that knowledge flows may be an extremely important agglomeration force, but they disagree with putting all of these flows under the common heading of localised knowledge spillovers.

7. Summary

It is extremely important to consider wider economic gains as well as health gains when assessing the economic benefits of medical research. Investment in medical research by one organisation may benefit not only that organisation but also other organisations in the medical sector, and in other sectors, i.e. the whole economy.

We have reviewed and presented the findings of the research spillovers literature in general and as applied specifically to medical research. The literature clearly suggests that R&D investment generates not only a direct return captured by the original investor, but also some indirect benefits 'spilling over' to third parties. There is evidence that R&D spending, both private and public, produces new knowledge, which can be accessed and exploited by other organisations for new technology development; that it contributes to the formation of a more skilled labour force; and more generally that it facilitates knowledge dissemination and technology transfer. The evidence shows that innovative activity tends to cluster more in industries where knowledge spillovers play a decisive role, and that new firm start-ups' decisions to locate are influenced by the opportunity to access knowledge generated by universities.

The literature is much sparser and more ambiguous about the quantification of spillovers than about the mechanisms through which they travel. There is some evidence for pharmaceutical R&D. This suggests that R&D spillovers are important, and that publicly funded research and private pharmaceutical R&D investment are complements rather than substitutes.

Annex to Chapter Seven

Lag structures

Given our data series for research expenditures for 1975–92 and for health gains for 1986–2005 the different lag structures we consider lead to different periods of research expenditure and of health gain being included in the estimated internal rate of return. This diagram indicates the first and last pair of years included in the analysis for each lag period.

This leads to certain apparent anomalies, in terms of the effects of changing lags, particularly where there is substantial year on year variation in the data series.

Figure A7.1: Lags used for CVD

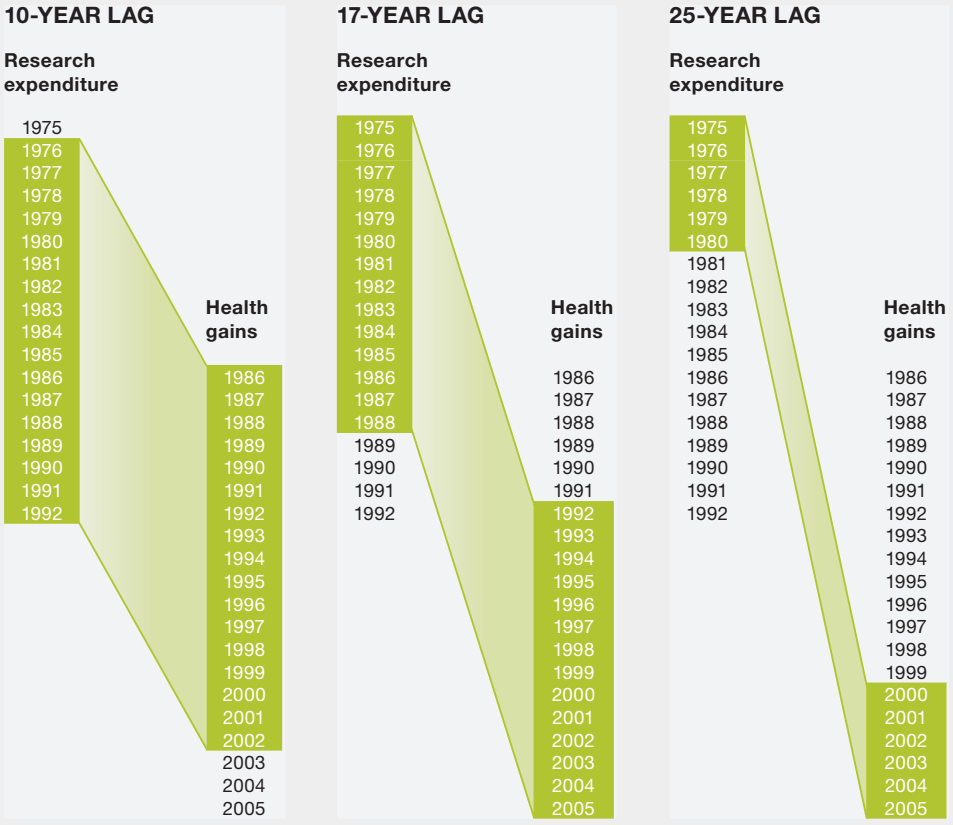
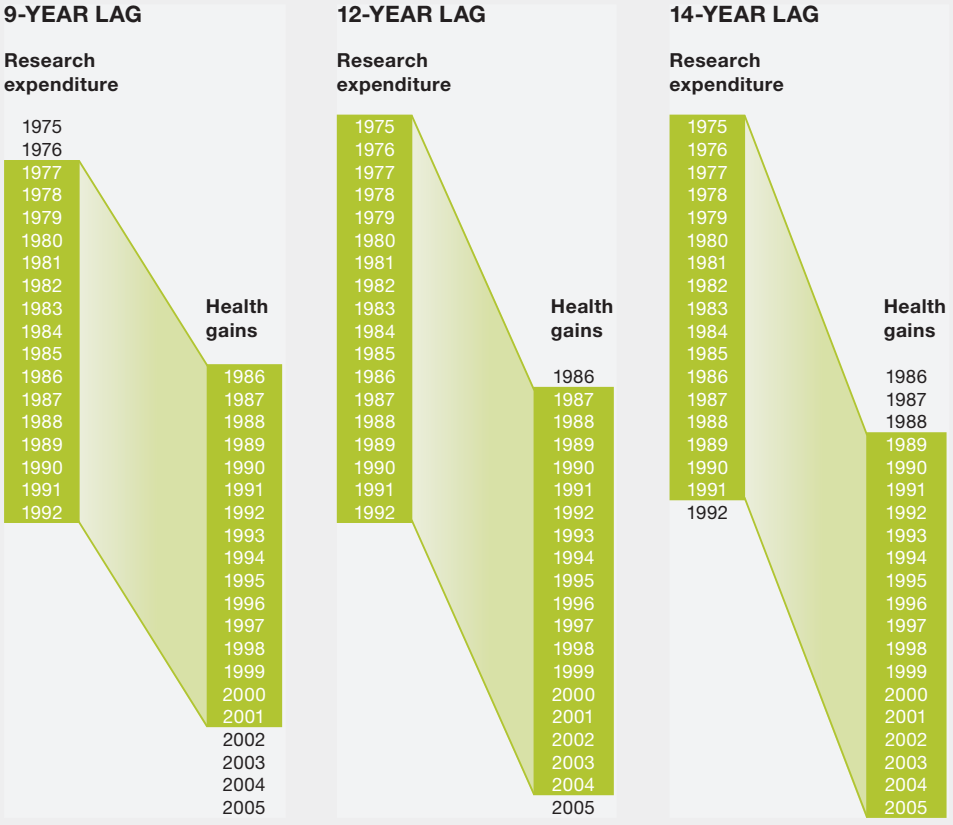


Figure A7.2: Lags used for mental health



Annexes to Chapter Eight

Annex 8A: Breakdown of public, non-profit and private expenditure on mental health research (in £m), by year, 1970–2005, current prices

	UK health expenditure – organisations (£m)					Mental Health – activity funding (£m)				Mental health – support funding (£m)			Pharma industry (£m)	Grand total exc. pharma (£m)	Grand total exc. pharma. deflated (£m)
Date	MRC[1]	Wellcome Trust[2]	NHS	DH (not NHS)	FC Health	WT	MRC	DH–A	Total	DH–I	Funding Councils	Total			
1970						0		0							
1971						0		0							
1972	29	5				0		0							
1973	30[3]			18[4]		0		0							
1974	36	5				0		0							
1975	**47**	**4[5]**	**137[6]**	**27[7]**	**84[8]**	**0**	**3[9]**	**5**	**9**	**11**	**8**	**19**	**15**	**28**	**155**
1976	**52**	**4**	**144**	**29**	**87**	**0**	**4**	**6**	**11**	**12**	**9**	**20[10]**	**20**	**31**	**149**
1977	**54**	**6**	**151**	**30**	**91**	**0**	**5**	**6**	**11**	**12**	**9**	**21**	**25**	**32**	**137**
1978	**62**	**6**	**158**	**31**	**95**	**1**	**5**	**6**	**12**	**13**	**9**	**22**	**30**	**34**	**130**
1979	**74**	**10**	**166**	**33**	**99**	**1**	**6**	**7**	**14**	**13**	**10**	**23**	**39[11]**	**37**	**123**
1980	**93**	**10**	**174**	**34**	**103**	**1**	**8**	**7**	**15**	**14**	**10**	**24**	**48**	**39**	**110**
1981	**107**	**12**	**183**	**28[12]**	**107**	**1**	**9**	**6**	**16**	**15**	**11**	**25**	**56**	**42**	**104**
1982	**113**	**12**	**191**	**29**	**112**	**1**	**9**	**7**	**17**	**15**	**11**	**26**	**68**	**44**	**103**
1983	**120**	**17**	**201**	**27**	**116**	**1**	**10**	**7**	**18**	**16**	**12**	**28**	**77**	**45**	**101**
1984	**124**	**17**	**210**	**26**	**121**	**2**	**12**	**7**	**21**	**17**	**12**	**29**	**92**	**50**	**106**
1985	**129**	**24[13]**	**221**	**24**	**126**	**2**	**11**	**7**	**20**	**18**	**13**	**30**	**104**	**50**	**102**
1986	**138**	**29**	**231**	**49**	**131**	**3**	**11**	**10**	**24**	**18**	**13**	**32**	**116**	**55**	**109**
1987	**150**	**35**	**242**	**47**	**137**	**3**	**13**	**10**	**25**	**19**	**14**	**33**	**127**	**59**	**110**
1988	**163**	**68**	**254**	**50**	**142**	**3**	**14**	**10**	**27**	**20**	**14**	**35**	**141**	**62**	**108**
1989	**191**	**43**	**266**	**58**	**157[14]**	**5**	**15**	**11**	**32**	**21**	**16**	**37**	**182**	**69**	**113**
1990	**202**	**54**	**279**	**71**	**187**	**5**	**16**	**13**	**34**	**22**	**19**	**41**	**217**	**75**	**114**
1991	**228**	**72**	**293**	**59**	**212**	**9**	**19**	**12**	**39**	**23**	**21**	**45**	**235**	**84**	**120**
1992	**251**	**92**	**307**	**55**	**208**	**18**	**18**	**12**	**48**	**25**	**21**	**45**	**270**	**93**	**129**
1993	288	167[15]		61	190[16]	49			49						
1994	298	242		59	186	30			30						
1995	305	230	347	56	187	20			20						
1996	309	168	408	62	186	27			27						
1997	321	222	401	59	205	37			37						
1998	316	212	403	60	222	32			32						
1999	345	354	410	63	243	40			40						
2000	368	480	423	55	250	38			38						
2001		388	445	59	257	32			32						
2002		419	461	53	280	31			31						
2003			533	60	306				0						
2004			575	54	317				0						
2005			586	48	327				0						

1 Data provided by the MRC.

2 Data provided by the Wellcome Trust.

3 Maddock (1975) estimates MRC expenditure in 1973/74 to have been £24.8m.

4 Figure taken from Maddock (1975).

5 Data for 1972–84 were provided in two-year bands; we have taken the average for annual estimates.

6 Data for 1975–92 were estimated by back-casting the figures provided for 1995–2005 using an exponential function.

7 Data for 1975–80 based on projecting data for 1973 and 1981–2005 using a linear function.

8 The 1975 to 1989 timeseries is estimated from a back-projection of the 1989 to 1992 UFC data for biomedical subjects in the UK, and the 1993 to 2005 HEFCE QR data for biomedical subjects in England. The latter is then inflated by circa 12% to make a UK-wide estimate.

9 Assumed.

10 Data for 1976 and 1977 interpolated using figures for 1975 and 1978.

11 Taken as average of the preceding and following points.

12 Data for 1981–85 entered by hand from *Annual Review of Government-Funded R&D* (Cabinet Office, 1984).

13 Data for 1985–87 was estimated using an exponential function to project funding for the period 1975–84, for which we were provided with data.

14 Numbers for these years are taken from UFC figures and are UK-based.

15 Calculated by taking the average of figures for 1992 and 1994.

16 From 1993 onwards, data is provided by HEFCE and is England-based.

Annex 8B: List of mental health guidelines analysed

List of mental health guidelines analysed

Guideline	Source	Publication date
Bipolar disorder	www.nice.org.uk/nicemedia/pdf/CG38niceguideline.pdf	2006
Dementia	www.nice.org.uk/nicemedia/pdf/CG042NICEGuideline.pdf	2006
Depression	www.nice.org.uk/nicemedia/pdf/cg023fullguideline.pdf	2004
Depression in children and young people	www.nice.org.uk/nicemedia/pdf/CG028NICEguideline.pdf	2005
Drug misuse: opioid detoxification	www.nice.org.uk/nicemedia/pdf/CG52NICEGuideline.pdf	2007
Drug misuse: psychosocial interventions	www.nice.org.uk/nicemedia/pdf/CG051NICEguideline2.pdf	2007
Mental Health NSF	www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4009598	1999
Obsessive-compulsive disorder	www.nice.org.uk/nicemedia/pdf/cg031fullguideline.pdf	2006
Antenatal and postnatal mental health	www.nice.org.uk/nicemedia/pdf/CG045NICEGuidelineCorrected.pdf	2007
Post-traumatic stress disorder	www.nice.org.uk/nicemedia/pdf/CG026NICEguideline.pdf	2005
Schizophrenia	www.nice.org.uk/nicemedia/pdf/cg001fullguideline.pdf	2003
Self harm	www.bps.org.uk/downloadfile.cfm?file_uuid=C11587F1-7E96-C67F-DD13-357E1AA3B75D&ext=pdf (linked through the NICE website)	2004
Violence	www.nice.org.uk/nicemedia/pdf/cg025fullguideline.pdf	2005

Annex 8C: Studies used to generate QALYs gained for each intervention in each patient group

Table A8C: Summary of studies used to generate QALYs gained for each intervention in each patient group

	QALYs gained per user year	Patients	Comparators	Country	Time horizon	Source	Notes
Patient groups/interventions							
Treatment of depression:							
SSRI	0.1306	Male and female patients, over 18 years of age, suffering from depression	SSRIs followed up by TCA in the case of dropout, TCA followed by a SSRI in case of a dropout and TCA only	UK	13 months	Kendrick *et al*. (2006)	We used the absolute QALY gain between baseline and 12 months. We calculated the integral between baseline (0.608) and 12-month (0.781) measurement of quality of life to obtain a QALY estimate for one calendar year.
Community psychiatric nurses	0.0017	Patients affected by non-psychiatric problems in need of psychiatric help	Direct CPN care, delayed CPN care (after 12 weeks) and continuing GP care	UK	24 weeks	Gournay and Brooking (1995)	We used the incremental QALY gain over standard care. Direct CPN treatment saved four days' absence from work. Preventing absence from work was approximately valued at 0.1 of a QALY per year. No other details were given in the study.
Behaviour or cognitive therapy	0.0800	Patients with DSM-IV diagnoses of major depressive disorder, dysthymic disorder, panic disorder, social phobia, and generalised anxiety disorder	The study compared three first-line treatments for depression and anxiety. The options were brief therapy, cognitive-behavioural therapy and care as usual	Netherlands	up to 1.5 years	Van Roijen *et al*. (2006)	We used the incremental QALY gain over GP care. The utility score at baseline was 0.52 in the CBT group. At one-year follow-up, the utility score was 0.68 in the CBT group. We assumed a linear increase in quality of life between baseline and 12-month measurement.
Treatment of schizophrenia:							
Atypical antipsychotics	0.0212	Patients with schizophrenia	One first generation drug (perphenazine) and four second generation drugs (olanzapine, quetiapine, risperidone, zipradone)	USA	12 months	Rosenheck *et al*. (2006)	We used the absolute QALY gain between baseline and 12 month. The utility values changed from approximately 0.682, 0.695 and 0.676 to 0.725, 0.73 and 0.725 for olanzapine, quietapine and risperidone respectively. We modelled the average linear increase between baseline and 12-month measurement.
Community psychiatric nurses	0.0017	Patients affected by non-psychiatric problems in need of psychiatric help	Direct CPN care, delayed CPN care (after 12 weeks) and continuing GP care	UK	24 weeks	Gournay and Brooking (1995)	We used the incremental QALY gain over standard care. Direct CPN treatment saved four days' absence from work. Preventing absence from work was approximately valued at 0.1 of a QALY per year. No other details were given in the study.
Other mental disorders:							
Community psychiatric nurses	0.0017	Patients affected by non-psychiatric problems in need of psychiatric help	Direct CPN care, delayed CPN care (after 12 weeks) and continuing GP care	UK	24 weeks	Gournay and Brooking (1995)	We used incremental QALY gain over standard care. Direct CPN treatment saved four days' absence from work. Preventing absence from work was approximately valued at 0.1 of a QALY per year. No other details were given in the study.

SSRI = selective serotonin reuptake inhibitors, CPN = community psychiatric nurse, CBT = cognitive behavioural therapy, FGA = first generation antipsychotics.

Annex 8D: Estimating the numbers of eligible patients, the number of initial contacts with community psychiatric nurses and the number of SSRI users

Table A8D delineates the data sources and assumptions used to generate the numbers of eligible patients in each patient group, the number of new patients seeing community psychiatric nurses and the number of SSRI users over the period 1985–2005.

Table A8D: Data and assumptions used to generate the numbers of eligible patients, CPN contacts and SSRI users

Patient groups/interventions	Data and assumptions
Treatment of depression:	
SSRI	Data for 1975–98 obtained from Middleton *et al*. (2001). These are prescription figures from the UK. For 1999–2005, we linearly extrapolated using the rate of increase in prescriptions between 1997 and 1998. Kendrick *et al*. (2006) suggests that 931 prescriptions are used for 81.6 patient years. To obtain the number of users, we divided the number of prescriptions by 11.04 in each year.
Community psychiatric nurses	Data for 1988 to 2003 obtained from *Patient Care in the Community – NHS Community Mental Health Nursing* (ONS and DH, 2003/2004). These figures are for England; UK figures are computed by multiplying the share in England by the UK population. The data gives the initial contact with a mental health nurse each year. Where a previous episode of care for the same patient did not end with a positive discharge from care, a new episode is recorded only if more than 6 months have elapsed since the last contact. For 2004–05 we extrapolate the data using the slope from 2003 to 2002.
Behaviour or cognitive therapy	Data for 1994–98 obtained from *Key Health Statistics from General Practice* (National Statistics, 2000). These are figures for England; UK figures are computed by multiplying the share in England by the UK population. For 1985–93 we assume the rate is the same as in 1994. For 1999–2005 we assumed that the rate is the same as in 1998.
Treatment of schizophrenia:	
Antipsychotics	Data for 1994–98 obtained from *Key Health Statistics from General Practice* (National Statistics, 2000). These are figures for England; UK figures are computed by multiplying the prevalence in England by the UK population. For 1985–1993 we assume the rate is the same as in 1994. For 1999–2005 we assumed that the rate is the same as in 1998.
Atypical antipsychotics	Data for 1994–98 obtained from *Key Health Statistics from General Practice* (National Statistics, 2000). These are figures for England; UK figures are computed by multiplying the prevalence in England by the UK population. For 1985–93 we assume the rate is the same as in 1994. For 1999–2005 we assumed that the rate is the same as in 1998.
Community psychiatric nurses	Information can be found under description of CPN user numbers for depressed patients.
Other mental disorders:	
Community psychiatric nurses	Information can be found under description of CPN user numbers for depressed patients.

SSRI = selective serotonin reuptake inhibitors, CPN = community psychiatric nurse, CBT = cognitive behavioural therapy, FGA = first generation antipsychotics.

Annex 8E: Estimating the uptake rates for specific interventions in each patient group

Table A8E: Data and assumptions used to generate uptake rates

Patient groups/interventions	Data and assumptions
Treatment of depression:	
SSRI	N/A
Community psychiatric nurses	Evidence from Gournay and Brooking (1994), Greenwood *et al*. (2000) and Hannigan (1999). Hannigan argues that the patient mix treated by CPN changed in the early 1990s to a case mix of patients with severe mental disorders. We used numbers on the patient mix from Gournay and Brooking (24% depressed before 1990 and approximately a quarter schizophrenic in 1994) and Greenwood *et al*. (12.6% depressed and 55% schizophrenic in 2000). Before 1990, we assumed that 24% of CPN patients were depressed. Following Gournay and Brooking, we further assumed a linear increase from 0% CPN treatment for schizophrenic patients in 1985 to 25% in 1994. After 2000, we used the 2000 rates for schizophrenic and depressed patients. The remaining percentages were attributed to CPN treatment of other mental disorders.
Behaviour or cognitive therapy	Data for 1993 obtained from *Psychiatric Morbidity Among Adults Living in Private Households*, *2000* (ONS and DH, 2001). This is a UK figure. CBT was introduced in the UK in the early 1990s. We therefore assumed the uptake rate to be zero prior to 1990 and linearly increasing between 1990 and 1994. For the period after 1998, we applied the 1998 uptake rate.
Treatment of schizophrenia:	
Atypical antipsychotics	Figures for 1994–98 from *Key Health Statistics from General Practice*. The figures are for England. Evidence from prescription data suggested that atypical antipsychotics were only used after 1989 in the UK. We assumed a zero uptake rate in 1989 and linearly interpolate between 1989 and 1994. From Department of Health (2007) we assumed linear increase. For the period after 1993, we extrapolated using the slope from 1992 to 1993. Between 1995 and 2005, the uptake rate of first generation antipsychotics (FGA) is decreasing. Since FGA and atypical antipsychotics are substitute therapies, we deducted the decrease in FGA users from the number of atypical antipsychotic users. Following this adjustment, we assumed that all considered atypical antipsychotic users in our model, would not have received any other antipsychotic medication otherwise.
Community psychiatric nurses	Information can be found under description of CPN uptake rates for depressed patients.
Other mental disorders:	
Community psychiatric nurses	Information can be found under description of CPN uptake rates for depressed patients.

SSRI = selective serotonin reuptake inhibitors, CPN = community psychiatric nurse, CBT = cognitive behavioural therapy, FGA = first generation antipsychotics, N/A = not applicable.

Annex 8F: Studies used to generate incremental costs for each intervention in each patient group

Table A8F: Summary of studies used to generate incremental costs for each intervention in each patient group

	Raw incremental costs	Time horizon	Cost base year	Source	Incremental costs (2005 UK£)	Notes
Patient groups/interventions						
Treatment of depression:						
SSRI	£87	12 months	2001/02	Kendrick *et al*. (2006)	£102	Consistent with the respective QALY estimate, we used the absolute cost of SSRI over one year
Community psychiatric nurses	£193	24 weeks	1988–91	Gournay and Brooking (1995)	£340	We used the incremental cost of direct CPN treatment compared to GP treatment
Behaviour or cognitive therapy	£550	17 months	1998/99	Scott *et al*. (2003)	£736	Consistent with the respective non-UK QALY estimate, we used the incremental cost compared to standard care from this UK study. However, the costs were for a 17-month treatment
Treatment of schizophrenia:						
Atypical antipsychotics	£763	12 months	2001/02	Davies *et al*. (2007)	£892	Consistent with the respective non-UK QALY estimate, we used the absolute cost of atypical antipsychotics from this UK study
Community psychiatric nurses	£193	24 weeks	1988–91	Gournay and Brooking (1995)	£340	We used the incremental cost of CPN treatment compared to GP treatment
Other mental disorders:						
Community psychiatric nurses	£193	24 weeks	1988–91	Gournay and Brooking (1995)	£340	We used the incremental cost of CPN treatment compared to GP treatment

SSRI = selective serotonin reuptake inhibitors, CPN = community psychiatric nurse, CBT = cognitive behavioural therapy, FGA = first generation antipsychotics.

Annex 8G: Sensitivity analysis

We undertook a sensitivity analysis to generate upper and lower estimates of the total QALYs gained and incremental costs around our central estimates. These were calculated as follows:

Our lower estimate of the net health gain made three adjustments compared with our base case:

- Our base case estimate may have overestimated the quality of life gain from SSRIs: it has been suggested that the QALY gain compared to placebo may be more modest as they are increasingly used in general practice and less severe patients (Kirsch *et al.*, 2008). In our lower estimate, we assumed that each SSRI user gained only half the QALY gain compared to that assumed in the base case.
- In our base case the cost of SSRI treatment per year was simply the prescription cost assuming that prescribing the drug had no effect on patient contacts with the health care system. In our low net benefit case, we used an estimate of the full cost of patient care, reflecting the alternative assumption that these patients would otherwise not be receiving active health service care (Kendrick *et al.*, 2006).
- Our lower estimate also used a more conservative estimate of the uptake rate for atypical antipsychotics between 1985 and 2005.

Our upper estimate made two adjustments from the base case:

- Our base case estimated the QALYs gain per year as a steady increase to observed improvements at one year. This may underestimate the QALY gain for those patients on medication longer than one year. For the upper estimate, we assumed that half the years of use were for new users and the other half for patients continuing on SSRIs and enjoying the full benefit throughout the year.
- Our base case estimate of QALYs gained for patients receiving atypical antipsychotics reflected a study in which patients switched from a current treatment to an atypical antipsychotic (Rosenbeck *et al.*, 2006). The gain for these patients may have been less than for patients who were not previously treated. For this higher net benefit estimate, we used a higher estimate based on a small earlier study of previously untreated patients (Chouinard, 1997).

Table A8G1: Results of sensitivity analysis, 1985–2005: lower estimate

1	2	3	4	5	6	7
		QALYs gained			Incremental costs	
Patient groups/intervention	Compliant user years (000s)	Per user year	Total (000s)	Total monetised (£ million)	Per user year (£)	Total (£ million)
Depression:						
SSRIs	9,160	0.0653	598	14,954	1,022	9,365
Community psychiatric nurses	356	0.0017	1	15	340	121
Behaviour or cognitive therapy	656	0.0800	52	1,312	736	483
Schizophrenia:						
Atypical antipsychotics	121	0.0212	3	64	892	108
Community psychiatric nurses	576	0.0017	1	25	340	196
Other mental disorders:						
Community psychiatric nurses	917	0.0017	2	39	340	312
Total	**11,914**		**656**	**16,408**		**10,585**

SSRIs = selective serotonin reuptake inhibitors

Table A8G2: Results of sensitivity analysis, 1985–2005: upper estimate

1	2	3	4	5	6	7
		QALYs gained			Incremental costs	
Patient groups/interventions	Compliant user years (000s)	Per user year	Total (000s)	Total monetised (£ million)	Per new user (£)	Total (£ million)
Depression:						
SSRIs	9,160	0.1518	1,391	34,766	102	931
Community psychiatric nurses	356	0.0017	1	15	340	121
Behaviour or cognitive therapy	656	0.1200	79	1,968	736	483
Schizophrenia:						
Atypical antipsychotics	248	0.1095	27	678	892	221
Community psychiatric nurses	576	0.0017	1	24	340	196
Other mental disorders:						
Community psychiatric nurses	917	0.0017	2	39	340	312
Total	**11,914**		**1,500**	**37,490**		**2,263**

SSRIs = selective serotonin reuptake inhibitors

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