Health Research – Making an Impact

The Economic and Social Benefits of HRB-Funded Research

Edward Nason, Barbara Janta,
Gillian Hastings, Stephen Hanney,
Mairéad O'Driscoll and Steven Wooding

RAND EUROPE

HRB
Health Research Board

Health Research – Making an Impact

The Economic and Social Benefits of HRB-Funded Research

EDWARD NASON, BARBARA JANTA, GILLIAN HASTINGS, STEPHEN HANNEY, MAIREAD O'DRISCOLL AND STEVEN WOODING

May 2008

Published by:
Health Research Board
73 Lower Baggot Street
Dublin 2
Ireland

t +353 1 234 5000
f +353 1 661 2335
e hrb@hrb.ie
w www.hrb.ie

ISBN-13 978-1-903669-13-6

ISBN-10 1-903669-13-8

Foreword

Research is often the 'unseen force' behind improvements in health care. Recent research has led to some of the most remarkable developments in our understanding of health and disease in history. Every diagnosis, intervention and new treatment carried out in our health service is based on research.

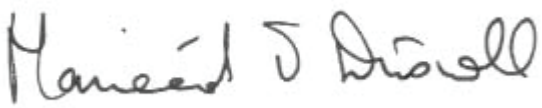
Simply put, today's health research is tomorrow's health care and all too often we take the benefits for granted while the real impacts of health research on policy, practice and the economy remain hidden.

Robust evaluation methods and the ability to demonstrate research outcomes are vital to provide evidence of value for money. Several reports, including ACSTI's Achieving a Step change in Health Research in Ireland and the government's Strategy for Science, Technology and Innovation 2006-2013 (SSTI) highlight the important role of research in the context of economic competitiveness and the health and well-being of the population.

However, there is a clear need to develop better frameworks, both at a sectoral and at a national level, to enable a systematic assessment of the impact that publicly funded research is having on both the Irish economy and society over the short and long-term. Working with the Health Economics Research Group in Brunel University and RAND Europe, the Health Research Board used a pioneering approach called the 'payback framework' to establish how some of the research that we have funded in the past delivers economic benefits, influences government policy/decision making and really makes an impact on people's lives.

We hope that the findings from this report, and the payback model we used, will help to inform debate at a national level on the best approach to measuring the return on public investment in research.

As the lead agency in Ireland supporting and funding health research, the HRB aims to improve people's health and the effectiveness of the health system. This report clearly shows that our funding is having a much wider impact.



Mairéad O Driscoll
Director - Research Strategy and Funding
Health Research Board

Preface

This report, prepared for the Health Research Board (HRB), examines the wider impacts of eight HRB-funded grants from the early and mid-1990s. These impacts are identified using a case study approach, built on the payback framework for research evaluation. The report then considers the economic repercussions of these wider impacts. The report does not, however, estimate the total monetary value of the economic benefit of HRB-funded research.

The HRB has funded health research in Ireland for over 20 years, covering basic biomedical research to health services research (HSR). The case studies in this report address four grants with a basic biomedical or clinical slant and four with a HSR, public health or primary care focus.

The report presents the historical context of health research funding in Ireland, which has undergone major changes in last 20 years. It then goes on to identify the economic impacts arising from the case studies, provides summaries for all eight case studies and places the findings in the rapidly developing context of Irish health research. Finally, it presents a way for the HRB to take this methodology forward and implement it in its own evaluation programme.

The report will be of interest to the HRB, those involved in policy-making in Irish health research, those involved in the translation of health research into economic and health benefits in Ireland and health researchers themselves. The discussion of implementing the payback methodology into an ongoing evaluation system will be of interest to any stakeholder interested in understanding the payback on the research funding they provide.

The research was led by RAND Europe in collaboration with the Health Economics Research Group (HERG) at Brunel University and the HRB. RAND Europe is an independent not-for-profit think tank and research organization that serves the public interest by providing evidence for policy-making and public debate. This report has been peer-reviewed in accordance with RAND's quality assurance standards (see http://www.rand.org/about/standards/).

For more information about RAND Europe or this document, please contact:

Dr Steven Wooding
RAND Europe
Westbrook Centre, Milton Road
Cambridge. CB4 1YG
Tel: +44 1223 353329
e-mail: wooding@rand.org
www.randeurope.org

Acknowledgements

This study would have been impossible without the generous support of those involved with the HRB, both as researchers and as interested stakeholders in the research environment. We thank them for providing invaluable information and for sparing their time for interviews. We would particularly like to thank those researchers whose grants were selected as case studies. We would also like to thank Brendan Curran at the HRB for his help and advice throughout the project. Finally, we would like to thank Professor Martin Buxton and Dr Evi Hatziandreu who acted as the quality assurance reviewers. We would also like to acknowledge the contribution of Alice Farrands, an analyst at RAND Europe whose involvement in this project was tragically cut short. This report is another aspect of her intellectual legacy.

Contents

List of Figures

List of Tables

Summary

The Health Research Board (HRB) has been a key funder of health research in Ireland over the past 21 years. In order to show the effectiveness of its research funding, the HRB has commissioned this payback study of eight grants funded in the early and mid-1990s. The objective was to show how HRB-funded research can lead to economic (and social) benefits for Ireland.

Health research in Ireland has undergone seismic changes over the last 20 years. In 1987, HRB funding for health research amounted to €2m with some other support from EU framework grants and Wellcome Trust. By 2007, the HRB budget was €50m, now alongside even more substantial funding from Science Foundation Ireland (SFI) and university infrastructure funding. The HRB funds health research from basic biomedical and clinical research through to Health Services Research (HSR), public health and primary care research.

The HRB has a broad mission to improve health and advance the knowledge economy so this report uses a very broad definition of economic impacts. This definition defines an economic impact as "an action or activity that affects the welfare of consumers, the profits of firms and/or the revenue of government" (Warry 2006). Economic impacts can range from monetary ones such as greater wealth, cheaper prices and more revenue, to wider ones, such as the effects on the environment, public health and quality of life.

Approach

The payback framework used in this study consists of two elements: a logic model of the research process that tells the story of each case study; and a multidimensional categorization of the benefits from the research. This categorization goes from the traditional knowledge outputs, for example publications, through research targeting and capacity building to impacts on policy, product development, health and wider economic benefits. For this study we carried out eight case studies of research grants funded by the HRB to illustrate the diversity and extent of impacts stemming from that research. Four of the case studies examined were basic biomedical or early clinical research and the other four focussed on HSR, public health and primary care research. The case studies were selected to mirror the variety of the HRB portfolio and to be based on the work of high impact researchers. This allows us to illustrate the benefits of HRB funding most effectively and provides a wealth of impacts to examine.

Findings

1. The case studies examined have had impacts in a wide range of health areas, including work on the development of pain relief drugs, the treatment of myocardial infarction, better treatment for psychosis and improvements in dental hygiene.

2. Work exploring the role of eicosanoids in pain, produced a range of impacts including an improved dosing regime and the withdrawal of a less effective drug. Work on low dose treatment regimens for arthritis should improve health through better treatment and lead to cost savings through reduced drug use. Arthritis is a significant burden in Ireland and has been estimated to cost the Irish economy €1.6 billion in lost working days. Finally, the project has led to three spin-off companies, one of which provides bio-informatics solutions for automatic proteomics analysis.

3. Research on time to treatment for acute myocardial infarction (AMI) (heart attack) has been partly responsible for reduced mortality from this disease in Ireland, with a drop of nearly 4,000 deaths per annum, of which around 5% can be attributed to treatment for AMI. Other follow-on research contributed to the Heartwatch health programme. Over two years this programme is estimated to have prolonged the life of around 80 individuals leading to a gain of over 500 life years. It has also lead to a reduction in the three main risk factors for cardiovascular disease (smoking, cholesterol and blood pressure) (National Heartwatch Programme 2006). Health economists estimate that suffering an acute coronary syndrome such as AMI, reduces the sufferer's quality of life by 5%, with an indirect cost of nearly €10,000 per person per year (Lindgren *et al.* 2007). More broadly still, the case study contributed to laying the foundation for organising health services research in Ireland, including founding the Health Services Research Centre (HSRC) at the Royal College of Surgeons in Ireland (RCSI).

4. Work on obstetrics and schizophrenia led to work on psychosis that has contributed to a pilot service demonstrating how providing care at first-episode psychosis leads to reduced symptoms of psychosis and suicidal behaviour. This early intervention leads to both improved health outcomes – on occasion saving lives – and savings on later treatment.

5. Research in dentistry has led to development of an assay to test whether children are brushing their teeth, which will allow targeted interventions to improve dental hygiene. This should reduce the need for later dental treatment; treatments can have drastic complications, with deaths of under-16-year-olds accounting for half of all deaths due to dental anaesthetic complications (Worthington *et al.*, 1998). Related work, which also received HRB funding, looked at the dental health system in Ireland, leading to more effective dental practice both country wide and at the practice level. On the commercial side, the work has led to a role with Wrigley and Unilever on saliva in dental health.

6. There are also a variety of pharmaceutical treatments arising from the case studies that are just entering development, including three compounds expected to enter phase I trials over the next couple of years. Developments cover such areas as Huntington's disease, Alzheimer's, TB, malaria, septic shock and rheumatoid arthritis, and retinal degeneration. Many of these developments are accompanied by the foundation of companies including two spin-off companies – one of which attracted €5.25m from US financiers. Further down the development pathway the work on IL-1 has lead to two drugs now being in phase II trials and one in phase III.

7. HRB-funded research investigating the neurobiology of ageing is leading to a better understanding of how to maintain cognitive activity into old age; allowing the Irish economy to benefit from a future "grey workforce".

8. Ireland's status as a small and fast-growing research system means that a number of economy-specific effects take on particular importance. Attracting and retaining researchers, companies or funding to Ireland are of economic benefit to Ireland, although in the global sense they are not a net benefit but a transfer of resources from one location to another.
9. HRB research produced a number of wider impacts of this type including maintaining Wyeth's involvement with Ireland; attracting funding from international research funders, including the EU and the US-based Stanley Foundation. In terms of maintaining industry's interest and building its commitment to Ireland, the case studies illustrate how HRB funding has played an important role in sustaining and building Ireland's research workforce.
10. The HRB-funded research was considered to have contributed to building Ireland's reputation for research, which is noted as an objective of the 2006 science strategy of the Department of Enterprise, Trade and Employment (DETE 2006).

Recommendations for evaluation

This report shows that the payback model provides an effective framework to evaluate research funded by the HRB. We suggest five ways this work could be built on:

Building a bank of payback case studies

The HRB could extend this work by carrying out additional case studies to build a bank of cases that would provide general insights into the development of HRB-funded research. Over time, such a bank would start to allow comparisons betweens different types or areas of funding.

Using case studies to investigate specific evaluation questions

Alternatively the HRB could select additional case studies specifically to address policy questions, for example comparing fellowships and project grants; or the influence of international experience of research impact.

Incorporating the payback model into other evaluations

Structuring other HRB evaluation activities in line with the payback framework would allow easier comparisons and aggregation of evaluation information within the organization.

Full economic analysis of impact

The data provided by these payback case studies could provide a starting point for a more quantitative assessment of the economic return of HRB-funded research.

Achieving a portfolio view of outputs and outcomes

Case studies provide a deep understanding through examining a small number of cases. However, a complementary approach is to develop an overview of the impacts emerging from the entire portfolio of HRB-funded research. Developing a 'light touch' payback questionnaire that could be incorporated into end-of-grant reports could provide the HRB with such an overview.

Glossary

AMI	acute myocardial infarction (heart attack)
AMD	age-related maculopathies
AMS	Academy of Medical Sciences
ARC	Arthritis Research Campaign
ASC	Advisory Science Council
ASCOT	Anglo-Scandinavian Cardiac Outcomes Trial
B/EC	basic and early clinical research
BHH	*Building Healthier Hearts*
CCU	coronary care unit
CHD	coronary heart disease
CIHR	Canadian Institute of Health Research
COX	cyclooxygenase
DARTS	Donegal Area Rapid Treatment Study
DETE	Department of Enterprise Trade and Employment
DHF	Dental Health Foundation
DoHC	Department of Heath and Children
EI	Enterprise Ireland
EIS	early intervention service
EU	European Union
GP	general practitioner
HERG	Health Economics Research Group
HRB	Health Research Board
HSE	Health Service Executive
HSR	Health Services Research
HSRC	Health Services Research Centre

I/CCU	intensive/coronary care unit
IDA	Industrial Development Authority
IHF	Irish Heart Foundation
IL-1	Interleukin-1
KII	key informant interview
LCA	Leber congenital amaurosis
MKWH	*Making knowledge work for health: A strategy for health research*
MRC	Medical Research Council
PCR	primary care research
PH	Public Health
PI	principle investigator
PRTLI	programme for research in third level institutions
QALYs	quality-adjusted life years
RCSI	Royal College of Surgeons in Ireland
RP	retinitis pigmentosa
SFI	Science Foundation Ireland
SSTI	Strategy for Science, Technology and Innovation
S&T	science and technology
TCD	Trinity College Dublin
TI	Technology Ireland
TLR	toll-like receptor
UCD	University College Dublin
WHO	World Health Organization
WT	Wellcome Trust

CHAPTER 1 Introduction

The Health Research Board (HRB) is the lead agency in Ireland supporting and funding health research. Its aim is to improve people's health, build health research capacity and make a significant contribution to Ireland's knowledge economy. This is achieved through funding researchers based in external institutions (extramural funding), conducting research internally in the HRB (intramural research) and maintaining health information systems (for example, the national disability database held by the HRB). The HRB has a clear mission; to "Improve people's health through research and information" (HRB n.d.a). In order to achieve this mission the HRB aims to shape the research agenda in Ireland; build capacity in research; establish Ireland as a contributor to health research policy; support research; make contributions to the economy; and increase the awareness of health research impacts and the value of health research.

It is in answering this latter point that the HRB has commissioned research to understand the impacts arising from its funded research portfolio. In particular, to identify the economic impacts of HRB-funded research by adopting the definition of "economic impact" set out by the UK HM Treasury in *The green book: appraisal and evaluation in central government* (HM Treasury 2003) and adopted more recently in Peter Warry's review, *Increasing the economic impact of the research councils* (Warry 2006) (see Box 1).

> An action or activity has an *economic impact* when it affects the welfare of consumers, the profits of firms and/or the revenue of government. Economic impacts range from those that are readily quantifiable, in terms of greater wealth, cheaper prices and more revenue, to those less easily quantifiable, such as effects on the environment, public health and quality of life[1]

Box 1. Definition of "economic benefit" used in this project

We use the above definition since it captures those less quantifiable impacts related to improved health, a key aspect of the HRB's mission statement. Using the above definition we are able to use health benefit as an assessment of economic benefit that is more multi-layered than a simple commercial definition of impact.

[1] The ways in which the secondary types of economic impact can be calculated are discussed in detail in Appendix B.

1.1 Irish health research context

Understanding the complex funding context in Ireland is essential to understanding the ways in which HRB-funded researchers are able to make an impact on the health and economy of Ireland. It is not an overstatement to say that the way in which health research in Ireland is funded today is a world away from where it was only 20 years ago, with the advent of multiple new funders, a new research infrastructure and a government that is pursuing an R&D agenda. To construct the picture of this changing context we conducted eight key informant interviews with stakeholders in Irish health research, ranging from those in government to researchers who have experienced the research system over the last 15 years or so.[2] To provide more detail, the HRB prepared a context paper on the Irish funding landscape from the 1980s, utilizing its in-house knowledge and expertise to contextualize the research findings. The context paper, together with the interviews, forms this section on the research context in Ireland.

Health research funding in Ireland in 2008 consists of a complex multi-funder environment. The HRB provides the main support for health research (through funding from the Department of Health and Children [DoHC]), but funding also comes from Science Foundation Ireland (SFI, the largest funding agency in Ireland), the Higher Education Authority (HEA) and two funding councils (the Irish Council for Science, Engineering and Technology and the Irish Research Council for Humanities and Social Sciences). Figure 1 shows the relationship between the government departments and funders.

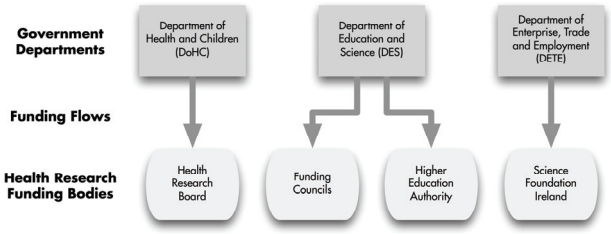


Figure 1. Relationship between government departments and funders of health research in Ireland

1.1.1 Understanding the history

The funding situation for research in Ireland has changed dramatically in the last 20 years. Before 1987 there was little public investment in research in Ireland. Although some work was done to develop national science policy through the National Science Council and, subsequently, the National Board for Science and Technology, very little funding was provided and the role of research in economic development was not well articulated. The Health Research Board (and previously the Medical Research Council [MRC] of Ireland) and what is now Enterprise Ireland (EI) provided some project funding, but the general absence of core funding encouraged a high degree of interest in EU framework programmes throughout the 1990s, with Irish researchers being relatively successful in competing for these. Consequently, before 1998 the main source of funding for academic research in Ireland was the EU framework programme. However, the dearth of funding was not the only reason why research was not taking place in Ireland. Because the health

[2] For a list of key informants, see Appendix A: Methodology.

system lacked incentives for research, it was a low priority for both universities and hospitals. In universities it was considered an add-on that was performed by staff who had a particular interest in it and it often took place in premises that were designed for teaching, not research.

It was the establishment of the Irish Council for Science Technology and Innovation in 1997 that first provided a structure for the development of science policy. A technology foresight study carried out by the Council in 1998 was the first serious attempt to consider the contribution of research to social and economic goals (with a firm emphasis on the latter). The study predictably identified biotechnology and information and communications technology as key areas for investment. More importantly, it legitimized the idea that had been long accepted in other countries: that investment in basic research was important for future economic development. It also laid the groundwork for the establishment of SFI in 2001. Once biotechnology had been identified as an investment area by the Council, the HRB were not involved in any of the groundwork for funding future biotechnology that eventually came through SFI.

The first concrete evidence of a change in public policy came with the establishment of the programme for research in third level institutions (PRTLI) in 1997, funded by the Higher Education Authority (HEA). The PRTLI was the first dedicated source of support for research in Irish universities (hitherto funded mainly for their teaching activities) and institutes of technology. PRTLI acknowledged explicitly that higher education institutions have a dual role, namely teaching and research. The first round of PRTLI (PRTLI1) saw an investment of €200m over three years, most of which went into facilities and equipment. Three further rounds have since been completed: PRTLI2 in 2000, PRTLI3 in 2002 and PRTLI4 in 2007; totalling €830m of research investment. A consistent feature of all rounds has been the strong showing of biomedical and health-related research.

The National Development Plan 2000–2006 led to the expansion of the PRTLI and the establishment of SFI, and two funding agencies, the Irish Council for Science, Engineering and Technology and the Irish Research Council for Humanities and Social Sciences under the auspices of the Department of Education and Science. SFI has played a particularly influential role. Originally established to support world-class research in biotechnology and ICT and with an emphasis on attracting research teams to Ireland, the agency has expanded its portfolio and is now the largest funding agency in the country. The second National Development Plan that runs from 2007–2013 incorporated the strategy for science technology and innovation (SSTI). The SSTI itself seeks to continue the government's commitment to research by setting the agenda across the public research system and addressing specific issues around education and training, commercialization, infrastructure, careers and innovations.

In addition to these changes, in 2005 the Irish health services were completely restructured. Local health boards were abolished and a single national agency, the Health Services Executive (HSE), was established. This is responsible for the delivery of all health and some social services, and receives most of the €14 billion health budget. The DoHC in 2005 also established the Health Information and Quality Authority (HIQA), which is responsible for setting standards in health and social services, monitoring the quality of health care, developing assessments of health technology and advising on the collection of

heath information across the services. These new bodies are likely to play a large part in the way that health research progresses in Ireland in the future.

Currently, national science and technology (S&T) policy is set out in the SSTI 2006–2013, which sets out the vision that "Ireland by 2013 will be internationally renowned for the excellence of its research, and will be to the forefront in generating and using new knowledge for economic and social progress, within an innovation driven culture" (DETE 2006, 8). The total funding for all SSTI-related activities in that period is estimated as €8.2 billion, though much of this is based on existing levels of service.

1.1.2 **Role of the HRB**

The HRB was established in 1986 as a result of the amalgamation of two separate bodies, the MRC and the Medico-Social Research Board. When the HRB was established it was allocated wider responsibilities in research than had existed under its parent bodies, though this was not reflected in its budget. The remit included medical research, health and health services research and epidemiological research. This was all in the context of the severe financial cutbacks that were imposed in the late 1980s.

The HRB's focus throughout the 1990s was on maintaining and increasing its budget. Funding for research was provided through project grants, postdoctoral fellowships, research units (that were essentially programme grants) and a small number of bursaries for students. With limited government funding, the organization also worked to alert researchers in Ireland to the opportunities available at European level. Considering the health research funding landscape in Ireland at this time, the HRB were the only real funders of dedicated health research, meaning that researchers who were funded in this period were unlikely to be able to continue researching without the support of the HRB unless they were successful in gaining EU funding.

Health research strategy at this time was dictated by the researchers themselves, since most HRB funding then merely responded to the best research proposals as selected by academic peer review: it was not directed towards strategic objectives. The health service, in fact, had no interest or involvement in setting a research strategy for health, leaving it predominantly to the researchers themselves to identify interesting research paths. Because most researchers were basic scientists, and it was perceived to be easier to identify high-quality basic science through the review process, most funding was distributed to basic science.

A major breakthrough for the HRB and for health research came in 1997 with a three-year funding partnership signed between the Irish Government and the Wellcome Trust (WT). Under the matching funding agreement, the WT agreed to make £3m available to prime the pump for biomedical and health-related research, provided the Irish Government matched this contribution (Wellcome Trust 2000). The Chair of the HRB at this time described this as a key moment, since there were concerns that the WT were considering reducing their funding in Ireland if the government was unwilling to match its support levels.

In real terms the agreement contributed only £6m of new money to Irish research. But its significance was greater than the actual sum of money, in that it marked the beginning of the change in direction for health research in Ireland. Between 1997 and 2007 the HRB's

total budget (current and capital) increased from €5m to nearly €50m. By the end of 2007 the value of its contracts was expected to be over €180m. This increase has facilitated an expansion not just in the level of funding for individual awards but in the scale of the HRB's activities.

The establishment of SFI and other support for research enabled the HRB to reassess its remit and focus on its core mission of research for health. In 2007, the HRB launched its five-year corporate strategy (HRB 2007a). The strategy identified six objectives towards achieving its mission of improving people's health through research and information, including:

1. Shaping the national agenda for research in health and personal social services,
2. Supporting research and health information systems linked to national health priorities, in order to improve people's health and the effectiveness of the health system,
3. Building capacity for world-class health research in Ireland,
4. Advancing the contribution that health research makes to a sustainable knowledge economy,
5. Increasing awareness and understanding of both the impact and the value of health research and information,
6. Establishing Ireland as a significant contributor to international policy on health research.

Increased funding has enabled progress to be made, particularly in capacity building. Major developments include support for three clinical research facilities in Dublin, Cork and Galway and for the Irish clinical research infrastructure network; a new scheme to support consultant researchers (i.e. clinician scientists); and to establish dedicated structured PhD training programmes in areas relevant to health and to increase support for clinical research training and additional support for funding in health services research.

1.1.3 Health research strategy

HRB funding does not occur in a policy vacuum and in November 2001 the Minister for Health and Children published *Making knowledge work for health: A strategy for health research* (MKWH) (DoHC 2001a). The strategy outlined a far-sighted approach to building health research capacity as part of the government's wider commitment to research for future economic and social development and to underpin a health system of high quality and effectiveness. The research strategy committed the government to enhancing substantially its support for "science for health" – investigator-led, bottom-up research – and for the first time to establish and support a research and development function in the health system.

The role of research was endorsed in *Quality and fairness: A health system for you* (the government's health strategy – DoHC 2001b) and its recognition that the health research strategy (2001) provides the framework in which investment in health research will be made. The priorities identified were a need to support health professionals to carry out research and applying their findings to improve service delivery. The link between

attracting and retaining high-quality professionals and providing them with research opportunities was also recognized. While some progress was made in implementing MKWH, however, the recommendation to establish an R&D office in the DoHC was never implemented, leaving it unclear exactly where responsibility for health research policy lay at the national level.

In 2006, the Advisory Science Council (ASC) identified health research as an area of specific interest and set about reviewing the actions needed for future development. The impetus for this was twofold. First, considerable investment in biomedical sciences through the PRTLI, SFI and HRB meant that the capacity of the third-level sector to conduct world class research had increased significantly. The benefits of this investment, however, could be realized only by translating this knowledge into new therapeutics and diagnostics and ultimately into better healthcare; in other words, through a health service which recognized research as a core function. Second, the enterprise agencies (the Industrial Development Authority [IDA] and Enterprise Ireland [EI]) were increasingly turning their attention to encouraging the pharmaceutical and biotechnology industries, but they recognized that attracting such high value industries also requires a research infrastructure and capability within the heath service.

The ASC report on health research, *Towards better health: Achieving a step change in health research in Ireland* (Forfás and the Advisory Science Council 2006), made a number of recommendations on national health research policy and strategy, governance, funding, human capital, education and infrastructure, innovation, regulatory affairs and research translation. One of the first recommendations to be implemented was the establishment of a health research group under the auspices of an interdepartmental committee that provides a structure to address many of the cross-cutting issues outlined in the ASC report and, previously, in MKWH. Figure 2 shows the major events in Irish health research over the last 20 years, illustrating the growth in the HRB budget during this period.

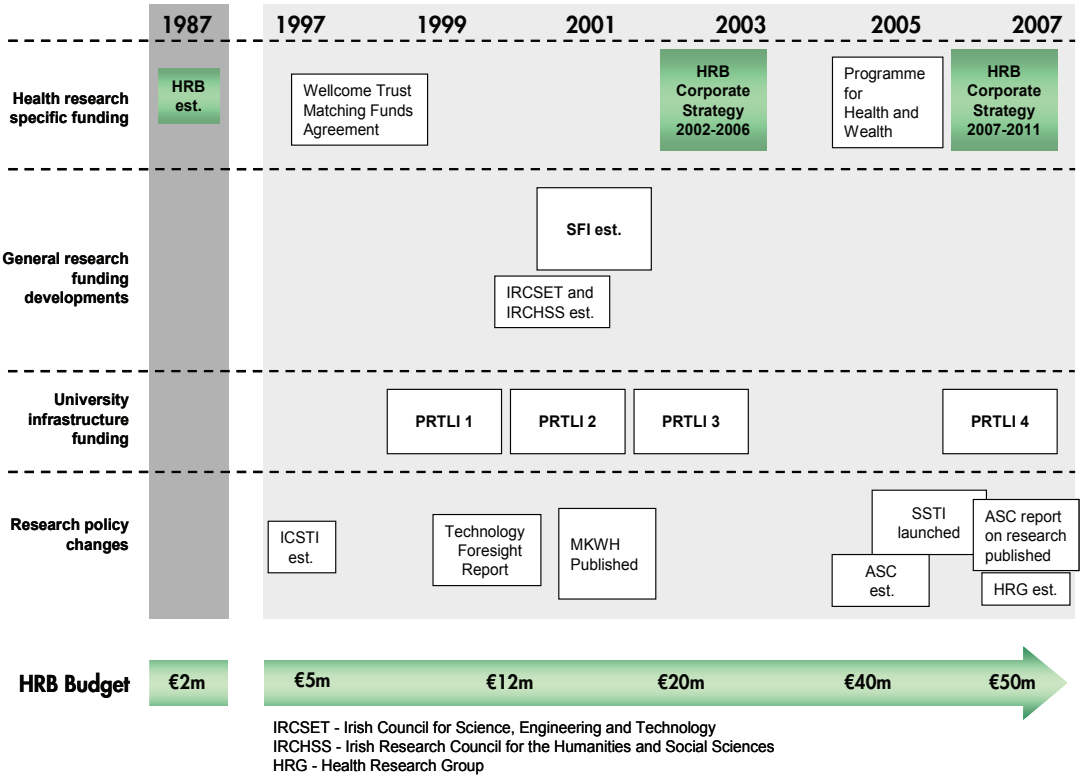


Figure 2. Timeline of major health R&D funding events in Ireland over the last 20 years

1.1.4 Current challenges for Irish health research

The SSTI, MKWH and the ASC report on health research set out clear agendas for developing research in Ireland to promote economic and social development, and health. However, challenges remain. Public funding for research in third-level institutions has increased dramatically since 1997 but expenditure on R&D as a proportion of GDP is still below EU and OECD averages. According to an OECD review of higher education in Ireland carried out in 2004, "claims that Ireland is already 'world class' in research in some areas may be justified but the overall research environment is not yet adequate to support the achievement of research of international quality in the range of fields necessary to promote the economic development that Ireland is looking for" (OECD 2004). The level of R&D activity in companies is low, as is the country's capacity to absorb scientific advances; and commercialization structures for realizing the research are underdeveloped.

In the health service, research is generally not seen as a front-line activity underpinning high-quality healthcare. The HSE does not yet have a dedicated research function or budget. Most health professionals do not have dedicated time set aside for research and there is a shortage of academic clinicians. Health professionals who have research funding often find it difficult to reconcile research with their service commitments. The infrastructure for health research is underdeveloped, though the HRB is taking significant steps to address this deficit. A number of actions are needed to develop translational research so that the investment in basic biomedical sciences can be translated into improved healthcare.

A key challenge in all sectors, including health, is to establish research priorities. Given its size, Ireland cannot expect to be world class in anything more than a small number of research areas. In health research a balance is needed between supporting excellence and relevance, and across areas of research. Finally, the increase in public funding for research has been facilitated by unprecedented economic growth but to ensure that R&D is embedded in social, economic and health policy, a long-term commitment is required.

It is in the light of these current challenges that the HRB is interested in understanding the impacts of the research they fund. By having a better grasp of what the outputs and outcomes are from its funded research, the HRB will be better placed to show the value of health research to all interested stakeholders, from the government to the general public, both in economic and in social terms.

1.2 Payback methodology

The analytical framework for the study was based on the payback framework. This framework was developed by the Health Economics Research Group (HERG) in the 1990s to assess the benefits of health research (Buxton and Hanney 1996). It is currently the most widely used and comprehensive method available for measuring payback in a systematic way. The payback framework has been used by the Canadian Institute of Health Research (CIHR), ZonMW in The Netherlands, and the Health, Food and Welfare Bureau in Hong Kong. In the UK it has provided the basis of a number of studies to assess the payback of health research and wider research fields, such as social science research (Wooding *et al.* 2005). The basic framework was extended in relation to economic benefits in work for the WHO reported in Buxton *et al.* (2004).

In the payback framework any assessment of the scientific quality of research (such as in journal articles, training future researchers and developing a career) is part of the broader assessment of impact. Its societal impact is the key issue in a multidimensional categorization of the benefits of health research. The payback framework consists of two elements: a model of the complete research process (for the purposes of research evaluation), and a series of categories to classify the individual paybacks from research.

The model, presented in **Figure 3**, provides a structure for analysing the progress of a research idea from inception (Stage 0) through the research process (Stage 2) into dissemination (Interface B) and on towards its impact on people and society (Stage 6). The model is meant as a research tool to facilitate cross-case analysis and consistency in research techniques across the case studies. It does this by providing a common structure for each case study, thereby ensuring cognate information for each study is recorded in the same place. The model is not meant to imply that the research process itself is linear. If necessary, individual pieces of information can be recorded in more than one place in the framework to ensure that they are picked up in any relevant cross-case comparisons or summary of case study impacts.

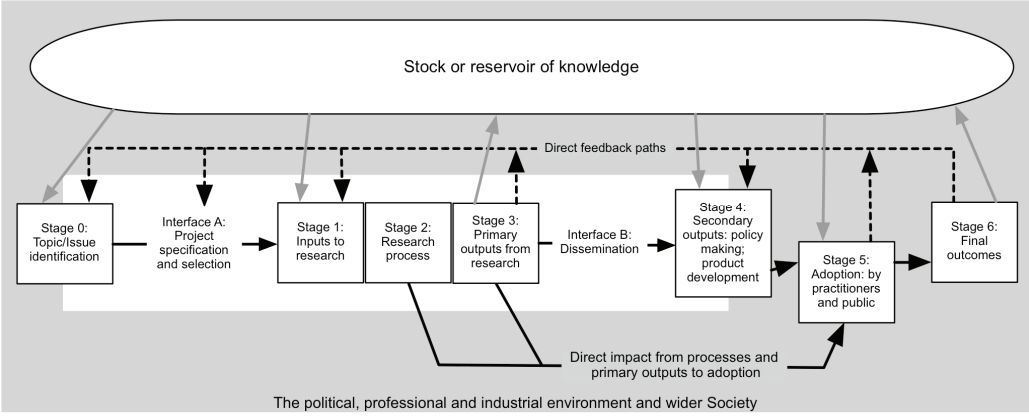


Figure 3. The version of the payback model used in this study (Hanney *et al.* 2004)

The second element of the payback framework is a series of categories for classifying the outputs and outcomes of research, these categories are shown in Box 2. While it is not completely possible to tie the categories of benefits to specific stages of the model, it is possible to identify broad correlations: the knowledge production and research targeting and capacity building categories together are generally the primary outputs from research; the informing policy and product development category relates to the secondary outputs; and the categories for health and health sector benefits and broader economic benefits, respectively, are generally the final outcomes. Hence, although each category of output was assessed for each stage of the model, certain stages tended to produce certain outputs. Below, each category is considered in turn in more detail.

Knowledge production

Journal articles, conference presentations, books, book chapters, research reports

Research targeting and capacity building

Better targeting of future research, development of research skills, personnel and overall research capacity, staff development and educational benefits

Informing policy and product development

Improved information bases for political and executive decisions, developing pharmaceutical products and therapeutic techniques

Health and health sector benefits

Improved health, cost reduction in delivering existing services, qualitative improvements in the process of delivery, improved equity in service delivery

Broader economic and social benefits

Wider economic benefits from commercial exploitation of innovations arising from R&D, economic benefits from a healthy workforce and reduction in working days lost

Box 2. The categories of the payback framework used in this study

1.2.1 Knowledge production

Producing knowledge is usually the first output from any research and codifying this knowledge is vital for it to become an output. Research results that are never published have no knowledge value in the framework. Results are traditionally published in peer-reviewed journal articles, but can also take the form of patent applications or research data deposited in public databases. Peer-reviewed journal articles can be assessed using citation

analysis that provides information on their impact. They can also be looked at in terms of in which fields they are published, to identify research that reaches outside its normal potential users. Previous experience suggests that knowledge production is particularly important for basic research, and it is certain that articles in basic research journals tend to be cited more frequently than those in clinical journals (Lewison and Dawson 1998).

1.2.2 Research targeting and capacity building

The better targeting of future research, both that conducted by the original researcher and/or others, is frequently a key benefit of research. Capacity building predominantly encompasses research training. This can be measured through the number of higher or research degrees that result from the research funding (Mushkin 1979; Verhorn *et al.* 1982). The career development of researchers can also go much wider than simply receiving specific training; and qualitative information on the career path of the principle investigators (PIs) and their research teams can be used to identify the wider outcomes of the HRB funding.

1.2.3 Informing policy and product development

Policy here is considered to be more than just national government policies and includes health service policies, clinical or local guidelines agreed by healthcare practitioners and training, curricula and evaluation criteria policies (Hanney *et al.* 2003). Basic research is generally considered to be less likely to inform policy than clinical, public health or health services research (HSR), since the questions addressed in basic research are less likely to be directly linked to a specific policy issue. Research can also be used to inform product development, such as an assay or drug development. Informing policies and product development are conceptually similar in that there generally has to be some subsequent adoption of the policy, or product, before any health or economic benefit can accrue.

1.2.4 Health and health sector benefits

For a funding organization such as the HRB, the health benefits resulting from the research funded represent the payback that most closely mirrors its mission statement. Greater clinical effectiveness resulting from developing research-informed drugs or procedures should lead to increased health. Measuring this health gain can be difficult, although measures do exist. At the most crude level, reductions in mortality and morbidity as the result of health research can be assessed. Quality-adjusted life years (QALYs) can be used to provide a consistent way of measuring the health gain from reductions in both mortality and morbidity. The health sector can also benefit from research findings, particularly in the form of cost savings in healthcare provision (through HSR, for example). Cost savings are viewed as health sector benefits when they allow re-investment elsewhere in the health sector.

1.2.5 Broader economic and social benefits

As shown in Box 2, there are several ways in which health research can have an economic benefit. These benefits can be considered along the lines of benefits traditionally seen as economic, such as creating employment in the production of pharmaceuticals or from the creation of spin-off companies, or they can be more complex benefits related to a healthier workforce, an improvement in the value of human life or even an improved international reputation, leading to increased foreign investment in the country. The next section

provides an overview of how to identify and measure economic benefits, while the methodological and evidence base underpinning these ways of evaluating economic benefits is described in more detail in Appendix B.

1.3 Economic returns on health research

As explained in the previous section the payback framework provides a mechanism to capture the diversity of benefits arising from health research – ranging from the knowledge produced through to the broader economic and social benefits. However, in the context of this study we also wanted to consider how these benefits could be translated, directly or indirectly into effects on the economy.

The UK Evaluation Forum, convened by the Academy of Medical Sciences (AMS), MRC and the WT, produced a report that suggested four broad areas of such consideration, detailed below (UK Evaluation Forum 2006). This drew on previous work by HERG (Buxton *et al.* 2004). The areas were:

1. evaluating direct cost savings to the health system,
2. evaluating benefits to the economy from a healthy workforce,
3. measuring the intrinsic value to society of the health gain,
4. evaluating the benefits to the economy of commercial development.

In overview these four areas can be thought of as three different types of benefit, one of which can be assessed in two ways, as broken down below.

1. **Benefits from improved health**
    a. evaluated as the additional contribution to the economy of a **healthier workforce**, ie one in which more people are fit to work
    b. assessed as the **intrinsic value of health**, ie the monetary value of reduced morbidity, or a longer life. Such values can be estimated using individual willingness-to-pay methods or by attaching a maximum value that a particular health care system is willing to spend on a unit of health benefit such as a QALY (quality adjusted life year).
2. **Cost savings** through more cost-effective new treatments or technologies, or savings to other parts of the healthcare system or beyond, such as reduced custodial care or more efficient community support.
3. **Benefits from commercial development**, that is, the value of subsequent commercialization of a product or technology. This includes the value of increased employment, tax revenues and exports, along with possible import substitution.

A further grouping is helpful when examining the benefits to a particular country, as that country will experience the benefits of resources attracted into its economy through the impacts of research; for example by attracting foreign investment, researchers or funding. On the global scale this is simply a transfer of resources, but from the perspective of an individual economy, particularly a small one, they can be significant benefits.

To complicate matters, some impacts will have effects through more than one of these mechanisms – a new treatment might reduce treatment costs, while also improving health outcomes and becoming a commercial success. And the benefit of that improved health could be quantified either through its contribution to a healthier workforce or the value placed upon those healthier lives. Having presented the findings of the case studies, we then consider the repercussions of the impacts identified according to the broad areas set out above.

In all the cases there are issues about how to attribute economic benefits to any funding input, but the aim of the payback framework is to provide a method for tracing, and investigating, the strength of such links to specific grants or investigators. For this reason, the payback framework has been widely adopted to try and address the attribution issue.

1.4 Case study selection and scope

In order to include case studies that would provide useful information on the activities of HRB-funded researchers, high impact researchers were selected using a framework that took into account various proxies for research impact, mostly from the careers of the researchers themselves. Whilst the researchers were thought to have conducted high impact research, this was not always the case for the specific study that was chosen to be the prime focus of the case study. Purposively selecting research grants that were of interest to the HRB is in line with established selection methodologies (Yin 2003) (Box 3). The projects selected as case studies were also split between basic and early clinical research (B/EC) and health services/public health/primary care research (HSR/PH/PCR). Four studies were chosen in each area (B/EC or HSR/PH/PCR), and selected to include researchers who had been funded recently at a breadth of research locations (not just in Dublin); and researchers of both genders. The selection was performed at a meeting attended by the research team and representatives of the HRB. The latter were able to provide knowledge of specific researchers and their respective fields of research (since the titles of the grants were the only information available on a researcher's area and they did not always make the research field clear). The process of selecting the case studies is described in more detail in Appendix A.

- Recommendations from key informant interviews (KIIs)
- Unit/programme funding
- Volume funding (IR£ and €)
- Number of HRB grants
- Additional SFI funding

Box 3. Proxies for research impact used in selecting the case studies

Determining which impacts should be linked to a case study and which considered the outcomes of subsequent research is always a challenging issue. In this study we have drawn the lines of attribution very broadly; however, in each of the case studies we discuss how each impact relates to the specific piece of the PI's research selected to be the initial focus of the case study. The justification for the broad consideration of impacts is that HRB

funding in the late 1980s was key to sustaining health research in Ireland; without it some of the case study researchers would have left health research or moved to research abroad.

1.5 Report structure

Having set the context for the work and explained the methodology, in the next chapter we provide a summary of all case studies – describing their development from research idea through to the wider economic and social benefits that have arisen from the research. Chapter 3 then examines the impacts on the economy of the diverse range of impacts identified. Chapter 4 places the findings from the previous chapters in the context of the Irish health research system and, finally, Chapter 5 outlines possible ways the HRB's evaluation work could be developed, such as in a deeper integration of the payback framework. Two appendices provide more detail on the methods used and the variety of methods that can be employed to understand the economic impact of health research.

CHAPTER 2 Individual case studies

In this chapter we present summaries of each of the eight case studies, which form the core of the study, organized along the lines of the payback model to provide the narrative structure for each study. The case studies provide an insight into the types of impacts that can arise from HRB-funded research and the narratives illustrate the variety and complexity of the routes to impact. At the end of the chapter, and using the payback categories, we classify all the outputs, outcomes and impacts arising from the case studies in Table 1. While the set of eight case studies does not represent the full profile of HRB funding, it aims to mirror the variety of the HRB funding portfolio by including case studies from all the key domains of research, balancing basic/clinical and HSR/public health/primary care research. In the next chapter we examine each of the impacts identified and assess their economic repercussions.

Case study data were collected through a combination of interviews and desk research. Each case study used a combination of approaches, all included some review of archival material and face-to-face interviews with the principal investigator (PI). Others interviewed in the course of the case studies include research collaborators, co-researchers, students, industrial partners, medical practitioners, policy-makers and research users in industry. Archival research sources included material from the HRB (grant applications, reviews, end-of-grant reports and others), the researchers, universities, academic publications, policy documents and other information relevant to the grant (e.g., drug company or public health websites).

The names of the researchers have been removed from the case studies, although, since it is in the nature of a case study to provide contextual detail, in some cases it is relatively easy to identify the PIs, in other cases they will be identifiable to those who know the field. This was made clear to the PIs and they have also reviewed the final case studies. With regard to academic and industrial collaborators we have provided as much detail as the case study PI felt was appropriate, hence there is some variation between case studies.

2.1 Case study A: Eicosanoids in vascular disease

This research programme assessed the role of eicosanoids in vascular disease. Cyclooxygenase (COX) is a family of enzymes that produce eicosanoids, which are signal molecules that exert a complex control over many bodily systems (mainly in inflammation, with a role in pain and vascular disease). COX comes in two main isoforms: COX-1 (responsible for basal prostaglandin synthesis) and COX-2 (which is important in

inflammation).[3] The pharmacological inhibition of COX can provide relief from the symptoms of inflammation and pain: this is the method of action of well-known drugs such as aspirin and ibuprofen.[4] The discovery of COX-2 in the late 1980s provided a new molecule to characterize and study (HRB 1995b.)

This case study is based on desk research of the HRB archival material; a review of the research literature feeding into and resulting from the study; further desk- and web-based research on other outputs and outcomes; and semi-structured, face-to-face and telephone interviews with the PI, a post-doctoral member of the programme grant team, two PhD students and one academic collaborator.

Stage 0: Topic identification

At this point, the research community did not understand the biology of eicosanoids and their receptors, nor the exact role of COX-inhibitor drugs, which can have serious side effects (HRB 1995a). The objective of the research programme was to investigate eicosanoids in cardiovascular disease combining in vitro and clinical work. It was thought that the programme could lead to an immediate practical use in vascular disorders through a modification of aspirin delivery (HRB 1995b). The PI submitted a multidisciplinary application with co-researchers to examine four aspects of eicosanoid biology related to vascular disease.[5]

Interface A: Project specification and selection

The research proposal was reviewed by four referees, three of whom were very positive and one who had concerns over the feasibility of the programme and the additional resources required. The PI responded to these concerns by explaining that staff and many techniques had already been transferred successfully from his previous laboratory and he provided a more detailed description of the additional resources that had already been secured (e.g., probes and antibodies for COX-1, COX-2 and the thromboxane receptors) (HRB n.d.b.).

Stage 1: Inputs to research

The HRB awarded the full amount requested, IR£382,224. The HRB funding was a core grant, but the research team was able to raise additional funding from other agencies such as Cancer Research Ireland, European funding agencies, the RCSI, Irish Heart Foundation (IHF), LTS Lohmann (for studies on aspirin), and Sterling Laboratories (for a study on controlled-release aspirin in pre-eclampsia) (HRB 1995a). The PI remarked that at that time no other agency in Ireland would support the study as a whole. On top of this funding, the research team received the lead compounds and vacuum equipment from the pharmaceutical company involved in the work.

---

[3] Although COX3 has also been identified, it is considered to be a splice variant of COX1. *Cf.* Chandrasekharan *et al.* (2002).

[4] For more information on COX inhibitors and other drugs see Dionne (2003).

[5] Molecular biology of eicosanoid receptors; Eicosanoid biosynthesis following free-radical induced cell injury; Characterization of the cyclooxygenase pathway in trophoblasts isolated from normotensive and hypertensive pregnancy; and Eicosanoids in the pathogensesis of homocyst(e)ine-induced vascular injury (HRB 1995a).

The PI's training as both a clinician and a researcher, as well as his links to clinics and patients, provided the basis for him to produce translational research. The PI also had experience in techniques for prostaglandin research and expertise in eicosanoids research. The research team included molecular biologists, epidemiologists and statisticians, cell biologists and analytical biochemistry expertise, permitting a multidisciplinary approach to the research. Most researchers had worked with the PI during his previous post, allowing the programme to start quickly. Study collaborators, including the department of chemistry and experts in animal models, crystallographic methods, eicosanoid measurement and cyclooxygenase research, also provided valuable intellectual input to the programme.[6] The PI mentioned that changes in Irish research funding at the time meant the best researchers could be kept in Ireland rather than losing them to the UK or USA.

Stage 2: Research process

During the research the team developed a new technique to develop assays more efficiently. This technique was used in subsequent research. Annual progress reports and the mid-term review allowed researchers to describe which tasks had been accomplished and which steps they would undertake next, while allowing the HRB panel to understand the direction of the research throughout the lifespan of the programme. The review panel noted that the PI's "understanding of the science underlying the whole area under investigation [was] impressive and the use of collaborations with outside laboratories was praiseworthy" (HRB n.d.c).

Stage 3: Primary outputs from research

Knowledge

The diverse portfolio of grants held by the PI during the time of the HRB unit grant means that it is very hard to attribute the publications resulting from this research to any one grant. In a subsequent application to the HRB (HRB 2000), the PI identified 24 articles that had been published in a variety of academic and medical journals such as *Circulation*, *Journal of Biological Chemistry, New England Journal of Medicine* and *Rheumatology*. Out of all the publications resulting from the programme grant, the 1999 *Journal of Biological Chemistry* article on metabolizing effects is considered by the PI to be the most influential (Adderley and Fitzgerald 1999). The PI also believes that the articles submitted to the clinical journals are important (since they aid translation of research to clinicians).

Benefits to future research and research use

As a result of the HRB funding, the PI is currently considered "an absolute expert in cyclooxygenase, eicosanoids and platelets" in the opinion of a US collaborator. This reputation has led to his participation in major international clinical trials. According to the international collaborator, the PI and his team have increased the research capacity and reputation of Ireland, and the HRB funding provided the opportunity for Ireland to become the vibrant and successful research community it is now. The five-year funding allowed PhD students to qualify more easily, attracted the best post-doctoral researchers

[6] It is worth noting, however, that the PI suggested there is a negative side to collaboration; that interacting with collaborators also led to an 'arms race' to publish results in the same field.

(one senior post-doctoral researcher has gone on to recently receive a large HRB translational research grant) and developed clinical collaborations. In addition, the range of contacts and collaborators of the PI facilitated the transfer of new technologies to Ireland and the establishment of Chemistry as a new department at the university. This development of a sophisticated scientific and technological workforce in Ireland consists of a distinct economic benefit to the country.

This HRB grant allowed the purchase of laboratory equipment, including a mass spectrometer, a radio scanner and a phase-contrast microscope, used in subsequent studies. The research findings enabled the team to produce the instruments that were used in further work to investigate the activity of the enzymes (COX-1 and COX-2) that, in the long term, could be used to design better clinical therapies.

The research on pain and the COX-2 inhibitor was taken up by clinicians who are still researching this subject (e.g. Manning *et al.* 2007). Similarly, the early prostaglandin work is being further researched by clinicians. The PI's own subsequent work includes projects on enzymes in oesophageal cancer cells, cell connections and how a COX-2 inhibitor controls colon cancer growth; as well as an examination of cancer drugs with fewer side-effects (HRB 2004).

Interface B: Dissemination

All interviewees agreed there was a great deal of dissemination, ranging from abstracts at national and international meetings (clinical and basic meetings) to regular speaking commitments at academic institutions. The PI chaired the working group on platelets and thrombosis at the European Society of Cardiology and is a member of many professional organizations. The PI lectures on various courses to medical and pharmacology students, training them on the effects of aspirin, COX-2 inhibitors and their role in cardiovascular disease. After-hours seminars gave postgraduate students in this project the chance to present to the public, although organized large-scale interaction with the public did not take place. Members of the research group participated in a number of meetings with prospective and existing industrial partners, and the PI had an advisory role with pharmaceutical companies.

Stage 4: Secondary outputs

Due to the clinical relevance of the research, the PI was able to attract various industrial partners. Although the success rate for developing useful therapeutics is low, the initial work provided the intellectual basis for characterizing new classes of compounds and making further advances. For example, the PI's expertise in platelet research was diverted into new thrombotic therapies. One important output was assay development. These assays have been taken up by academic researchers and industry worldwide and are currently considered the standard approach to test aspirin activity and resistance. The PI worked on drug development with a number of pharmaceutical companies. This included pre-clinical trials, synthesis of aspirin compounds, measuring product responses to drugs, understanding the dosing regimens of aspirin and those for arthritis drugs. Much of the work on dosing was done in close contact with clinicians and led to an increased understanding of a low-dosage regimen for the drugs studied.

Closer to clinical application, the PI worked on the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT 2006). This international research project conducted over a six-year period examined 19,000 patients for the effects of blood pressure medicines and the relationship of cholesterol-lowering drugs with coronary heart disease and stroke. The ASCOT study showed there were significant advantages in taking a combination of a calcium-channel blocker and an angiotensin-converting enzyme inhibitor for blood pressure problems (ASCOT 2006). The study was widely reported in the media and has gone on to influence the two main UK guidelines for managing high blood pressure.[7] The HRB grant is not solely responsible for the PI's participation in ASCOT, but it did play a role.

Another indirect secondary output of the PI's research includes drugs taken off the market. Good clinical collaboration and access to patients allowed the PI to provide evidence on the problems associated with high dosages of COX-2 inhibitor (considered to increase the risk of heart attacks, thrombosis and stroke). This work prefaced the withdrawal of COX-2 inhibitors from the market. For example, rofecoxib (marketed under brand names Vioxx, Ceoxx and Ceeoxx) is a selective COX-2 inhibitor developed by Merck & Co. to treat osteoarthritis, acute pain and dysmenorrhoea. After rofecoxib had been approved in 1999, Merck voluntarily withdrew it from the market in 2004 because of concerns over the side-effects of its long-term, high-dosage use. Similarly, its successor, Prexige, was also taken off the market in 2007 as it was found to cause severe liver damage (Merck n.d.). Despite the difficulties caused in the basic science–pharmaceutical relationship caused by the withdrawal from the market of COX-2 inhibiting drugs, the PI's work still attracts a great deal of interest from industrial partners such as Bristol-Myers-Squibb and other nutrition-based pharmaceutical companies.

The study on COX-2 inhibitors helped to locate the source of pain, allowing therapeutic compounds to target it directly. However, the potential risk of COX-2 inhibitors gave rise to some concerns about its possible therapeutic applications. The effects of COX-2 inhibitors have already entered clinical guidelines and become known to professional societies through the PI's membership of policy groups and societies such as the European Society of Cardiology.

Stage 5: Adoption by practitioners and the public

By working in the hospitals in Dublin during the grant, the PI developed close links with the medical community which, in turn, facilitated effective collaboration with doctors. This collaboration, combined with the PI's teaching role, directly affected clinicians in Dublin.

Stage 6: Final outcomes

The PI has identified three spin-off companies that can be linked to this work on eicosanoids. The first spin-off, Genset, is a pharmacogenetics company jointly owned by

[7] The British Hypertension Society and the National Institute for Health and Clinical Excellence guidelines (Williams *et al.* 2004): both suggest caution when using a beta-blocker and a diuretic together as it may increase the risk of developing diabetes. These used the ASCOT study results as they appeared through the study, rather than at the time of the final report.

the RCSI and a French genomics company. The second was a clinical research organization in the RCSI that has since become a private company. The third is Biontrack, a software analysis company providing software solutions to support protein researchers in industry and academia.[8]

In terms of the drug development, this has not yet reached production so no new products have been registered so far. As one researcher noted, "Because the timeline on drug development is long, we are not at the end yet". There is, however, potential for developing new therapeutics.

2.2 Case study B: Unit for retinopathies research and therapy

In those parts of the developed world where registers of visual handicap are available, retinitis pigmentosa (RP) and Leber congenital amaurosis (LCA), which is essentially a congenital form of RP, represent the most prevalent causes of blindness in working people and children, respectively. Moreover, age-related maculopathies (AMD) represent the most prevalent cause of registered visual handicap in elderly individuals, affecting up to 8m people in Europe, 5m people in the USA and probably up to 35,000 people in Ireland at present. The social and economic impact of such conditions is thus immense. Studies of the molecular genetics of retinopathies, including RP, and, more recently, of novel approaches to therapeutic interventions have represented a major component of the research of this PI for over 15 years. The overall aim of the programme was to explore methods to prevent and treat degenerative retinopathies, making extensive use of mouse disease models generated by gene targeting.

This case study is built on information from interviews with the PI; a collaborator on the Trinity College Dublin (TCD) team; and Professor of Biochemistry at the University College Cork who collaborated on the programme. Information was collected from the literature in the HRB archives on the grant in question and the subsequent grants of the PI, as well as additional open-source literature related to the grant and its outputs and outcomes.

Stage 0: Topic identification

Previous research resulted in a significant breakthrough in localizing the first genes to be involved in autosomal dominant RP (McWilliam *et al.* 1989) This subsequently led to the implication of rhodopsin and RDS-peripherin in the aetiology of the disease (Farrar *et al.* 1991). The researchers subsequently reported on the retinopathy induced in mice by a targeted disruption of the rhodopsin gene in the mice. There were indications that a mouse

[8] It should be noted that the software developed arose from research funded by SFI and Siemens in collaboration with the university, thus it has only an indirect link with the PI's work on this HRB grant. PI's eicosanoid work was based on mass spectrometry and this expertise led the interest of researchers to developing proteomics (some eicosanoids modify proteins). As a result, the first proteomics unit was established in Ireland. Biontrack evolved from that new development, as an effort to automate the proteomics analysis.

with a targeted knock out of the rhodopsin gene was developing a severe retinal degeneration similar to a recessive form of RP. These results, combined with the particularly favourable environment where large families were prepared to facilitate genetic research, allowed the PI to make extensive use of the mouse disease models that had been generated by these studies.

Interface A: Project specification and selection

A number of issues raised at the application stage required action from the PI. In his response, he submitted additional information to supplement his application, particularly in relation to the development of gene therapy and transplantation. There was no resulting impact on unit activities and the long-term objectives of the grant remained unchanged.

Stage 1: Inputs to research

The PI and his collaborators, involving three universities, received a total of IR£375,000 over a five-year period and it is believed that this particular mode of funding contributed to the overall success of the teams involved. Capital support granted to TCD in 1993 provided a state-of-the-art mouse model facility that enabled the PI to use the space and equipment in TCD and improved the quality of the research. Many new techniques and approaches emerging in the late 1990s facilitated this research. The five co-applicants involved were all very experienced research scientists and they directed the work of the less senior PhD students and the post-doctoral fellow.

Stage 2: Research process

Given developments in previous research, issues relating to gene replacement and/or mutation suppression (Millington-Ward *et al.* 1997) in the tissues of the retina could now be addressed. To undertake such work, a series of animal models that would exhibit a range of symptoms akin to human disease was required. In parallel, methods for the stable and safe delivery of therapeutic genetic material to retinal tissues needed to be developed. By the time of the mid-term review, reviewers reported that the TCD project had been a very highly successful and productive project that had achieved significant scientific advancements at a very low level of investment by the HRB. Relationships were strengthened between all three universities involved and further collaborations were established with research teams in Canada and the USA.

The PI directed the research from TCD and spent approximately ten hours per week working on the programme. His role was facilitated by the work of collaborators in his own laboratory, in University College Dublin (UCD) and in University College Cork (UCC), all devoting similar time to the research. The research personnel in the three Universities worked on the research full-time.

Stage 3: Primary outputs from research

The primary outputs from the project can be broken down into two categories: knowledge production; and benefits to future research and research use. These are the immediate outputs of the research project since they can be directly linked to the project itself.

Knowledge
Two PhDs were awarded to the two research graduates who worked on the programme. One of these was awarded to the TCD team member. The programme as a whole produced over 27 peer-reviewed publications, 22 of which were produced by the TCD team.

Benefits to future research and research use
Many of those involved in the programme remained in TCD for some time afterwards and still work with the PI today. The second co-applicant is now Co-Director of the Ocular Genetics Unit. The laboratory currently employs 22 personnel. The HRB grant enabled them to leverage further funding from a number of sources and the PI was awarded his second HRB five-year programme grant to explore therapeutic interventions at the genetic level of degenerative diseases of the retina. He was also part of the successful team that applied for a large infrastructure award for €13m, jointly funded by the HRB and the WT.

A number of fruitful collaborations also arose out of the initial HRB funding; and the particular techniques in relation to animal models also provided the building bocks upon which subsequent collaborations and studies were built. Further research was also funded by the HRB and the US Foundation, Fighting Blindness.

Interface B: Dissemination
The PI has communicated the outcomes of his research by giving talks to regional nurses, secondary school teachers and GPs, and has been involved in other outreach activities.

The PI has involved himself in a number of committees and overseas advisory panels. These include the Vision Research Working Party/Neurosciences Panel of the WT, Genetics Advisory group of the WT, The College of Experts of the MRC of the United Kingdom, Focus Group on Genetics of the United States RP Foundation, Medical and Scientific Advisory Board of the International Retinitis Pigmentosa Association and the Scientific Advisory Board of AMD Alliance.

The Society of Physicians of Britain and Ireland invited the PI to give their Keynote address (The Osler Lecture). Many Irish clinicians are present at these meetings and, because the community in Ireland is so small, it is easy to disseminate findings and it is almost impossible for those involved as practitioners not to know about the research.

Stage 4: Secondary outputs
The studies of the PI and his team on the molecular genetics of RP and their experimental approaches to therapy could lead to treatment for RP and other diseases. The team is currently exploring new avenues of therapeutic intervention using cell and animal systems. However, the PI is fully aware of the requirements involved in reaching stage 1 of human clinical trials and emphasizes how demanding those requirements are. Work is in place to support their rationale for these trials and their efforts will be increased in order to meet the requirements, as they move towards getting approval for novel therapeutic research.

Stage 5: Adoption by practitioners and the public
The PI noted that the ophthalmology community is very small, which enables him to engage easily with clinicians. Disease foundations in Ireland have strong relationships with

the research teams and the researchers get to know them intimately. As a result there is a great deal of interaction between both parties.

The research outcomes in relation to therapies will not have a large effect on clinical practice for some time yet. However, there is a potential for their rapid application in the future, as the awareness of the research among clinicians is so strong.

Stage 6: Final outcomes

The team set up a company aimed at facilitating the development of the concept of gene suppression and replacement, in order to minimize the costs associated with the protection of intellectual property. The founders of the company are the three original applicants on the 1996 programme grant; and the establishment of the campus company is partly due to the success of this programme. The research has created 15–20 jobs for highly skilled workers who have been sustained over the past 20 years through funding both from the HRB and other agencies.

The final outcomes in the form of improved health have not yet been realized but potential benefits may arise if the team are successful in providing a rationale for human therapeutic trials. Due to the similarity that exists between retinal and brain cells, the same procedures could be used for the brain cell defects which cause Alzheimer's disease, multiple sclerosis and Parkinson's disease.

2.3 Case study C: Identification of the immediate post-receptor proteins which couple to the signalling domain of the Interleukin-1 Type 1 receptor

As one of the world's leading researchers on the molecular basis for inflammation, the PI has published over 100 papers in this area. His research mainly describes processes inside cells that lead to an enhancement in the expression of immune and inflammatory genes, most notably those emanating from the cytokine Interleukin-1 (IL-1) and the family of toll-like receptors (TLR). The cytokines have been shown to play a key role in joint breakdown in arthritis. The PI's project in 1996 was part of a major effort to understand precisely how IL-1 and other cytokines like it work, with a view to blocking these effects.

This case study is built on information from interviews with the PI; a professor of clinical medicine who collaborates with the PI; a PhD student who worked on the study; and a consultant rheumatologist involved in clinical research. The information was collected from the literature from the HRB archives on the grant in question and the subsequent grants to the PI as well as additional open source literature related to the grant, its outputs and outcomes.

Stage 0 – Topic identification

This study attempted to elucidate components in cells activated by IL-1 that gave rise to inflammation, as pharmaceutical companies and rheumatologists, in particular, had become interested in the latest discoveries in the field and the prospect of targeting a drug.

Interface A – Project specification and selection

The research was at such a fundamental level of biomedical science that not much negotiation with practitioners took place at the time of application. The PI did not recall any peer reviewer recommendations that affected the original objectives or research methods.

Stage 1 – Inputs to research

The PI's extensive research experience in the area of IL-1, his previous HRB grants, together with the number of publications to his credit in this area, contributed to his prominence in the field which, in turn, led to a number of international collaborations, including one with the Pasteur Institute. This contributed to the productivity of the researchers and the PhD student working on this grant in the laboratory. The PI's past experience allowed him to apply previously developed research techniques to this project. For example, tissue culture technology used to produce various cell lines had already been set up, according to the PhD student who worked on the project.

Stage 2 – Research process

While the original avenues of research proposed in the grant application changed during the project, the overall objective did not and several discoveries were made that have identified specific processes activated by the IL-1 pathway which, if manipulated therapeutically, could give rise to clinical benefits in treating rheumatoid arthritis. This important breakthrough has improved understanding of how IL-1 acts, indicating possible novel drug targets that may block the ability of IL-1 to induce inflammation and joint breakdown in rheumatoid arthritis.

Stage 3 – Primary outputs from research

The primary outputs from the project can be broken down into two categories: knowledge production; and benefits to future research and research use. These are immediate outputs of the research project since they can be directly linked to the project itself.

Knowledge

One of the two published works appeared in the *Journal of Biological Chemistry*, an accomplishment that the PI strongly aspired to for his students. The quality of this journal increased chances of further funding both for the PI and the PhD student herself. The external examiner reported her PhD thesis to be "outstanding" and she still works in the laboratory today on a part-time post-doctoral position.

Benefits to future research and research use

The laboratory success enabled the PI to offer further proposals to the HRB and the PI; and the team were soon to be seen as the pioneers for TLRs. While they did not make the original discovery of TLRs, knowledge fed through from the 1996 project made a significant contribution to its discovery. The former PhD student subsequently published one of the first papers ever on TLRs. This was published in *Nature* (Fitzgerald *et al.* 2001) and has since been cited 441 times by researchers across a broad research spectrum. The discovery was of a protein, named MAL, which is specifically involved in signal transduction by TLR-4 and could be used as a drug target for conditions such as septic shock. There are now drugs being developed to target TLRs. The PI states that these

results can be traced back to the 1996 project, which was a great breakthrough for immunology. Ireland's performance is 30% higher than the average impact level worldwide in the area of immunology and the PI's work has contributed to this reputation (HRB 2007b). It has had a dramatic effect on the field and led to a paradigm shift in this area of research. Innate immunity, which had been neglected as a research area for so long, had now suddenly opened up again and this was a major step forward for immunology.

The discovery of MAL has also been a driving force in establishing relationships with researchers abroad. It strengthened the existing team of researchers and retained them in the country. While they were building up a critical mass in Ireland, they began applying to SFI and more funds became available in the system. This encouraged many people to return to Ireland. The PI noted that if the HRB had not been around in the early days, there was a good chance that he himself would have left the country.

Interface B – Dissemination

The PhD student on the 1996 grant has given a number of national and international presentations in Jerusalem, Dublin and Hilton Head, USA. She was assisted with costs by a travel bursary from the HRB. The PI gave presentations to industry through seminars which led to two grants being awarded by a pharmaceutical company in the USA. The research team did not disseminate research outcomes specifically to policy-makers, since this was basic biomedical research and would not have been of interest to policy-makers at that time.

Stage 4 – Secondary outputs

As mentioned, this research was at a very early stage and it was still very early to be of interest to the policy-makers. However, the original 1996 project delivered some interesting outputs that resulted in identifying specific processes activated by IL-1 in cells. These have contributed to the development of new drug targets and will most likely have a policy impact later on. Subsequent research, based on similar approaches and techniques used in the 1996 project, would not have been possible without the support of the HRB, according to the PI. One significant outcome of this research is drug development in the start-up company, founded by the PI and two other leading Irish immunologists in 2004, which is based on the TCD campus. There are two lead products in development, both novel anti-inflammatory agents. These products target key inflammatory processes and in particular, TLRs, either directly or via the targeting of downstream signals. Opsona Therapeutics Ltd is planning Phase I clinical studies to commence in 2009.

Stage 5 – Adoption by practitioners and the public

There has probably been no direct effect on practice that can be attributable to the 1996 project. However, the success of the PI's research during the 1990s resulted in increased research funding for his laboratory and, by 2000, he had strengthened his links with clinicians in the field in order to get closer to the clinic. Practitioners then became very interested in the research when they recognized the possibility of developing new drug targets. The PI has attracted much media interest, especially in relation to the MAL discovery. As recently as November 2007, Ireland's main broadcasting television network ran a series about Ireland's prime researchers and their discoveries, during which a 30-minute episode was dedicated to the PI's work on MAL and his subsequent collaborations.

Stage 6 – Final outcomes

The single most important outcome for the PI, he says, was that HRB funding allowed him to build his laboratory and therefore his team of researchers, which had a knock-on effect on the important outcomes that followed. For instance, recent results from the PI's collaborations show that a MAL functional variant is associated with protection against invasive pneumococcal disease, bacteremia, malaria and septic shock (Khor *et al.* 2007). This groundbreaking research has therefore provided substantial support for further studies to work on the development of MAL, as a potential vaccine candidate for prevention against these diseases and with the potential to save millions of lives each year.

Another important outcome is Opsona Therapeutics Ltd, a spin-off of the TCD labs that provides employment to over 19 staff, including 14 scientists with PhDs. Opsona Therapeutics Ltd is a drug development company that focuses on the regulation of the human immune system and it is a perfect example of fundamental research being translated into products with a commercial potential. Opsona completed a financing round worth €6.25m in 2005, €5.25m of which was received from the USA. The financing was co-led by its investors, Inventages Venture Capital (Bahamas) and Seroba BioVentures (Ireland), along with co-investors, US-based Genentech and EI. In 2006 the company entered into a collaboration with Wyeth Pharmaceuticals, a division of Wyeth (NYSE: WYE), for the discovery, development and commercialization of compounds to treat inflammatory diseases based on TLR targets. The collaborations of the PI and his research team and drug companies have increased markedly and the team have worked with Wyeth. A collaboration of this sort also reaffirms Wyeth's continued investment in the Irish biotechnology sector.

2.4 Case study D: An investigation of the putative role of Interleukin-1 in age-related impairments in the rat

IL-1 is a cytokine, an important pro-inflammatory molecule in the body which has effects on physiological processes from appetite to fever. As a molecule produced by neuronal cells in response to stress or damage, increased levels of IL-1 have been associated with neurodegenerative conditions (Murray and Lynch 1998). This grant aimed to investigate the role that IL-1 expression plays in neuro-degeneration, using the rat as a model organism. The PI's previous work had looked mainly at fatty acids and their role in long-term potentiation.[9]

This case study is built on information from interviews with the PI, a former PhD student of the PI, and two industrial collaborators; literature from the HRB archives on the grant in question and the subsequent grants of the PI; and additional open source literature related to the grant and its outputs and outcomes.

[9] Long-term potentiation is the effect of continued electrical stimulation of a nerve synapse. It is associated with learning and memory.

Stage 0 – Topic identification

The PI on this project was an expert in neuro-degeneration and was specifically interested in understanding the molecular mechanisms behind it. The team had been working on neuro-degeneration using rats as a model for a number of years before this study. Through their work on synaptic plasticity[10] and fatty acids in the early 1990s they had identified a link between fatty acids and neuro-inflammation, since the inflammation was known to reduce membrane fluidity.[11] This link led to a new area of research on the inflammatory agents that are prevalent in the nervous system, with a focus on IL-1 since it was known to be involved in inflammation in the brain. This linked to the work on free radicals in the brain that was being undertaken in the mid-1990s, since free radicals were known to be involved in inflammation responses (Winrow *et al.* 1993). Before planning the project the PI consulted a biochemist colleague for information. This was not a change of research direction for the PI, but a fork which added another, and complementary, route to understanding the molecular mechanisms of ageing and neuro-degeneration.

Interface A – Project specification and selection

Although the reviewers' comments on the application for this project are not available, the PI could remember that no changes were made to the grant based on the review by the HRB, which is likely since, according to the PI, this area of research was being performed only by groups outside Ireland and there were no researchers in Ireland who had sufficient expertise to make suggestions for improvement.

Stage 1 – Inputs to research

This was the PI's third grant from the HRB since returning from a research position in London in 1992. The grant was for around IR£30,000, with a concurrent student stipend of IR£7,500 per annum for the three years of the grant. The role of the HRB had begun before this grant was made, however, when the PI received on her return to Ireland the first summer student funding made by the HRB. This initial funding paid for laboratory start up and a student.[12] The PI noted that this study would not have been funded elsewhere, since there were no other research funders for this type of research in Ireland at the time. The scientific input came from the PI and the student on the project, with the primary drive coming from the PI herself.

A key input to the work of the PI from the mid-1990s was her interaction with an industry partner (industry partner 1)[13], who provided support to the PI in the form of free fatty

[10] Synaptic plasticity defines the ability of a synapse to change the way that it fires (often referred to as changing the strength of the synaptic connection), affecting the information that can be transferred or stored within the nervous system, for example the ability to retain memories.

[11] This information came from personal communication with the researcher who worked as a post-doctoral student with the PI.

[12] The funding in 1993 from the HRB was followed with a project grant that allowed the laboratory to increase in size.

[13] Further into the case study a second and different, industry partner is also referred to; therefore, this partner is referred to as "industry partner 1" and the other as "industry partner 2" to differentiate between them.

acids to research on and characterize. This resource allowed the PI to focus resources elsewhere and it established a strong relationship with industry partner 1.

Stage 2 – Research process

The PI modified other research teams' protocols for work on IL-1 and the biochemistry surrounding IL-1. Her team used additional techniques to identify the release of the neurotransmitter glutamate and developed a kit that would allow them to analyse the levels of glutamate release. They used this kit in subsequent studies on IL-1 in order to measure glutamate levels, but did not commercialize the product.

Stage 3 – Primary outputs from research

The primary outputs from the project can be broken down into two categories: knowledge production; and benefits to future research and research use. These are immediate outputs of the research project since they can be directly linked to the project itself.

Knowledge

Six papers that are directly related to the grant,[14] were published within the three years following the award (between 1997 and 1999) in journals that span clinical and basic research (such as *Brain Research*). These six papers were published during a particularly prolific publishing spell for the PI (31 publications in total between 1997 and 1999). The PI has published over 90 papers since starting this grant in 1996.[15] The papers from the grant have also had considerable impact since their publication; accruing over 280 citations up to 2007 (see Figure 4).[16] The key publication in terms of citation numbers is that in the *Journal of Neuroscience*, one of the top neuroscience journals.[17]

[14] These are publications that the PI identified as arising from the grant when applying for further research funding in 1999 (HRB 1999).

[15] Information based on a search for the PI's name and address details in the Web of Science. This is an estimate of the total number of publications during that time period, since some may not have had address details or may not have been included in the Web of Science database (ISI Web of Knowledge n.d.).

[16] It should be noted that this is not a formal bibliometric analysis, but uses citation figures obtained from Web of Science for specific publications. This is merely indicative of the quality of the research outputs and should not be considered a formal assessment of quality (ISI Web of Knowledge n.d.).

[17] Based on the journal impact factor assigned by ISI and when compared with other neuroscience journals, the *Journal of Neuroscience* is the 15th highest impact factor neuroscience journal of 200 in the field (ISI Web of Knowledge n.d.)

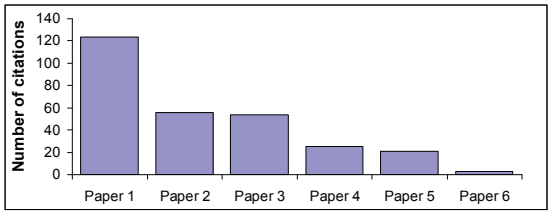


Figure 4. Citation numbers for publications arising for case study grant D (taken from the Web of Science)

Benefits to future research and research use

The PhD student was awarded a PhD during the grant. The PI herself added to the research portfolio, advancing into an area new to her that was intrinsically linked to her previous work on fatty acids. The PI is now a professor of neuroscience and is the director of a new institute of neuroscience in an Irish university, and this is partly attributable to this grant.

The work on IL-1 led to a number of subsequent grants from the HRB (£100,000 over the following four years)[18], European funding, ad hoc funding from EI with industrial partner 2, and further research funding for new students from the two industrial collaborators. Although figures are not available for the European funding obtained by the PI, her team's ability to bring in external funding represents an economic benefit for the country. By working with industry, the PI has also benefited future research in the private sector.

Interface B – Dissemination

The PI has presented the research results at academic meetings and conferences in the UK and in Ireland. These conferences included those based around clinical conditions, for example, Alzheimer's disease conferences. The PI also expects her PhD students to present their research results at a conference at the end of their first PhD year.

It was through discussions with colleagues in the university that the PI's industrial partnership 2 arose, since the CEO of this company knew a colleague of the PI, with whom they discussed work on inflammation and the brain. Industrial partnership 1 started at around the time of the grant and was through the CEO having personal academic knowledge of the PI. This type of informal networking has also provided a way of engaging the interest of clinical researchers in the study area.

Stage 4 – Secondary outputs

Through the work with the two industrial partners, a number of drugs are being developed in clinical trials. Industrial partner 2 has a work stream specifically dedicated to neuro-inflammation drugs and an international team of scientists, including the PI, working on the development and classification of their lead product to combat the effects of Alzheimer's disease. The PI has conducted pre-clinical work on this drug to investigate its ability to reduce inflammation across the blood–brain barrier and improve correlates of memory and learning functions.[19] This lead drug is now entering stage II trials. The

[18] This total represents the three grants funded between 1998 and 2000.

[19] Taken from the company website. This information is open source. However, since it names the PI and we wish to maintain a level of anonymity in the case study, the company and website have not been named.

industrial partner commented that the research findings and publications of the PI play a role in selling the drug to large pharmaceutical companies to gain investment funding, and in showing stakeholders that development is progressing, despite the time it takes to get a drug to market.

Industrial partner 1 has one drug product in development, based on the action of hippocampal IL-1β, the focus of the grant under study. This drug is for a syndrome called "age-associated memory impairment", a syndrome relating to memory changes associated with normal ageing. The PI identified the drug as an active compound that could have a role in improving memory and cognition for those with age-associated memory impairment, a role industrial partner 1 suggested has been critical in the drug's development. The drug is now entering stage IIa clinical trials.[20] A second drug being developed by industrial partner 1 (a long chain highly unsaturated fatty acid with applications in Huntington's Disease) has also received an input from the PI in preclinical research. The PI's work here centred on the mechanism of the action of the drug. This drug is now into final stage III clinical trials and has been the subject of meetings with the US Food and Drug Administration over submitting a new drug application. This new drug is the lead product of industrial partner 1.

Stage 5 – Adoption by practitioners and the public

Both the PI and the former researcher (now a lecturer and researcher in the nursing faculty at a top Irish university), have noted that medical researchers and clinicians have expressed great interest in how the PI's research will help with the clinical problems associated with impaired cognition and memory function, mechanisms of ageing and how diet can affect memory, as well as a general interest in using anti-inflammatories in a clinical setting. The researcher said that this feeds into the teaching in the new nursing degree. Despite the interest expressed in this work, there are no examples of it being fed into current clinical practice, mainly because the research involved here is basic neuroscience work.

The part of the PI's research that investigated the effect of diet on long-term potentiation has fed into a wealth of research on the role of different types of unsaturated fatty acids on health that is now public knowledge.[21] For example, the concept of fish as brain food is linked to the role that unsaturated fats such as omega-3 play in improving memory and cognition (Morris *et al.* 2003, which cites the PI's research).

Stage 6 – Final outcomes

This work has led to the development of drugs for clinical trials, as mentioned above, and has the potential to improve the health of those with neuro-degenerative diseases such as Alzheimer's and Huntington's disease. The IL-1β research has not started any company, but it does provide a lucrative research area for the two industry partners, who have around 14 staff based in Ireland between them (with an additional 140 or so outside the country).

---

[20] Taken from the company website. As with the other industry partner, this information is open source, but names the PI, therefore the company and its website have not been named.

[21] For example see http://healthcarecentre.blogspot.com/ (accessed 26 January 2008), which highlights, on a website aimed at the public, the role unsaturated fats can play in learning and memory.

This research is not solely responsible for their employment, but it does contribute to their presence in Ireland.

Industry partner 1 commented that their company had identified six centres of excellence around the world for the research they are involved in, one of which is the PI's laboratory in Ireland. This kind of enhancement of the international reputation for science in Ireland is exactly the goal of the latest science strategy for Ireland, which states that "Ireland by 2013 will be internationally renowned for the excellence of its research" (DETE, 2006).

In terms of economic impact, the PI can be linked to a very large economic impact (although this has happened outside Ireland) through her work on the characterization of industry partner 1's leading drug product, now at stage III clinical trials. At the time of their first involvement with the PI, the partner was a small Scottish firm based around this lead product. As a result of the successful trials and characterization of the lead drug, the Scottish firm was bought by a larger Canadian firm seeking to acquire the rights to the lead drug and the knowledge of those involved in developing it. This acquisition occurred in 2004, and constituted a net preliminary purchase price of $4.6m.[22]

2.5 Case study E: Seasonal variations of some salivary components within an individual

In general Irish dental health has been improving, along with that of western Europe, over the last 30 years or so. However, there remain certain groups, such as adolescents, for whom there are still high levels of tooth decay, dental caries (cavities) and other dental health problems. By investigating the salivary components of a group of adolescents in North Wales over a two-year study period, the PI hoped to identify any particular markers of who was most likely to be at risk of dental decay, regardless of the seasonal and biological changes that influence saliva production and chemical balance (Chicharro *et al*. 1998; Mandel 1974). The study aimed to quantify the seasonal variations in saliva and also to identify whether an average sample would be more effective in identifying an increased risk of dental decay in an individual.

This case study is built on information from interviews with the PI, a senior member of the Dental Health Foundation Ireland (DHF Ireland),[23] a member of the HSE with experience of regional health boards, and a senior member of the DoHC involved with dental health; literature from the HRB archives on the grant in question and subsequent grants of the PI; and additional open source literature related to the grant and its outputs and outcomes.

Stage 0 – Topic identification

At the time of this research, the PI was working on a number of research projects spanning the field of dental health research. This ran from surveys of dental health and dental health

[22] This figure comes from publicly available company accounts, but to maintain anonymity, the name of the companies and the drug in question are not identified.

[23] The DHF Ireland is a charitable trust that aim to create initiatives for oral health in Ireland and whose work is reviewed by the DoHC.

procedures for regional health boards through to EU-funded research on the fluoridation of water systems. Among these applied public health questions, the PI maintained an interest in the science that underpins dental health and informs public health work and future industry research. In this particular project, the PI was interested in understanding how to risk-stratify adolescents with respect to their likelihood of suffering dental disease, using saliva, already known as a marker of sensitivity to dental decay through calcium and phosphate levels and salivary flow rate, and its ability to overcome acid buffering. Furthermore, it is easy to collect saliva and less likely to transmit infections than blood.

Interface A – Project specification and selection

The HRB and the PI did not maintain records of the grant application for this study and so there is no record of the reviewer's comments on the study. What can be said is that in the early 1990s the HRB was not funding a large amount of research that was linked to public health, most of the funding being directed at more basic biomedical research, so the PI would have been competing for funding with more basic research.

Stage 1 – Inputs to research

The PI was unable to identify the exact amount that any specific project provided in terms of grant income at the time of this grant, but suggested that the most of the funding income at this time was from the EU, and the HRB funding provided only around one eighth of their resources. Although this was only a fraction of the funding needed, the HRB were the only group willing to fund basic, underpinning dental research, and the project would therefore not have taken place without it.

Since the PI was based at the premier dental research centre in Ireland at the time of this research, she had a large amount of research expertise to call upon in performing studies. In this work, the collaboration with the other senior researchers at the university and the co-researcher provided a very valuable intellectual input into the work. The other projects undertaken by the PI at the time also provided an input into this project by providing a different viewpoint on the basic research.

Stage 2 – Research process

In identifying the content and composition of the saliva samples, the PI and co-researcher employed no new techniques. However, the combination of techniques and using saliva as a tool of analysis did led to further research into developing an assay to detect whether children have brushed their teeth or not (to be discussed in more detail in the next section).

Stage 3 – Primary outputs from research

The primary outputs from the project can be broken down into two categories: knowledge production; and benefits to future research and research use. These are the immediate outputs of the research project since they can be directly linked to the project itself.

Knowledge

Although the funding produced interesting results that have gone on to create further work, the PI has found it difficult finding time to write up the project as a peer-reviewed journal article. However, the PhD student on the grant wrote up the findings in two

journal publications, both in the *Archives of Oral Biology* (Kavanagh and Svehla 1998; Kavanagh *et al.* 1998). The PI also used the findings from this research in her Medical Doctor of Public Health (MDPH) thesis.

Benefits to future research and research use

After the PI showed how to use the composition of saliva to investigate behaviour, the DHF Ireland became interested in finding a way of identifying whether children had been brushing their teeth or not. This research uses the levels of fluoride present in children's saliva. The DHF funded a pilot project which proved successful and which led to funding from the DoHC in Ireland and from the Northern Irish research directorate (in the Northern Irish Department of Health) to perform a cross-border study and compare regions with fluoridated and non-fluoridated drinking water.[24] This has led to a new HRB-funded project that is going to attempt to create a standardized and easy-to-use measure of whether or not children are brushing their teeth (HRB 2007c).

The PI noted that being given HRB funding in general is an essential part of research training in the institute, since it allows new researchers to get involved in dental research, as well as in the work being done in public health research around dental epidemiology and in HSR. The work from the original HRB research project has also fed into undergraduate courses taught by the PI. Since this research, the PI has gone on to become a director of the dental health research institute they work in. The PI considers the HRB funding for the more basic research an essential component in her research education and portfolio.

The PI's other research areas in dental epidemiology and health services research have led to additional resources for research, including major projects from the EU and a masters degree programme in dental health services designed for dental practitioners. The public health research portfolio of the PI was a factor in the HRB-funded "Mant report" on the future of primary care R&D in Ireland. This report highlighted the strengths in primary care research in Ireland and the ways to take it forward, and explicitly mentions the department run by the PI (Mant 2006).

Interface B – Dissemination

The research has fed into a chapter of the book "Saliva and oral health" (Whelton 1997), which is aimed principally at practitioners, although it has been suggested that the book can also be used by undergraduate and postgraduate dental students and by health professionals outside dentistry (*British Dental Journal* n.d.). The three different groups of policy-makers all suggested that the networks of the PI were crucial in getting research results across and informing policy and practice. The PI is well networked with other research groups, policy-makers and public health officials, as well as with dental practitioners.

[24] Ireland has fluoridated water in all areas, Northern Ireland does not. The study investigated the difference between children's behaviour in Dublin and Belfast (Dental Health Foundation 2006).

Stage 4 – Secondary outputs

The key secondary output of this project was the assay for identifying whether children have been brushing their teeth. This assay was demonstrated in the "Winning Smiles" research programme (Dental Health Foundation [DHF] 2006). Although it is not a direct health intervention, tracking whether children are brushing their teeth or not is seen by the PI and the DHF interviewee as having the potential to reduce dental disease in children so they have fewer oral complications and a better quality of life, together with a lower risk of dental complications later on,[25] particularly in the socio-economic groups in which children are at higher risk. The PI has started a small spin-off company to facilitate the development of the assay. She works with industry and has been funded by private companies, including Wrigley and Unilever, as well as collaborating with the UK-based Unilever dental research group and bringing international funding to Ireland.

One outcome of the saliva research is that the assay validates, rather than sets, policy goals. According to the DHF interviewee, the 1994 dental health action plan produced by the DoHC contained a clear statement promoting the use of fluoride toothpastes, and the production of an assay to test whether children brush their teeth helps to determine whether the Department are delivering on this intent.[26]

The PI's other work in public health and HSR has led to major changes. A senior figure in dentistry at the DoHC said that the PI was considered "the national researcher" in this area, and her epidemiological and HSR has provided the evidence base to underpin changes in the structure of dental services in Ireland. The PI has also contributed to a policy paper due to be published in mid-2008 (DoHC 2007).

Another related research area that the PI works in is running randomized clinical trials at the dental research institute. Between 2002 and 2004, for example, the PI managed six trials with over 800 participants (Oral Health Services Research Centre, 2004). The PI is also now involved in developing clinical guidelines for Ireland (HRB-funded project, 2007).

Stage 5 – Adoption by practitioners and the public

As the assay to determine whether children brush their teeth is still being developed, the grant under question cannot be considered as having been adopted in practice yet. However, the PI's work around water fluoridation has adopted by policy-makers in public health policy. According to the HSE interviewee, without the evidence base provided by the PI's work in fluoridation, the policy in this area would look very different. The PI is a member of the national fluoridation forum and has provided expert advice to WHO on fluoride levels.

The masters programme for dental practitioners has enabled individual practitioners who read for this degree to manage their provision of services better.

---

[25] This has an additional benefit of reducing the need for dental anaesthesia on children, who are considered a high risk group for anaesthetics, with approximately 50% of dental anaesthetic deaths being those under 16 years old. (Worthington *et al.* 1998).

[26] The DoHC has tried to improve the use of toothpaste by children through a number of routes, including national advertising campaigns (discussed in Friel *et al.* 2002).

Stage 6 – Final outcomes

From a small project that investigated the composition of saliva in adolescents, the potential for a widely used public assay to determine whether children brush their teeth seems to be a most welcome and positive outcome. The next stage for the assay is to develop it for wider national and international public use. The interviewee at the DHF notes that this assay would allow early intervention, saving money for the health service and targeting early treatment at those groups most at risk, providing a cost-effective solution to children's dental health problems and saving lives.

One outcome from the project grant as part of the total research output of the PI is the increased international reputation of the researcher.[27] Having a researcher involved in high profile international research enhances the international reputation of Ireland and addresses the requirement of the latest science strategy for Ireland, which states that "Ireland by 2013 will be internationally renowned for the excellence of its research" (DETE 2006, 8).

Water fluoridation has had a significant impact on public health in Ireland. This is demonstrated by the work by the PI comparing dental decay rates in Northern Ireland (where there is no fluoridation of water) and The Republic of Ireland . This found that the rates are 50% higher in the former than the latter, even though they were similar before fluoridation (Whelton *et al*. 2003). The interviewee at the DoHC observed that by providing evidence showing where the system can be more cost-effective using the PI's work in epidemiology and HSR, the DoHC has been in a stronger position to ask for funding from the Department of Finance, thus saving money in the health system.

The PI's other research has had significant effects, and as the HRB has had a role in funding projects in all these areas (fluoridation in Ireland, dental health services research and clinical guideline development), when assessing the impact of HRB funding, we should not ignore the impact of the PI's wider portfolio. In the words of the PI: "without the HRB funding, I would not have developed the expertise that allows me to do this research … HRB funding is essential for the genesis of new research ideas".

2.6 Case study F: The relationship between obstetric complications and adult psychiatric illness

Schizophrenia affects approximately one in every hundred people. In addition to the personal tragedy for individuals and their families, the economic consequences are vast. In his end-of-grant report, the PI stated that schizophrenia is many times less common than heart disease yet it is estimated to cost a country 50% as much – principally in relation to indirect costs. While it is well known that genetic factors make a contribution to this illness, environmental factors may also play a role. One such factor that has been implicated is obstetric complications. This study aimed to compare the rate of labour and delivery complications among individuals who developed schizophrenia with controls so as to establish whether any specific complication is associated with later schizophrenia.

[27] See Oral Health Services Research Centre (2004, 8–16 for a list of the international projects in which the PI is involved

This case study is built on information from interviews with the PI; a principal investigator at the HRB, who had previously worked on the project; a professor of neuroscience who collaborates with the PI; and a trainee psychiatrist who had worked on the project. Information was collected from the literature from the HRB archives on the grant in question and the subsequent grants of the PI as well as from additional open source literature related to the grant and its outputs and outcomes

Stage 0 – Topic identification

As a trainee psychiatrist, the PI became interested in mental health research because he was interested in what people perceived to be mental illness. He began work on his MD in the area of obstetric complications and schizophrenia and in 1992, motivated by Ireland's tradition of excellent obstetric record-keeping and the invaluable resource of the Dublin Psychiatric Case Register, he applied for funding from the HRB and received a three-year grant. This project aimed to determine whether obstetric complications occur to excess in individuals who go on to develop schizophrenia, compared with controls.

Interface A – Project specification and selection

The PI received advice from a number of researchers when applying for the grant application who were very knowledgeable about how the study should be conducted. Some ethical issues in relation to data handling arose, but these were quickly resolved and the PI made no changes to the project plan.

Stage 1 – Inputs to research

The PI had an existing track record with the HRB which worked to his advantage in receiving this award. He had gained substantial research experience in his collaborations with his mentor, and the knowledge and expertise he contributed to this study, were borne out of his MD and previous independent research projects. Researchers and practitioners in the field were available to share knowledge with the PI and his research assistant.

Stage 2 – Research process

The PI directed the project while a full-time student was employed on the research and received a masters degree as a result of it. Some of the PI's colleagues, who were not very familiar with this area, did not participate in the original grant application but they did contribute their expertise to the study and co-authored the resulting publication in 2000 (Byrne *et al*. 2000).

Stage 3 – Primary outputs from research

The primary outputs from the project can be broken down into two categories: knowledge production; and benefits to future research and research use. These are immediate outputs of the research project since they can be directly linked to the project itself.

Knowledge

While the overall results showed that the rate of complications for those who developed schizophrenia did not differ from that of controls, it was found that men who experienced onset before the age of 30 were subjected to more severe and a greater frequency of labour complications than the controls. This was the largest study of its kind in the world, and the data were utilized in a number of subsequent studies (Byrne *et al*. 2000). The Masters

student developed this dataset during her PhD studies in the 1990s and, according to her, it is still in use today. It was included in a large collaborative international study and the PI published subsequent papers in 1997 and 2004, using the same data.

Benefits to future research and research use

As a result of her research experience, the Masters student was able to build teams of researchers that had enabled her to establish collaborations with researchers abroad. She went to Denmark, where she worked as assistant director for the National Centre for Register-Based Research and has published a paper in *Schizophrenia Research* (Byrne *et al*. 2007), on the topic of obstetric complications. She is currently training to become a clinical psychologist.

The early research projects furnished the PI and his team with the tools to apply for further funding to the Stanley Research Foundation in the USA. By earning themselves credibility as a research team, with an advantageous track record, they were granted ten years of uninterrupted funding between 1994 and 2004. The PI has since received further grants, the total of which amount to approximately $1.8 million USD. This allowed them to expand their research agenda considerably. According to the PI, this would not have been granted had they not received the commitment from the HRB before this application. With the further funding from the Stanley Foundation, the PI, now a clinical psychiatrist, began research into the area of early intervention for a patient presenting with first-episode psychosis, as the illness became recognized as something akin to cancer or heart disease. People began to identify mental illness as something that could be treated effectively and it became a popular subject for research, according to the PI. Six researchers that worked with the PI on this topic received an MD during this period of funding from the USA.

Interface B – Dissemination

Obstetricians had a particular interest in the research and the PI addressed groups at the National Maternity Hospital, Dublin and the Institute of Psychiatry, London. He attended conferences at which he networked and instigated collaborations. He is a member of the European first episode schizophrenia network, which is an informal network of clinical scientists who are active researchers in first-episode psychosis and schizophrenia. This group aims to exchange information and encourage European collaborations.

Stage 4 – Secondary outputs

Although the first study did not lead to any secondary outputs, the PI's follow-up work did. The results from the PIs work on first-episode treatment was subsequently integrated into a research protocol specifying the provision of care for this group of patients. Ethical approval was not necessary as the work was a study of best practice. It was recommended that, as the protocol was so beneficial to the patient, that all patients should receive this level of assessment. It was then approved as a best practice intervention. The sample of patients was also epidemiologically representative, which added particular quality to the research, giving the PI a competitive advantage in this field.

The follow-on work has led to a pilot project on psychosis, called DETECT. This Early Intervention Service (EIS), was used as an example in a recommendation designed to inform government policy. It advises that a EIS pilot project should be undertaken with a population characterized by a different socio-demographic profile, with a view to

establishing the efficacy of EIS for the Irish mental health service. His work on the "Determinants of Quality of Life at first presentation with schizophrenia" (Browne *et al.* 2000) was cited by the report of the expert group for mental health policy (DoHC 2006).

Stage 5 – Adoption by practitioners and the public

The 1992 project attracted considerable interest by practitioners, but the concept is still very far from outcome and it has not had any significant impact on obstetric practices.

Stage 6 – Final outcomes

DETECT focuses on the early detection of established cases of psychosis and offers intensive, specialized interventions. Research evidence suggests that Early Intervention Services reduce the duration of untreated psychosis, the severity of symptoms, suicidal behaviour and the rate of relapse and subsequent hospitalization, and they are highly thought of by both those who use such services and their families (McGorry 2005). From a health economic perspective EIS involvement has been shown to be cost-effective (Mihalopolous *et al.* 1999). If this service was rolled out nationally, the continued investment in EIS would help to substantially reduce costs of treatment and would save lives. The potential economic benefits that may accrue to such an investment can be traced back to initial research funded by the HRB.

2.7 Case study G: Opportunistic MMR immunisation amongst Dublin Paediatric A&E attenders

In the early 1990s a large number of children regularly presented to A&E hospital departments in Dublin with preventable illnesses. There had been an outbreak of measles in Ireland at this time but it was apparent that very few children had been immunized against the disease. The PI decided to attempt to deliver a service to this vulnerable group. The objective of his study was to establish the need for opportunistic (measles, mumps and rubella) MMR immunization among children attending three Dublin paediatric hospitals and to examine the relationship between their immunization status and socio-economic background. The PI had hoped that an opportunistic MMR immunization policy in A&E departments would be set up that would contribute to increasing the overall figures for immunization. While opportunistic immunization has not been initiated in paediatric A&E departments in Ireland, the research experience contributed to the PIs career and enabled him to leverage further funding for subsequent, more fruitful research studies.

This case study is built on information from interviews with the PI; a general practitioner who has built on the work of the PI; the Masters student who worked on the project; and a research user referenced in the report of the cardiovascular health strategy group (Department of Health and Children 1999). Information was collected from the literature from the HRB archives on the grant in question and subsequent grants to the PI as well as from open source literature related to the grant and its outputs and outcomes.

Stage 0 – Topic identification

This PI was first lecturer in the general practice unit in UCD at the time of application to the HRB, and had just completed his general practice training. This was the first time he

had subjected himself to peer review. His research objectives were to establish the need for opportunistic MMR immunization among children attending Dublin A&E paediatric hospitals and to examine the relationship between their socio-economic background and immunization status. This was partly in response to WHO recommendations, in its expanded programme for immunization, that contact with the health services made for other reasons should be exploited for the purposes of immunization (WHO 1986).

Interface A – Project specification and selection

The grant was designed without any significant input from policy-makers, practitioners or reviewers, but the PI received some advice from more experienced colleagues around the time of application. The reviewers did not raise any concern nor did they ask for any changes to be made to the plans for the research project.

Stage 1 – Inputs to research

The PI collaborated with a number of others, including two GPs, his mentor in UCD who was a Professor in the Department of General Practice, and one other, who had a specific expertise in databases and also provided advice on the cross-sectional study design techniques that would be used for the study.

Stage 2 – Research process

During two months in the summer of 1991 data on 337 children were collected and compared with their parental history of MMR immunization data in the Eastern Health Board immunization records. MMR immunization had been given to 66% of the children, but 30% had no history of immunization and 4% did not know whether they had or had not been immunized. Analysis of small areas of households and multiple regression analysis showed little association between immunization uptake and the children's socio-economic background. While parents are now more knowledgeable and the quality of data collection has improved, opportunistic immunization has not been initiated in paediatric A&E departments (Murphy *et al*. 1994).

Stage 3 – Primary outputs from research

The primary outputs from the project can be broken down into two categories: knowledge production; and benefits to future research and research use. These are immediate outputs of the research project since they can be directly linked to the project itself.

Knowledge

One peer-reviewed journal paper that can be directly linked to this project was published in the *Irish Medical Journal,* a highly respected medical journal.

Benefits to future research and research use

While this study was funded for just one year, the PI continued his research in the area of A&E medicine and the knowledge and expertise he gained from this study facilitated his research in subsequent studies. However, by the mid-1990s, the PI decided to move to the management of chronic disease in the community, which is a more common clinical presentation in general practice.

The PI completed his MD and continued lecturing. His collaborations with his mentor in UCD led to a study on acute cardiac emergency care. In the late 1990s he was appointed Foundation Chair in the National University of Ireland, Galway, which was the first appointment in the University of general practice specialist. When funding became available, he decided to examine the provision of secondary cardiac prevention measures in a hospital clinic. One student was awarded a masters degree as a result of this research. The foundations were in place for a subsequent application to the HRB for a fellowship examining the provision of secondary cardiac preventive measures in general practices. The findings of the fellowship provided part of the basis for a subsequent HRB programme grant funding a randomized controlled trial based on the secondary prevention of heart disease in general practice. A PhD was awarded to the Fellow and the data produced was of such good quality that a GP subsequently received his MD from a separate study that used this data (Glynn *et al*. 2007). The outcomes from this research study led to an impact on clinical guidelines on chronic kidney disease management.

Interface B – Dissemination

The PI presented his results from the case study grant to paediatricians at a conference in Sligo and he was awarded a prize by the Irish Paediatric Association for best presentation. He did not have much knowledge about the translation of research findings at that time, nor did he understand very well the potential impact that such findings may have had on health policy at the earlier stage in his research career.

Stage 4 – Secondary outputs

There were no secondary outputs from the case study grant, but the follow-on research fellowship provided the first baseline data on the provision of secondary cardiac care in Irish general practice, showing that 3.2% of the population have established cardiovascular disease and can benefit from secondary prevention cardiac care (Byrne *et al.* 2002). The PI was able to demonstrate the need for care. The PI was Chair of the primary care subcommittee of the national cardiovascular advisory forum formed to develop and prioritize a cardiovascular health strategy and the Forum agreed that the secondary prevention of cardiac disease was a priority for primary care. He then chaired an implementation group which was charged with the task of agreeing the principles of secondary prevention implementation. The successful outcome to this process was an agreed national programme named Heartwatch.

Stage 5 – Adoption by practitioners and the public

The original work did not lead to adoption, but the subsequent work that led to Heartwatch is currently funded for 20% of the population and involves 480 general practices throughout Ireland. Unfortunately the programme has been taken up by only 20% of GPs. It was hoped that this would have been extended to 40% after the first three years, but the urgent need for extending the programme to the whole population has been recognized.

Stage 6 – Final outcomes

We are aware that the 1993 study did not produce significant outcomes that have altered practice or impacted upon policy. It is clear, however, that the funding received through his first grant influenced the PI's ability to leverage further funding which led in turn to

increased research capacity and has been a valuable input to his subsequent research. This also increased take up of research findings and influenced the targeting of further research.

While we know that 3.2% of the population can benefit from the outcomes, it is too early to tell if any significant health benefits arise directly out of the randomized clinical trial. However, the potential impact of the Heartwatch policy can already be seen. It is estimated that 81 deaths were prevented or postponed and 522 life years gained over the two years of the programme (National Heartwatch Programme 2006).

There have also been significant improvements in reducing the levels of the three main risk factors (smoking, cholesterol and blood pressure) since the initiation of the programme (National Heartwatch Programme 2006).

2.8 Case study H: Factors influencing delay to treatment for acute myocardial infarction in Ireland

The study examined the factors influencing delays in treating acute myocardial infarction (AMI) in Ireland. Early presentation of AMI means that thrombolysis can be delivered, enabling reduced morbidity and mortality. Benefits of thrombolysis outweigh risks up to 12 hours after the onset of symptoms. When the study was planned (early 1990s), deaths from AMI in Ireland were almost twice the EU average. Data from an international study on thrombolysis showed Irish patients experienced the longest delays to treatment of all 14 countries investigated. The researchers studied population-specific information on the natural history of AMI, including mortality rates and health service use.

This case study is based on desk research of the relevant HRB archival files, study grant publications and subsequent related projects, and semi-structured face-to-face and telephone interviews with the PI, two members of the research team and a consultant in public health medicine.

Stage 0: Topic identification

The research proposed for the study grant evolved from the second international study of infarct survival (ISIS-2) (Baigent *et al.* 1998) trial and the 1992 Irish Heart Foundation (IHF) one-week national census of patients admitted to coronary care units or combined coronary/intensive care units (I/CCU) for AMI in Ireland (O'Callaghan *et al.* 1995). Because Irish data from ISIS-2 indicated delays for AMI treatment, it was considered important to examine the factors associated with the presentation of AMI in Irish hospitals. This would provide an evidence base on how to improve the management of AMI (McGowan *et al.* 1991). Additionally, the 1992 IHF census suggested that time to treatment and thrombolysis uptake could still be improved (HRB 1996).

In the early 1990s the PI, a health psychologist, was working in a medical school researching cardiovascular diseases – primarily patient perceptions of illness and response to symptoms. Patient perceptions are one important component of time to treatment for symptoms. Funding for the study of psychological or social aspects of physical health problems was virtually non-existent in Ireland in the early 1990s. Partly to target funding priorities in a scarce funding environment, and partly because of the absence of basic 'epidemiology of behaviour ('help-seeking for cardiac symptoms') data, the PI focused this

study on the time to treatment. It was also considered that having a more detailed picture of the AMI services would help to direct future studies towards cardiac rehabilitation and perceptions of illness. The lead investigator for the Irish component of ISIS-2 was the cardiologist co-applicant PI for the study grant.

The aim of the study was to document the existing pattern of presentation for hospital I/CCU treatment by patients with AMI. The study involved an evaluation of the various components of time to treatment and included all the centres in Ireland who directly admitted patients with suspected AMI to I/CCU – the same 40 centres as those in the 1992 census (McGee *et al.* 1996).

Interface A: Project specification and selection

The limited availability of HRB archival material for the study makes it impossible to document the changes in the project design negotiated after the submission of the initial application. However, the general method of operation of HRB research sub-committees at that time was to accept research protocols without requirements for change or provision of external reviewer feedback. A high level of rejection was guaranteed by the very limited level of funding available. The application was assessed by the Cardiovascular Committee (as at that time the HRB Health Services Research Committee had not yet been established) .

Stage 1: Inputs to research

The HRB archives do not contain the funding details for this grant – it paid for a one-year junior researcher salary and limited administration (postage and travel) costs. There were no institutional overheads. The project was 'housed' in a general hospital. The PI believed with abysmal funding available for any research in Ireland at this time, no other Irish agency would have supported the study; effectively a health services research (HSR) study before such studies were viable in Ireland. For example, a subsequent study application to a salient agency to do a one year follow-up of these patients; asking for a salary for one junior researcher for a year-long national data-collection study, was met with a request for it to be halved. Also in the 1990s, eight regional health boards functioned relatively independently of each other and were interested in their research findings for their own area. Thus no single agency necessarily wanted to fund an overview of HSR data for Ireland. The HRB did fund the one-year follow-up study of this group of patients (n=900).

The co-applicant PI was a consultant cardiologist and head of the cardiac rehabilitation unit in a major Dublin hospital. This expertise was vital for the project and helped build the cardiac community's confidence in the study. Previous studies (ISIS 2 and the AMI census) provided baseline Irish data in a collegial manner in the cardiology community; while the primary PI's personal drive, determination and vision for the future of HSR in Ireland helped the study forward.

The PI believed the active involvement of healthcare staff in hospitals made the project a success. All centres participated – cardiologists and research nurses collected data –, their buy-in to the project was essential. Potential barriers were overcome through good communication. The PI expressed the opinion that the research work bridged the academic and clinical community, and the findings were useful for all participating individuals. Part of the success of the endeavour was the fact that it built on previous work

(ISIS-2 and the AMI one week census in 2002). The micro-culture was also one of an active European dimension – many in the Cardiology community were actively involved in the European Society of Cardiology which supported 'big picture' regional and national clinical and service delivery evaluation profiles through research.

Stage 2: Research process

Project researchers trained hospital staff to collect data, helping them understand the methods employed in HSR and made them aware of the delay to treatment problem. The later stage of the study involved setting up a database[28] and statistical analysis. While causation is difficult to speculate on, the PI observed that the case study findings were associated with changes in some of the ways in which doctors manage AMI patients, such as where thrombolysis is administered and how quickly patients receive the treatment. While there was a general view that patients contributed to delay, study findings showed a significant level of delay within the hospital system itself.

Stage 3: Primary outputs from research

Knowledge

The PI reported that the grant did not result in a large number of publications due mainly to the short duration of researcher contracts. The national report presented the collated results from all participating hospitals (McGee *et al.* 1996). One of the main findings was that time to treatment for AMI had been reduced substantially during the previous 10 years and the proportion of patients receiving thrombolysis had increased over the previous two years (1992–1994). However, the time to treatment was still longer than the international recommended target (cf. Pell in McGee *et al.* 1996). They also produced individual reports for each participating hospital which included hospital-specific data and analysis. The academic publications include a short report in the Irish Medical Journal (McGee *et al.* 1997) and an abstract in the British Heart Journal (McGee *et al.* 1995). As is typical with HSR findings, efforts to publish the study results in international medical journals were not successful since the national context made it mainly of interest to Ireland.

Benefits to future research and research use

The 1993 research grant was an important starting point for developing HSR in Ireland. Projects that followed on from the initial HRB study grant included: a survey of the early period of AMI recovery (200 patients); and a national study of clinical outcome, health service use and costs in the year following AMI admission (900 patients)(HRB funded). The 1994 census was also repeated nine years later to assess potential changes in time to treatment (in 2003)(Department of Health funded).

The results of the two studies on time to AMI treatment (1994 and 2003 assessments) were recently used by the DoHC to scope two future projects, one on improving care for AMI patients using Institute of Healthcare improvement methodology, and one on reducing in-patient AMI mortality by implementing and ensuring best practice in caring for AMI patients (Health Service Executive (HSE), 2007). These projects brought together

various organizations including the HSE National Hospitals' Office, HSE Population Health, Department of Health and Children, the Clinical Indemnity Scheme and Patient Representation. The time to treatment research findings were also used to plan and execute the Donegal Area Rapid Treatment Study (DARTS) which investigated pre-hospital thrombolysis administration by rural GPs in rural areas and highlighted the importance of GP's role in managing AMI (Donegal Area Rapid Treatment Study n.d.).

The PI and other study team members now teach medical students about psychosocial aspects of health and illness;, experience from cardiological investigation in Irish hospitals being useful in that regard. Teaching health psychology in Ireland has also been organised more formally as a consequence of the PI's work. In addition, HSR is now a standard part of health service management teaching on masters degrees in health services. Masters courses in health psychology have also been established at Irish universities.

The 1993 research grant was the PI's first and was a catalyst for all their further research funding. This research grant was only one year; not long enough to fully qualify PhD students, but a researcher later registered for a PhD and completed it under the PI's supervision. One of the junior researchers, after completing their PhD, was employed by a national health agency and is still working on time management in the hospital system. The other researcher is now a lecturer in research methodology/health psychology. The PI and health psychology colleagues in Europe arranged an Erasmus Programme in health psychology which three of the PI's junior researchers attended in the mid-1990s, when opportunities for overseas education and training were very limited.

Interface B: Dissemination

Each participating hospital received an individual report and a copy of the national report. According to the PI, a surprising finding for many was the time taken to receive treatment following arrival to hospital. In addition to these reports, researchers provided extra training for health workers in the hospital setting. The study team presented their research findings at the British Cardiac Conference and conferences and special sessions organized by the IHF. These meetings were reported on national television and in national newspapers. The PI also attended Irish Cardiac Society and European Society of Cardiology meetings.

Stage 4: Secondary outputs

With no specific cardiac strategy in Ireland, in the 1998 the newly established Health Service Research Centre (HSRC), of which the PI was nominated as director, started work on the cardiac health services strategy. The first cardiac strategy came with the publication of *Building healthier hearts* (*BHH*) (DoHC 1999). *BHH* has been used to make the case for additional funding to develop cardiology services in Ireland and to raise awareness of the need for further improvements in cardiac care. From the outset, the PI was seen to play an active part in the strategic discussions, while the research findings from the PI's work were used in the document itself. Some specific recommendations in the report linked directly to the PI's project evidence base include the case study on the delay to treatment for AMI. The report also included a number of recommendations on cardiac rehabilitation that can be attributed to the PI's subsequent work. Since *BHH* there have been two progress reports

on the implementation of the Cardiovascular Health Strategy, the first published in November 2001 and the second in March 2003 (DoHC 2001, 2003).

Stage 5: Adoption by practitioners and the public

The adoption of the research findings by practices and the public can be analysed by comparing results from the initial 1994 study and the follow-up studies from 2003 (same PI). The 2003 results have been published in a Coronary Care Unit (CCU) report (Doyle *et al.* 2004) and a number of peer-reviewed journal articles.[29] Findings showing changes since 1994 are shown in Box 4.

- The median door-to-needle time for thrombolysed patients had been reduced from 76 minutes in 1994 to 45 minutes in 2003 (a 41% reduction in 9 years).
- In 1994 96% of thrombolysis occurred in I/CCU with 2% in A&E. In 2003, 48% occurred in the Emergency Department and 48% in the I/CCU.
- No significant impact on hospital presentation time was seen from patients presenting with suspected AMI who had a previous history of AMI.
- Time from onset of symptoms to hospital arrival has not improved since 1994.

Box 4. CCU 2003 study, main findings (Doyle *et al.* 2004)

This reduced time to treatment was also observed in rural areas. The DARTS study showed that even patients living far from a hospital can receive treatment within the 90 minutes recommended in BHH (an average call-to-needle time of 62 minutes). The study also demonstrated that pre-hospital thrombolysis can be administered safely and effectively by rural GPs (DARTS n.d.). Doctors adopted the recommendations in their practice, so most positive changes resulted from the involvement of the medical community.

The researchers found that progress has been made since 1994 in terms of door-to-needle times for thrombolysed patients (Doyle *et al.* 2005). Yet only 35% of patients were thrombolysed within the 30-minute time frame recommended in the Cardiovascular Health Strategy. The findings from the 1994 research showed that the patients' delay in seeking medical help contributed to poor returns on treatment strategies. A public awareness campaign was launched with national advertising, but 2003 study findings showed public behaviour had not changed much.

Stage 6: Final outcomes

There are two main final outcomes; it affected the development of HSR in Ireland and resulted in a health gain. The PI established the biggest cardiovascular health services project in Ireland at a time when such projects were very scarce. The PI's work was key to placing more emphasis on HSR in Ireland. By conducting a national project, and achieving complete participation by all centres, the PI introduced the value of HSR and communicated it to a wider clinical community. The results of the research were taken up by the national 'heart' charity. The studies increased medical awareness of the importance of time to treatment for AMI. The PI and researchers observed that the time to treatment

[29] The journals include: *European Journal of Cardiovascular Prevention and Rehabilitation*, *Journal of Psychosomatic Research*, *BMC Health Services Research* and the *European Journal of Cardiovascular Nursing*.

project greatly influenced cardiac practice in Ireland and put more emphasis on secondary prevention by highlighting its importance. It was also an impetus for many small hospitals to organise their cardiac rehabilitation programmes. The project also raised the profile of health psychology and HSR in general. One researcher described the PI's role as "instrumental in developing health psychology as a subject in both Ireland and Europe".

Table 1. Outputs and outcomes from the eight case study grants and investigators

Payback category	Case study A (Programme grant)	Case study B (Programme grant)	Case study C (Project grant)	Case study D (Project grant)
Knowledge production	• Twenty-four articles published in basic and clinical peer-reviewed journals. • Better understanding of the role of eicosanoids, characterizing the way this new class of compounds acts.	• Twenty-seven peer-reviewed publications receiving an average of 36.4 citations per year since 1996.	• Two Peer-reviewed publications with an average citation rate of five per year. • Improved understanding of how IL-1 acts, indicating possible novel drug targets for rheumatoid arthritis.	• Six peer-reviewed publications in a variety of neuroscience and neurology journals. • Large number of citations to the publications.
Research targeting and capacity building	• New science facilities (infrastructure). • New university department. • Teaching pharmacology and medical students. • Career development for the PI and study team researchers (post-doctoral and PhD students). • Development of a scientific and technological workforce in Ireland. • Further research by the clinical and industry sectors.	• Two PhD degrees. • Successful on-going collaborations with researche involved and additional collaborators. • Further research funding, including from the HRB and the US Foundation, Fighting Blindness. • Leaders in Ireland in gene therapy for eye disease. • Development of techniques applied to subsequent research projects. • Development of viral delivery systems for exploitation in four areas of gene delivery. • Development of new mouse models.	• One PhD and post doctoral position in the same laboratory. • PIs career advancement, leveraging further funding. • Research training for laboratory group. • The techniques and approaches developed used in later studies. • Subsequent research discovered a variant to the MAL protein that predicts malaria, TB and other infectious diseases and made a significant contribution to the discovery of TLRs, leading to a paradigm shift in the field.	• PhD student trained on the grant. • Interaction with pharmaceutical company has led to funding for students in the PI's laboratory which continues today. • Work on preclinical research for industry has identified which compounds should be further investigated as being potentially useful for clinical development.
Informing policy and product development	• Assay development for prostaglandin metabolism. • Advisory role in clinical trials. • Drugs taken off the market. • Drug development. • Advisory role to pharmaceutical companies. • Clinical guideline development for cardiology.	• Development of therapeutics targeting primary disease mechanisms or secondary mechanisms of neuronal cell death are underway. This will be applicable to a broad sector of the patient population. • It is hoped that their research will reach phase 1 of clinical trials in 2010.	• Two lead drug products in development, both novel anti-inflammatory agents; target key inflammatory processes – specifically target TLRs. • It is hoped to commence phase 1 clinical trials in 2009.	• IL-1 work has fed into drug development, now into phase II trials. • Identified point of action of another drug for Huntington's disease, drug now into phase III trials.
Health and health sector benefits	• Understanding dosing regimens of aspirin and pre-sampling drugs used in arthritis, leading to lower side-effects of high dosage. • Decreased side effects due to COX-2 inhibitor drugs taken off the market.	• No direct health benefits arising out of this programme grant funding. • There are potential benefits that may lead to improved health of the sufferers of retinal degeneration and other degenerative diseases if the team are successful in providing a rationale for human therapeutic trials.	• No current health benefits arising directly out of the early research project. • Subsequent research has the potential to lead to health benefits for sufferers of TB, malaria, septic shock and rheumatoid arthritis, and may have the potential to save many lives globally.	• Work on neuro-inflammation has sparked interest in the medical community on neuro-degeneration and ageing, but has not yet led to specific benefits. • The PI's total research stream helps to explain why unsaturated fats in diet can be good for maintaining memory and learning abilities in old age.
Broad social and economic benefits	• Attracting and maintaining high-quality researchers in Ireland. • Three spin-off companies (employment and products). • Helping Ireland to achieve its current strong scientific reputation.	• A spin-off campus company was set up to facilitate the patenting process for IP. • Economic returns are evident on the level of sustained employment generated by the success of the laboratory and the increase of international research funds leveraged. • Potential health gains could contribute to a healthy workforce and improve quality of life.	• Subsequent research has led to the establishment of a drug development company which employs 19 people (14 researchers). • Spin-off company refinancing from US worth €5.25m. • Interaction reaffirms Wyeth's continued investment in the Irish biotechnology sector. • Subsequent research by the team has the potential to contribute to a healthy workforce and a reduction in days off work.	• Input into drug development for lead drug, which was the major reason behind the purchase of the drug company in 2004 (net preliminary purchase price of $4.6m). • Economic benefit of pulling in additional EU research funding. • Benefit of identifying Ireland as a centre of excellence.

Payback category	Case study E (Project grant)	Case study F (Project grant)	Case study G (Project grant)	Case study H (Project grant)
Knowledge production	• Two peer-reviewed journal articles. • MDPH thesis and book chapter used findings. • Research results were presented to academic and policy audiences.	• Three Peer reviewed publications, two in respected journals of psychiatry, receiving an average of 6 citations per year	• One peer-reviewed publication in a leading Irish medicine journal. • One award-winning presentation to the Irish Paediatric Society.	• National census report and 38 individual hospital reports. • Two publications in peer-reviewed journals.
Research targeting and capacity building	• Follow-on research project to develop saliva assay, funded by the DHF originally, then by DoHC and Northern Irish health research funders. • Research has fed into undergraduate courses taught by the PI. • Career progression of the PI is attributable to the full research portfolio. • HRB-funded research allows the generation of new ideas for public health and HSR work by the PI.	• Successful on-going collaborations. • Other researchers citing work from this project. • Ability to leverage grant funding from the Stanley Research Foundation and the HRB. • Research techniques applied to further grants that encouraged collaborations. • Subsequent research led to protocol being approved as a best practice intervention. • One masters degree and research experience facilitated career path in research.	• Successful ongoing collaboration and interdisciplinary contribution to PI's academic research. • Benefits to co-authors from publishing in peer-reviewed journal. • Improved track record leading to further grant funding. • Other researchers citing the work. • Development of databases. • Contribution to the PIs career path.	• Career development of PI in cardiology and HSR (professorship at RCSI, head of HSRC). • Postgraduate (PhD and master courses) research training on HRB projects. • Development of health services management and HSRC courses at RCSI. • Development of health psychology as a subject. • Erasmus programme in health psychology • Establishment of HSRC at RCSI.
Informing policy and product development	• Saliva assay for public health in development. • Works in association with Wrigley and Unilever based on saliva work. • Other research (including work funded later by the HRB) has had a big impact on policy; specifically fluoridation research informing fluoridation policies, epidemiology research underpinning policy changes for groups at risk and HSR, allowing the DoHC to make funding cost-effective.	• Difficult to attribute policy or product developments directly to this study • Subsequent research has led to a pilot service providing care for individuals experiencing first-episode psychosis and their families. • Recommendations have been made to policy-makers to extend this service.	• It is difficult to attribute any policy or product developments directly to this study. • The follow on research led to clinical guidelines in chronic kidney disease management. • Chaired the group that implemented the Heartwatch secondary prevention strategy.	• Helping DoHC to identify the scope for future AMI improvement programmes. • Planning and executing the community project on rapid thrombolysis in the Donegal region. • Work on the first cardiac health services strategy and BHH report, including recommendations on cardiovascular disease.
Health and health sector benefits	• Assay work yet to have an effect on health or the health sector, but if it is taken on as a public health tool it will prevent decay and reduce the cost of dental problems. • It may also reduce the risk of death due to dental anaesthesia for children. • Other research is leading to a more cost-effective dental health system and to reduction in dental decay through fluoridation. • Potential to increase health equity through targeted treatment for disadvantaged groups.	• Original project has not led to any significant health benefits, but has increased awareness of the usefulness of obstetric history in diagnosing schizophrenia. • Research into the relationship between obstetric complications and schizophrenia is far from outcome and had no significant impact on obstetric practices. • Too early to tell whether the pilot project has had significant health benefits but there are strong potential health benefits, e.g. shows how to reduce duration of untreated psychosis, severity of symptoms and suicidal behaviour.	• Without a direct link to this study, there is increased parental knowledge of importance of immunization. • A hundred per cent increase in numbers immunized in general practice (though this is not attributable to grant). • Follow-on research showed that 3.2% of population can benefit from secondary prevention cardiac care. • An estimated 81 deaths were prevented or postponed and 522 life years gained over the two years of the Heartwatch programme. • Reduction in the main risk factors for cardiovascular disease.	• Improvement in service delivery (time to AMI treatment in hospitals and by the GPs in rural areas). • Decrease in cardiovascular disease mortality in Ireland. • Change in the recovery from AMI due to faster thrombolysis resulting in the improved quality of life. • Health service research introduction as a discipline can lead to cost savings in health service.
Broad social and economic benefits	• The saliva assay work has been part funded by Northern Ireland, bringing in external research funding to Ireland. • Assay work will allow disadvantaged groups most at risk from dental complications to be targeted for intervention and reducing costs. • International reputation of the researcher.	• It is difficult to attribute socio-economic benefits to the original project. • Subsequent research has potential economic benefits as EIS have been shown to be cost-effective. • Brought in substantial external research funding from the Stanley Foundation.	• It is difficult to attribute any socio-economic benefits to the project. • Economic benefits to the workforce of reduced mortality and morbidity.	• Development of health services research and planning in Ireland. • Benefits to the workforce from decreased morbidity and mortality.

The second final outcome of the research is connected with the health gain in the Irish population. Of all the factors explaining the fall in coronary heart disease (CHD) mortality of 3,760 in Ireland in the period 1985 to 2000, AMI treatment contributed to a 5% improvement overall (Shelley, personal comm.) although not all of this can be attributed to the PI's study.[30]

2.9 Concluding comments

The studies in this chapter demonstrate the wide variety of impacts associated with HRB-funded research that spread across all of the categories of the payback framework. There are also some interesting lessons on the processes driving research impact: For example, in case study G, the PI came up with findings from the research that suggested that MMR immunization in A&E would be beneficial to the health of the Irish population, but this finding was not taken on board. The PI believed the reason for this was that those in general practice did not want to give up their role in immunization.

The following chapter reviews the impacts identified and considers their economic repercussions in more detail.

[30] This is based on the IMPACT model (Division of Public Health n.d.) which examines the health gains for cardiac disease by analysing particular factors that influence changes in coronary heart disease (CHD) mortality. The model estimates that half of the decrease in deaths rates can be attributed to changes in risk factors, and half to treatment and interventions (Shelley 2006).

CHAPTER 3 Case study findings and benefits to the Irish economy

The HRB has a broad mission to improve health and further a knowledge economy. Its impacts, identified in the previous chapter through the application of the payback framework, illustrate many aspects of this mission. This chapter focuses on the ways in which the work of the HRB supports and develops the Irish economy.

As noted earlier, the UK Evaluation Forum – convened by the Academy of Medical Sciences (AMS), MRC and the WT – produced a report that suggested four broad areas of economic returns (UK Evaluation Forum 2006). These areas are: evaluating direct cost savings to the health system; evaluating benefits to the economy from a healthy workforce; measuring the intrinsic value to society of the health gain; and evaluating the benefits to the economy of commercial development.

As we discussed, these four areas can be thought of as three different types of benefit. One of these types, benefits from improved health, can be considered either as the benefits of a healthier workforce or, more broadly, as the intrinsic value of health to society; cost savings; and the benefits from commercial development. Finally we noted a final grouping, that for when research attracts resources into the national economy providing a benefit to Ireland.

Having presented the findings of the case studies in narrative form in the previous chapter, we now show how the benefits can be organised according to the groupings set out above.

Where appropriate, we have included the monetary value of particular impacts, but these values come with two caveats. First, this analysis aims to show where HRB-funded research has an economic impact: it does not attempt to quantify the total value of the impact of HRB funding. Second, the values relate to the economic impact of an action (such as the sale of a company) and we do not try to attribute a percentage of that value to the HRB input into that impact. The figures mentioned illustrate the scale of some economic impacts that arise in connection with the HRB grants studied.

3.1 Benefits from improved health

The economic benefits from improved health are of key importance, and they can be examined in several ways. The two main ways of quantifying these benefits are to either examine the value of a healthier workforce, or to quantify the intrinsic value of health;

attempts to combine the approaches would amount to double counting of the same health gain, but the two approaches do raise different issues and so some analysis of both is presented here.

3.1.1 Benefits in terms of a healthier workforce

Reducing the main causes of days lost to the workforce is one way to benefit the economy. Although the identification of topics for research projects at the HRB in the mid-1990s did not explicitly attempt to do this, the presence of scientists with an interest in public health issues has meant that a number of key issues in this respect have been worked on. Since statistics are not readily available for Ireland, we refer to the two main causes of days lost at work in Northern Ireland, where public health problems are similar to the Republic, which are stress and musculoskeletal problems (Health Services Executive Northern Ireland 2004). Two of the basic research studies (case studies A and C) investigated the anti-inflammatory drugs that are used to treat arthritis, which, according to the Chairman of Arthritis Ireland, accounts for approximately €1.6 billion lost per year through days off work (irishhealth.com 2005). Case study B identified two novel anti-inflammatories that can help with arthritis and that are due to commence clinical trials, whilst case study A has led to a greater understanding of how to use COX-2 inhibiting drugs in arthritis, showing that low-dose regimens provide a more effective treatment.

Work in case study H showed the health improvements attainable by reducing the time to AMI treatment in hospitals and general practitioner (GP) surgeries. In an international study of cardiovascular disease, health economists showed that every year that a person has an acute coronary syndrome, the number of quality-of-life years lost (QALYs) by that person decreases by over 5%, with an indirect cost of nearly €10,000 per person per year (Lindgren *et al.* 2007). By reducing the time to treatment, the PI has had an effect on the effectiveness of treatment in Ireland, leading to better recovery from AMI and reducing these costs to the workforce.

Case study G led to follow-on research on the Heartwatch programme, a programme which helped to reduce morbidity by an estimated 522 life years over the two years it ran. The programme has also led to a reduction in the three main risk factors for cardiovascular disease (smoking, cholesterol and blood pressure) since its initiation (National Heartwatch Programme 2006).

There are also benefits from reducing mortality in maintaining a healthy workforce. The best example of this comes from case study F, where reducing the number of suicides through early intervention retains additional people in the workforce. Case studies G and H have reduced mortality in working-age people through their work on acute cardiac events. It is estimated that the follow-on research from case study G has led to saving or prolonging the lives of 81 individuals (National Heartwatch Programme 2006).

Looking ahead, the work of the PI in case study D investigates the neurobiology of ageing. As Ireland has an ageing population (OECD 2007), there is likely to be a need for the age of the working population to increase. With a better understanding of how to maintain good cognitive activity into old age, the Irish economy should benefit from a future grey workforce.

3.1.2 The benefits in terms of the intrinsic value of health

Since we know that evaluating health gain is notoriously difficult, here we present the health gains themselves that have been produced in connection with the HRB projects. As the mission statement of the HRB is to improve people's health through research, this output is the key to understanding the economic impact of HRB work and would warrant further study if the HRB wished to perform a full examination of the worth of HRB funding.

From those case studies in the applied health sciences (public health, HSR, primary care), there are already health gains that can be linked to the projects. Case study H on time-to-treatment for AMI in Ireland has been partly responsible for reduced mortality in Ireland, with a drop of nearly 4,000 cardiovascular disease deaths per annum in the country, of which around 5% can be attributed to treatment for AMI. Not all of this change can be attributed to this one project, but our research suggested that it was a factor in the process. Case study G led to follow-on research that has a significant health impact through the prevention of heart disease. Case studies E and F are on the way to providing health benefits. Case study E involves the production of an assay to test whether children brush their teeth, which, if rolled out, is expected by the Dental Health Foundation (DHF) to reduce dental disease in children, and also to reduce the need for dental surgery, which puts under-16-year-olds (who account for 50% of deaths due to dental anaesthetic complications Worthington *et al.*, 1998) at risk from anaesthetic complications. Case study F has the potential to lead to improved mental health through early intervention in psychosis, as showcased by the successful pilot work in practice.

The more basic case studies, as with changes to the health system, have further to travel along the research implementation pathway to lead to health gains. Some, however, are already there and the others are showing great promise. Case study A has already had a health benefit by identifying the effectiveness of the low-dosing regimen for arthritis. The work by the research team showed that a leading COX-2 inhibiting drug was not safe to use, and this played a key role in its removal from the drug market.[31]

Case study D has a number of products in development that could lead to improved treatments for Huntington's and Alzheimer's disease. Case study C also has resulted in the development of drugs that, if effective, could target TB, malaria, septic shock and rheumatoid arthritis, with a potential impact on global mortality every year. Case study B has a potential health impact for those with retinal degeneration.

3.2 Cost savings

By creating a more cost-effective health system the Irish government can more effectively allocate its resources. Several of the projects studied produced impacts that can be felt in

[31] This can be seen as an economic disadvantage in one sense, since the pharmaceutical company could lose that market to a competitor; but it can also be seen as a net benefit since the health complications associated with the drug lead not only to reduced health outcomes, but also to a tarnished reputation for the drug manufacturer. An example of this is the descent into insolvency of German pharmaceutical company TeGenero after their drug trial in the UK in 2006 left six people seriously ill (BBC News 2006).

the organization of the health system. Case study H is perhaps the most obvious example of this. It describes work done that formed the basis for organised HSR in Ireland and it was the starting point for founding the HSRC at the Royal College of Surgeons in Ireland (RCSI). Ireland's HSR allows identification of the areas of the health services where effectiveness and efficiency can be increased. The outcomes of the project itself also benefit the health system, since having a training regime for medical staff in hospitals ensures that the most effective procedures for acute myocardial infarction (AMI) are performed. By improving the time to treatment, the service delivered is more effective and takes less time than previously.

Two of the other case studies on more applied research have also led to impacts on the health system. The work on obstetrics and psychosis (case study F) has contributed to the PI gaining further funding in a related field and this, in turn, has led to a pilot service demonstrating how providing care for individuals experiencing first-episode psychosis leads to reduced psychosis symptoms and suicidal behaviour. This early intervention provides savings in terms of later treatment that is now not required. This was only a pilot study and the recommendations from this pilot, if adopted, may lead to savings for the system as a whole. The work on dentistry (case study E) has had direct effects through the development of an assay to test whether children brush their teeth. This is being finalized and will lead to reduced costs to the dental health system, targeting the care needed for groups at risk. This PI, who has a strong research stream in dental health in developing countries, has no intention of commercializing this assay, preferring it to be developed as a tool for public health that can be used anywhere. Linked work that also received HRB funding by this PI has looked directly at the inefficiencies of the dental health system in Ireland and this has led to more effective dental practices and an understanding of where to focus resources for the DoHC, as well as a training course for dental health practitioners in how to run their practices more efficiently.

It is more difficult to assess the impact of more basic biomedical research on the health system, since it takes longer for results to filter through to the health service and attributing the benefits to specific projects is harder, since changes in the health system are often the effect of many pieces of research. However, case study A on the role of eicosanoids in pain has had an effect on the health system itself, by characterizing the action of COX-2 inhibiting drugs and showing that low-dosage therapy was a more appropriate method for arthritis patients.

3.3 Benefits from commercial development

Several of these case studies have gone on to interact strongly with industry and commercialize their research findings. Case study D is a striking example, where the work done on Interleukin-1 (IL-1) has fed into the development of two drugs now in phase II clinical trials, while related research has fed into another drug that is now in phase III trials. This phase III drug was the lead product of a small Scottish company, which was then bought by a large Canadian company for $4.6m in 2004 on the strength of their lead

drug.[32] Case study C has also had a large economic impact but this time through refinancing of the spin-off company from the research, bringing in €5.25m from US financers.

Case study C has led to the development of two novel anti-inflammatories that specifically target TLRs, which are part of the inflammatory process rather than disease-specific targets. These anti-inflammatories are planned to go into phase I clinical trials in 2009. Case study C has led to a spin-off company that currently employs 19 people. Case study A has led to three spin-off companies that bring economic benefits through employment and the sale of their products (for example, one company provides bio-informatics solutions for automatic proteomics analysis to universities and industry). Case study B has a therapeutic product in development that it is hoped will enter phase I clinical trials in 2010, and has also led to a spin-off company that facilitates the patenting process for new therapeutics discovered by the study team.

HSR, public health and primary care research are less suited to the commercialization of results, but case study E provides an exception, perhaps because the research in this case study was more basic in nature: looking at properties of saliva in adolescents. This project has led to the assay on whether children brush their teeth already mentioned, which will not be commercialized, but which has fed into the work the PI is involved in with Wrigley and Unilever on the role of saliva in dental health. This is particularly relevant for Wrigley, who advertise the dental health benefits of chewing gum as increased saliva levels (Wrigley n.d.).

There are also likely to be further commercial benefits from the research as, although the benefits from current commercialization have been considered, the on-going linkages between PIs and industry have not been. Previous work has suggested that the networks of the PIs are key to promoting research findings (Wooding *et al.* 2004). Hence, the relationships that PIs for case studies A, D and E have with industry, where they all provide advice, information and research to companies, are likely to be an important facilitator of future economic impacts.

3.4 Benefits to the Irish economy

The ability to bring in additional funding is good for individual researchers, but does not represent an economic benefit for Ireland unless that research funding comes from outside the national economy. However a number of the researchers have attracted significant funding from international sources, including several of the case study researchers who have since been funded by the European Union (EU), the World Health Organization (WHO), Northern Irish research funders, and the Stanley Foundation in the USA, as well as by overseas pharmaceutical companies. There are also examples of funding from international projects (e.g., with Scandinavia on the Anglo-Scandinavian Cardiac Outcomes Trial's [ASCOT] study of cardiovascular disease drugs for case study A).

[32] This is based on the 2005 annual report for the company, which suggests that the company was purchased in order to acquire the licenses and patents for the lead drug.

Improving the reputation of Ireland as a location for research has the follow on benefit of attracting skilled researchers to Ireland. The DETE set a science strategy in 2006, in which it suggested that "Ireland by 2013 will be internationally renowned for the excellence of its research" (DETE 2006, 8). The PI and his team in case study A were described by a US collaborator as being partly responsible for the increased research capacity and reputation of Ireland. The PI for case study D is considered by one industrial partner to be so important that their laboratory in Dublin has been designated one of six worldwide centres of excellence for work on the neuroscience of ageing. The PI in case study E is one of a panel of experts for WHO on water fluoridation issues, and the PI in case study H has set up a Europe-wide Erasmus programme in health psychology to train young researchers across the EU. These examples show the importance of HRB funding in supporting excellent researchers who are building Ireland's international reputation.

Building and maintaining a highly skilled research workforce in Ireland is also important for building an international reputation. The PI in case study A commented that the HRB grant they received allowed them to get the best young researchers in Ireland and, perhaps more importantly, to keep them in Ireland, when they might otherwise have gone to the USA or the UK to pursue a research career. From case study H, it can be seen that establishing the HSRC also produces employment opportunities for a highly skilled workforce in Ireland. Building this scientific research workforce constitutes an immediate economic impact in terms of employment, but also builds capacity for future economic impacts and the R&D base that Ireland is striving to achieve.[33] Building research capacity in the workforce is not the only economic benefit that HRB funding has had on these grants, since it is also important that policy-makers can understand the science that should underpin health-related decision making. PhD students from a number of the case studies have gone on to work in important policy roles, including cross-border research initiatives and positions with regional health boards.

[33] Emphasized in the IDA mission statement: "We will win for Ireland, its people and its regions, the best in international innovation and investment so as to contribute to the continued transformation of Ireland to a world-leading society which is rich in creativity, learning and personal and social well-being" (IDA Ireland n.d.).

CHAPTER 4 Contextualizing the findings

Funding for health research does not occur in a vacuum, thus it is particularly important to consider the Irish context to understand factors that have affected the impact of HRB-funded research. First, and most pertinent, is the seismic change in the funding structures in place for health research since the late 1980s. From the late 1980s to the mid-1990s there were both limited numbers of funders for health research and a limited pot of money for projects. During this time the HRB was the biggest player in the field, with researchers having to pick up EU, WT or charity funding if they wanted to try and support their research elsewhere. This means a proportion of the cohort of researchers who are now the big players in Irish research, those who have helped to cement the growing reputation of Ireland as a centre of excellence in a number of research areas, are those who have managed to get through to this period because the HRB had enough funding to keep them in the country at a time when many top Irish researchers were lost to the USA or the UK. In addition, a proportion of researchers have returned from abroad, now that Ireland has the research capacity to support them. The PIs themselves interviewed for these case studies said that without the HRB support at that time, they would not be doing the research they are today. One case study grant even encouraged the PI back to Ireland; while other researchers started out on their Irish research career on HRB-funded projects.

Since the HRB has been key in setting the research base for health in Ireland, it can rightly claim a stake in the successes of those researchers who have gone on to make a major impact through their careers. For instance, the work of the PI in case study H is attributable to her expertise and high-quality research, but the case study funding was her first research funding, so the PI's research career started out because of HRB support. This is also an interesting example, since it was a researcher in HSR and health psychology who was trying to apply her knowledge to issues in cardiology, something that other funding agencies (such as the Irish Heart Foundation) were unwilling to support fully. That PI has gone on to have a huge impact on the way that HSR is accepted and used in Ireland, she has developed health psychology as an accepted discipline in the country and contributed to better treatments for heart attack – all of which started with the HRB's willingness to fund something a little different.

It is clear that the HRB has had a role in setting up the successes of Ireland's health research system, but what is its role in the new funding environment where there are larger funders with specific remits for commercializing research and producing economic

impacts?[34] The initial KIIs all remarked that the roles of SFI and the HRB are completely different and their mission statements reinforce this point (Box 5). SFI has a specific role in taking research and turning it to economic benefit, in a commercial way. This remit is not just in health research, but spreads across all science in Ireland. The HRB have a primary responsibility for improving health, with a role to contribute to the knowledge economy.

> **SFI vision statement:** Through strategic investments in the people, ideas and partnerships essential to outstanding research in strategic areas, SFI will help build in Ireland research of globally recognized excellence and nationally significant economic importance.
>
> **HRB mission statement:** To improve people's health through research and information, with a vision to enable a world-class health system in Ireland through excellence in research and to contribute actively to the knowledge economy.

Box 5. Mission statements of SFI and the HRB (SFI n.d.; HRB n.d.a)

As we have seen, the HRB can deliver on its mission to improve health and to contribute to the knowledge economy. The research they fund has a complementary role to that of other agencies such as SFI, and several PIs pointed out during this study that the HRB funding allows them to investigate things that its other funding streams would not.

When different sources of funding in Ireland came into play in the mid to late-1990s, HRB funding became a smaller part of the overall picture. However, this is not the whole story, since the major funding increases at that time were all complementary to the role of the HRB. The PRTLI funding provided, for the first time in Ireland, significant infrastructural funding for researchers in universities, thereby increasing the importance of research in tertiary education. This has provided greater opportunities for the capacity building of the research workforce, something that is seen to be one of the HRB's particular strengths. In the case study research, a number of researchers gained research degrees, while the new PhD scholars' programme has been hailed by researchers and those in university policy alike for its broad approach to improving PhD training.[35] SFI's introduction has provided additional funding for health researchers in Ireland, but this has not been at the expense of HRB funding for the same researchers. SFI funding for basic biomedical researchers has supplied a basis for further research on HRB-funded projects that can lead to health gains. There is thus a synergy between HRB funding and other research funding in Ireland, and the multidisciplinary nature of HRB-funded research (from HSR to basic research) is something that no other funder provides and, as such, serves to integrate health research and improve health in Ireland.

All these changes have affected the way that health research can have an impact on the economy, policy and health in Ireland. Now that the government has a greater understanding of the way that research can feed into health policy, they are more fully

[34] SFI has €1.4 billion to invest between 2007 and 2013; the HRB currently invests around €50m a year.

[35] This is based on interviews with researchers in the case studies and the KIIs with those involved in university policy-making.

engaged with researchers. This is an area in which the HRB is particularly strong, since the government funds HSR, public health and primary care research.

Increasing the emphasis on economic returns on basic research through the development of SFI and the IDA of Ireland has also facilitated the move of HRB-funded research towards commercialization. Ireland has a clear goal of moving towards a knowledge economy with a sound R&D basis, and in this environment industries are better able to utilize research findings. This also encourages R&D to become established in Ireland, where the health industry was previously mainly limited to manufacturing pharmaceutical products and medical devices, in the opinion of nearly all KIIs. It also has introduced new ways for companies and researchers to work together, such as using IDA funding to encourage companies to work with academics, and SFI funding to take early research findings forward. Case study A provides a good example of this, since the early HRB work led to the knowledge of proteomics and bioinformatics that later SFI and industry funding developed into a spin-off company.

The picture of health research in Ireland now looks very different from when these case studies started out in the early and mid-1990s. The HRB still has a considerable role to play in the development of health research towards economic benefits, particularly when taking into account the economic impacts that go beyond commercializing research findings. Although the impacts of research often take time to appear (from previous payback studies we estimate this to be at least 10–15 years), we have shown in these case studies that HRB-funded research has produced many outputs that are likely to continue to develop into health and economic benefits (e.g. the volume of initial drug development identified). The following chapter describes why there is a need to incorporate this kind of evaluation into HRB standard practices; who else is implementing this; and how the HRB can best use the payback methodology to both further inform its own funding decisions and illustrate the impacts that the research it funds has on the wider society.

CHAPTER 5 Implementing the Payback model

This study has shown the range of impacts that develop from HRB-funded research and illustrated how these impacts contribute not just to improved health but how they also affect the Irish economy. Alongside this we have confirmed that the payback framework is an effective framework for examining HRB-funded research, and that the impacts it identifies can be assessed through the lens of their effects on the economy. This chapter reviews what we have learnt about evaluating HRB-funded research and provides a number of recommendations on how the payback framework could be used most effectively in the future.

5.1 Why implement the payback model?

The HRB has already carried out a number of evaluations. It has identified three key reasons for evaluation (HRB n.d.):

1. to show accountability for the public funds spent on research,
2. to ascertain the efficacy and effectiveness of its funding policies and the variety of funded schemes it operates,
3. to assess the scientific, societal and economic impact of the HRB's investment in health research and ultimately its impact on people's health.

A fourth reason, which is to justify further research funding by identifying the impacts of research, can be added.

As mentioned, the HRB already has a strong programme in research evaluation, with the "Picture of Health" series providing a more detailed view of the specific research projects in its portfolio. The payback methodology adds to this evaluation strength by capturing multiple impacts, while providing a framework for comparing impacts from different funding. The UK Evaluation Forum report on ways to assess returns on health research funding concluded that the payback model has the advantage of encouraging "a more comprehensive and consistent approach to research evaluation" than previous techniques that focus on a single aspect of research impact (UK Evaluation Forum 2006, 31).

By implementing the payback framework in its research evaluation, the HRB can identify the multi-modal impacts arising from the research it funds and compare different funding mechanisms (for example, the Arthritis Research Campaign [ARC] study used the payback framework to compare project grants, programmes and fellowships (Wooding *et al.* 2004),

relate impacts to specific funding and understand how it has facilitated (or indeed, may better facilitate in the future) impacts arising from its grants.

5.2 Learning about outputs and outcomes

The case studies have provided insight into the outputs and outcomes that arise from HRB-funded research in Ireland. These have covered a wider spectrum than is often acknowledged for health research. By understanding the variety of outputs and outcomes for Irish health research, it is possible to go on and identify what might be expected in collecting information on further grants funded by the HRB. Table 2 shows what has so far been identified from HRB-funded research. Knowing the full range of these outputs and outcomes will allow the HRB to create appropriate indicators for monitoring the impacts of its funding grants.

Table 2. Outputs and outcomes in the payback categories from case studies

Payback category	Impacts from the case studies
Knowledge production	• Peer-reviewed articles and citations • Presentations • Research awards • Research reports
Research targeting and capacity building	• Further research funding • Career progression and research degrees obtained • Research used in teaching • Research conducted in industry or by other academic groups • Development of research techniques for use in further research • Development of training courses, research units or university departments
Informing policy and product development	• Assay, drug or device development • Drugs taken towards (or away from) the market (including clinical trials) • Advisory roles in industry • Advisory roles to government or policy-makers • Use of research in clinical guidelines • Use of research in policy papers and strategies
Health and health sector benefits	• Actual health benefits • Savings to the health system through gains in efficiency • Reducing inequalities in health care
Broader social and economic benefits	• Sale of pharmaceutical products or devices • Employment in spin-off companies and sales of products • Sale of companies • Reduction in days lost to ill health for the workforce • Attracting and maintaining a high-quality research workforce in Ireland • Bringing in non-Irish research funding • Improving the reputation of Ireland for health research

The HRB has recently commissioned a bibliometric analysis of health research performed in Ireland (HRB 2007b) that shows the country to be particularly strong internationally in research on:

- cardiac and cardiovascular systems
- dermatology

- gastroenterology
- immunology
- obstetrics and gynaecology
- clinical neurology
- peripheral vascular diseases
- rheumatology
- transplantation.

As a note of caution, while the direct outputs from research are relatively easy for researchers to identify, the long-term outcomes are more difficult, since they are further away from the research and are often fed by multiple research findings. Outcomes related to specific research funding must therefore be treated cautiously.

5.3 Learning about evaluation

Learning about the kinds of economic impacts that have occurred so as to learn what can occur is an important part of making sure that the payback framework is appropriate for use in the Irish health research context. We have shown that this framework is an appropriate way of collecting information on case studies of Irish health research and that the impacts arising from it can be transferred to the payback categories. In this project we have modified the final category of the model from "broader economic benefits" to "broader social and economic benefits". This was done to ensure that the category can capture all the benefits that can arise from health research that do not represent an economic benefit per se and are not adequately captured in the "health benefits" category. An example of this is the development of an assay for public health that will not be marketed but will be an open source resource to improve public health. The health benefit that arises from this is considered to be a health benefit, but the benefit of having it as an open source resource is a benefit to society itself.

As mentioned in section 5.2, the case studies have identified interesting outputs and outcomes linked to the HRB-funded projects. Some of these impacts are particularly relevant because of the Irish research context. For example, the ability to attract and maintain a highly skilled research workforce is specifically related to the brain drain that Ireland sustained in the 1980s and 1990s; while the ability to bring in external research funding is important in looking at Irish research, as the level of internal funding for research has traditionally been small. The concept of an improved reputation for Ireland is intrinsically linked to the Irish government strategy that "Ireland by 2013 will be internationally renowned for the excellence of its research, and will be to the forefront in generating and using new knowledge for economic and social progress, within an innovation driven culture" (DETE 2006, 8).

Having shown that the framework works for HRB-funded research, and that it can be applied in the Irish context, and capture the outputs and outcomes that relate specifically

to Ireland as well as more general impacts, we go on to investigate the ways in which the HRB could implement this framework for ongoing evaluation.

5.4 Possibilities for implementation

There are a number of ways in which the HRB could implement the use of the payback framework that are not mutually exclusive. The only limiting factor is likely to be the resources for doing so in the HRB. We present five options here that we recommend, since they perform different evaluative functions.

Building a bank of payback case studies

The case studies in this project show that a number of impacts from the case study grants have already occurred and a number are yet to occur, even in cases of research that occurred over 10–15 years ago. It would therefore be valuable to the HRB to understand how different impacts occur from the research over time, allowing it to track the development of health research towards both health and economic benefits. Not only does this provide information on individual case studies, but it also allows a better understanding of the stage reached by other pieces of research in developing a health and economic impact. This bank of case studies could use the cases from this project as a baseline, but would require additional cases of research that had been funded at different times. Another benefit of this approach is that having a bank of case studies of research started at different times will allow the HRB (and other research funders) to understand the role of the changing Irish health research system in facilitating different types of research outcome.

Using case studies to investigate specific evaluation questions

Rather than collecting information from case studies over time, payback studies can be used to compare the characteristics of specific grants. For example, it can be used to compare funding from fellowships, project grants and programme grants by creating a matrix of case studies that would allow the impacts of each type of funding to be compared. This approach was used in the work by RAND Europe and HERG for the ARC (Wooding *et al.* 2004). ARC is the fourth largest medical charity in the UK and spent over £18m on research in 2006 (ARC 2006). Other evaluation questions that can be addressed using the payback case study methodology include comparing funding in different research disciplines to understand whether some are better at producing specific impacts; or investigating the factors that lead to different types of impact through a more detailed analysis of the pathway to impact using the payback framework to underpin the analysis.

Incorporating the payback model into other evaluations

As previously mentioned, the HRB already has a strong group that evaluates a number of different aspects of its work. By incorporating the payback framework into the other streams of evaluation currently being undertaken at the HRB, it will be possible to create a dataset in which all evaluations can be compared. For example, collecting metrics and data along the lines of the payback categories will allow a particular scheme to be compared

with any other evaluation and will also lead to a wealth of data on the impacts of HRB-funded research that can feed into any meta-evaluation of HRB activities.

To incorporate the framework and categories into the other evaluations we recommend that data are collected using the framework; and that the impacts identified are then classified into the payback categories. Finally, the economic impacts could be examined using the approaches discussed in this report.

Full economic analysis of impact

In this study we have identified the economic benefits of HRB-funded research, as well as possible ways to measure those economic benefits. Should the HRB wish to perform a full economic study on the impacts of its research, then the data provided by the payback case studies will begin to provide the basis for this analysis. As set out in Chapter 3, when the focus is specifically on economic benefits there are several main areas that can be analysed. In order to measure the benefits of the improved health it would be necessary to take one of two approaches. Either calculate the value of the production no longer lost because of a reduction in mortality and morbidity, or identify the health gain resulting from research (probably in terms of QALYs) and decide on the intrinsic value of such health gain. To make an assessment of the cost savings it would be necessary to consider either the extent to which new interventions are less expensive than previous ones and how far they have been implemented, or how far some new interventions have reduced the need for other health care interventions. Assessing the value of the commercialization of the finding from research, includes collecting information on the value of commercialization of intellectual property, sales from products and the number and nature of spin-off companies, including their levels of employment. Finally the additional economic benefits tend to be related to the Irish context, since they evaluate the building up of a high-quality scientific research workforce (measured through the qualifications of the workforce and their bibliometric impact, for example), with an ability to bring in funding from outside Ireland, simply measured by the volume of external research funds.

Achieving a portfolio view of outputs and outcomes

RAND and the Health Economics Research Group (HERG) are currently developing a 'light touch' payback questionnaire. This work, supported by ARC, aims to provide an impression of ARC's impacts across its entire portfolio of research, by replacing the current end-of-grant reporting system. Although the questionnaire will not supply as much information as case studies, it can be applied to all grants, and as the results can be easily aggregated it will allow an analysis of the strengths and weaknesses of the research portfolio. It could also help to identify candidate research for case studies in order to investigate issues of interest. If the questionnaire was used at the end of the grant, and again at a later date (between 3–5 years), it is expected that the progress of research findings towards final outcomes (health benefits, commercialization, etc.) could be tracked. This work is currently still in the pilot phase, but it would be possible for the HRB to build on this using the case study information collected in this project to develop an HRB-specific questionnaire. This could provide a cost-effective method of generating and overview of HRB impacts as well as reducing the burden on researchers at the end of grants. Such a structured approach to end-of-grant evaluation is that it can help to identify

where to focus case studies to investigate issues of interest to the ARC (such as grants that have been successful at commercializing research).

For the HRB to implement such a questionnaire, it would be necessary to create a survey based on the case study information accrued in this project, since some outputs and outcomes identified here are specific to the HRB context. There would be additional work in creating and implementing this kind of questionnaire but it could prove cost-effective by reducing the burden on researchers at the end of their grant, easier analysis of end-of-grant reports (since they have already been coded) and a better focus for full evaluations. For example, this would allow the HRB to identify which grants it expects to have a high impacts in different categories and highlight the grants that would provide good stories for the "Picture of Health" series or would be appropriate for full case studies for other reports.

5.5 International developments

An evaluation framework allows an organization the opportunity to compare evaluations within the organization as well as to potentially make comparisons with other organizations that use the same framework. A number of different countries have used the payback framework in evaluating health research: the UK for the Health Technology Assessment Programme (Hanney *et al.* 2007); the Dutch public health research authority, ZonMW (Oortwijn *et al.* In press); the Health, Food and Welfare Bureau in Hong Kong (Kwan *et al.* 2007); Australian primary care research (Primary Health Care Research and Information Service 2006); and the Alberta Heritage Foundation for Medical Research (Buxton and Schneider n.d.).

Perhaps most importantly, in Canada the CIHR has implemented a version of the payback framework to assess its research portfolio in an ongoing evaluation. CIHR decided on the payback model based on a national project to understand the needs of their own researchers and policy-makers and on input from a number of international participants, including the WT, the Australian National Health and Medical Research Council and academics in the field of research evaluation. CIHR settled on the payback model with slightly modified payback categories, as is often the case when the payback framework is applied to different situations, in order to effectively capture the outputs in a context-specific fashion. CIHR is using this framework in a number of ways: through case studies of grants to show their impacts; by creating a set of indicators by which all grants can be assessed; through a long-term evaluation of funding systems; and by collaborating with partnering funders to evaluate funding arrangements.

The HRB is already involved in this global debate on research evaluation, partly through commissioning this report, but also through participating in the 2007 international meeting on valuing the economic benefits of health research held in Sweden and facilitated by the Swedish Research Council. By now placing themselves at the front of the debate by implementing the payback framework into their ongoing evaluation, the HRB could make an important contribution to trying to understand how their research funding goes on to have wide impacts, particularly health and economic ones.

REFERENCES

Reference list

Adderley, S. and D. J. Fitzgerald 1999. Oxidative damage of cardiomyocytes is limited by ERK1.2-mediated induction of cyclooxygenase-2. *Journal of Biological Chemistry* 274: 5038–48.

Advisory Council for Science, Technology and Innovation 2006. *Towards better health: achieving a step change in health research in Ireland.* Dublin: Advisory Science Council.

Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) 2006. Available online at http://www.ascotstudy.org/ Accessed 30 January 2008.

Arthritis Research Campaign 2006. Annual review 2005–2006. Available online at http://www.arc.org.uk/aboutarc/documents/AnnRev05–06.pdf Accessed 3 February 2008.

Baigent, C., R. Collins, P. Appleby *et al.* 1998. ISIS-2: 10 year survival among patients with suspected acute myocardial infarction in randomised comparison of intravenous streptokinase, oral aspirin, both, or neither. *British Medical Journal* 316: 1337–43.

BBC News 2006. Drug maker files for insolvency. BBC News website. Available online at http://news.bbc.co.uk/2/hi/health/5146692.stm Accessed 4 February 2008.

British Dental Journal n.d. *British Dental Journal publications: saliva and oral health*. Available online at http://www.nature.com/bdj/publications/saliva/index.html Accessed 29 January 2008.

Browne, S., M. Clarke, M. Gervin, J. Waddington *et al.* 2000. Determinants of quality life at first presentation with schizophrenia. *British Journal of Psychiatry* 176: 173–6.

Buxton, M. and S. Hanney. 1996. How can payback from health services research be assessed? *Journal of Health Service Research and Policy* 1: 35–43.

Buxton, M., S. Hanney and T. Jones 2004. Estimating the economic value to societies of the impact of health research: critical review. *Bulletin of the World Health Organization* 82 (10): 733–9.

Buxton, M.J. and W.L. Schneider. n.d.. Assessing the payback from AHFMR-funded research. Available online at http://www.ahfmr.ab.ca/analysis/docs/payback99/payback.php Accessed 3 February 2008.

Byrne, M. and A. Murphy 2002. Secondary prevention of heart disease: a baseline survey of patients' lifestyles and service provision in the North Western and Western Health Boards. Report Number 2 of Research and Development. Galway: Department of General Practice, NUI.

Byrne, M., E. Agerbo, B. Bennedsen *et al.* 2007. Obstetric conditions and risk of first admission with schizophrenia: a Danish national register based study. *Schizophrenia Research* 97 (1–3): 51–9.

Byrne, M., R. Browne, N. Mulryan *et al*. 2000. Labour and delivery complications and schizophrenia. *British Journal of Psychiatry* 176: 531–536.

Chandrasekharan, N.V., H. Dai, K.L.T. Roos *et al.* 2002. COX-3, a cyclooxygenase-1 variant inhibited by acetaminophen and other analgesic/antipyretic drugs: Cloning, structure, and expression. *Proceedings of the National Academy of Sciences of the United States of America* 99 (21): 13926–31.

Chicharro J.L., A. Lucía, M. Pérez *et al.* 1998. Saliva composition and exercise. *Sports Medicine* 26 (1): 17–27.

Comroe, J. and R. Dripps 1976. Scientific basis for the support of biomedical science. *Science* 192: 105–111.

Davy, G. 1996. *Bioscience research, development and industry: impact on health and economic growth in Wisconsin*. Madison/Milwaukee, WI: Wisconsin Association for Biomedical Research and Education. Available online at http://www.wabre.org/report_one/index.html Accessed 20 February 2008.

Dental Health Foundation 2006. *Winning smiles: schools oral health promotion programme for 7 to 8-year-olds.* Dental Health Foundation Ireland. Available at http://www.dentalhealth.ie/download/pdf/winning_smiles_report06.pdf Accessed 20 February 2008.

Department of Health and Children (DoHC) 1999. *Building healthier hearts. The report of the Cardiovascular Health Strategy Group.* Dublin: DoHC.

Department of Health and Children (DoHC) 2001a. *Making knowledge work for health.* Dublin: DoHC.

Department of Health and Children (DoHC) 2001b. *Quality and fairness – a health system for you.* Dublin: DoHC.

Department of Health and Children (DoHC) 2001c. *Implementation of the cardiovascular health strategy work program 2001–2004.* Advisory Forum on Cardiovascular Health Dublin: DoHC.

Department of Health and Children (DoHC) 2003. *Ireland's changing heart: second report on the implementation of the cardiovascular health strategy.* Dublin: DoHC.

Department of Health and Children (DoHC) 2006. *A vision for change*. Report of the Expert Group on Mental Health Policy. Dublin: DoHC.

Department of Health and Children (DoHC) 2007. Minister announces the development of a new national oral health policy. Available online at http://www.dohc.ie/press/releases/2007/20070925.html Accessed 4 February 2008.

DETE 2006. *Strategy for science technology and innovation, 2006–2013*. Dublin: Department for Enterprise, Trade and Employment Available online at http://www.entemp.ie/publications/science/2006/sciencestrategy.pdf -Accessed 26 January 2008.

Dionne, R. 2003. Relative efficacy of selective COX-2 inhibitors compared with over-the-counter ibuprofen. I*nternational Journal of Clinical Practice.* Supplement 135: 18–22.

Division of Public Health n.d. *IMPACT stroke model*. University of Liverpool. Available online at http://www.liv.ac.uk/PublicHealth/sc/bua/impact.html Accessed 10 January 2008.

Donegal Area Rapid Treatment Study (DARTS) n.d. *Final report,* Available online at http://www.nwhb.ie/files/boardreports/2003/October/DARTS%20Final%20Report.doc Accessed 30 January 2008.

Doyle, F., D. De La Harpe, H. McGee *et al.* 2004. CCU 2003 National survey of the presentation and management of acute myocardial infarction (AMI) and other acute coronary syndromes (ACS) in Irish hospitals. Dublin: DoHC.

Doyle, F., D. De La Harpe, H. McGee *et al.* 2005. Nine-year comparison of presentation and management of acute coronary syndromes in Ireland: a national cross-sectional survey. *BMC Cardiovascular Disorders* 5: 5.

Drummond, M, L. Davie and F. Ferris 1992. Assessing the costs and benefits of medical research: the diabetic retinopathy study. *Social Science and Medicine* 34 (9): 973–81.

Farrar, G.J., P. Kenna, S.A. Jordan *et al.* 1991. A three-base-pair deletion in the peripherin-RDS gene in one form of retinitis pigmentosa. *Nature* 354 (6353): 478–80.

Fitzgerald, K.A., E.M. Palsson-McDermott, A.G. Bowie *et al.* 2001. MAL (MyD88-adapter-like) is required for Toll-like receptor-4 signal transduction. *Nature* 413 (6851): 78–83.

Forfás and the Advisory Science Council 2006. *Towards better health – a step change in health research.* Report of the Advisory Science Council. Available online at http://www.sciencecouncil.ie/reports/acsti061123/forfas061123_acsti_health_research_full_report.pdf Accessed 20 February 2008.

Friel, S., A. Hope, C. Kelleher *et al.* 2002. Impact evaluation of an oral health intervention amongst primary school children in Ireland. *Health Promotion International* 17 (2): 119–126.

Funding First 2000. *Exceptional returns: the economic value of America's investment in medical research*. New York: Lasker Task Foundation. Available online at

http://www.laskerfoundation.org/reports/pdf/exceptional.pdf Accessed 20 February 2008.

Gadelha, C. 2000. *Vaccine research, development and production in Brazil. Lessons in research to action and policy.* Geneva: COHRED Working Group on Research to Action and Policy.

Glynn, L, D. Reddan, J. Newell *et al*. 2007. Chronic kidney disease and mortality and morbidity among patients with established cardiovascular disease: West of Ireland community-based cohort study. *Nephrology Dialysis Transplantation* 22 (9): 2586–94.

Hanney, S., M. Buxton, C. Green *et al.* 2007. An assessment of the impact of the NHS Health Technology Assessment Programme. *Health Technology Assessment* 11 (53) 1–200.

Hanney, S., M. A. Gonzalez-Block, M. J. Buxton *et al.* 2003. The utilisation of health research in policymaking: concepts, examples and methods of assessment. *Health Research Policy and Systems* 1 (2) Available online at http://www.health-policy-systems.com/content/1/1/2 Accessed 20 February 2008.

Hanney, S., J. Grant, S. Wooding *et al.* 2004. Proposed methods for reviewing the outcomes of research: the impact of funding by the UK's Arthritis Research Campaign, Health Research Policy and Systems, 2(4) Available online at http://hdl.handle.net/2438/675 Accessed 20 February 2008.

Hanney, S., B. Soper and M. Buxton 2003. Evaluation of the NHS R&D methods programme. HERG Research Report No. 29. Uxbridge: HERG/Brunel University.

Health Research Board (HRB) 1995a. Application for the HRB grant. Eicosanoids in vascular disease. Dublin: HRB archival material.

Health Research Board (HRB) 1995b. Research proposal evaluation form for the HRB grant. Eicosanoids in vascular disease. Dublin: HRB archival material.

Health Research Board (HRB) 1995c. Application for the HRB grant clinical outcome, health service use and costs in the year following admission to hospital for acute myocardial infarction: a national study of 950 cases. Dublin: HRB archival material.

Health Research Board (HRB) 1996. Presentation and management of acute myocardial infarction in Irish hospitals: a national census. Research summary for HRB. Dublin: HRB archival material.

Health Research Board (HRB) 1997. Report for the research unit for the period ending 31 Oct 1997. Dublin: HRB archival material.

Health Research Board (HRB) 1999. Analysis of the mechanism underlying the inhibitory effect of whole body irradiation on long-term potentiation: A role for IL-1. Project grant application. Dublin: HRB archival material.

Health Research Board (HRB) 2000. Application for the HRB grant regulation for cardiomyocyte cell death by eicosanoids: potential for limiting cardiac toxicity of chemotherapy. Dublin: HRB archival material.

Health Research Board (HRB) 2004. A picture of health. A selection of Irish health research 2004. Dublin: HRB.

Health Research Board (HRB) 2007a. HRB corporate strategy, 2007–2011. Dublin: Health Research Board.

Health Research Board (HRB) 2007b. A bibliometric study of Irish health research in an international context. Dublin: HRB.

Health Research Board (HRB) 2007c. The use of equilibrium salivary fluoride levels to measure compliance with advocated frequency of toothbrushing. Dublin: HRB.

Health Research Board (HRB) 2007d. Developing evidence-based clinical practice guidelines for the health board dental services in Ireland. HRB-funded project Available online at http://ohsrc.ucc.ie/html/about.html Accessed 20 February 2008.

Health Research Board (HRB) n.d.a. About HRB. Available online at www.hrb.ie/display_content.php?page_id=2 Accesssed 4 February 2008.

Health Research Board (HRB) n.d.b. Correspondence between PI and the HRB. Archival material.

Health Research Board (HRB) n.d.c. Review of HRB Eicosanoids in cardiovascular diseases Research Unit. Dublin: HRB archival material.

Health Research Board (HRB) n.d.d. Evaluation at the HRB. Available online at http://www.hrb.ie/display_content.php?page_id=204 Accessed 3 February 2008.

Health Services Executive 2007. Acute myocardial infarction/Institute of Healthcare improvement. Available online at www.ich.ie/projects_all.htm Accessed 6 February 2008.

Health Services Executive Northern Ireland 2004. 1,000 workers are absent from work every day due to work-related ill health News release Available online at http://tinyurl.com/37tbxp Accessed 2 February 2008.

HM Treasury 2003. *The green book: appraisal and evaluation in central government*. London: Stationery Office.

IDA Ireland n.d. Homepage. Available online at http://www.idaireland.com/home/index.aspx?id=8 Accessed 2nd February 2008.

IrishHealth.com 2005. Arthritis in Ireland – the painful truth. Available online at http://www.irishhealth.com/index.html?level=4&id=7666 Accessed 2 February 2008.

ISI Web of Knowledge n.d. ISI Journal Citation Reports, ranking of neuroscience journals. Available online with subscription at http://portal.isiknowledge.com/portal.cgi. Accessed 2 February 2008.

Jacob, R. and M. McGregor 1997. Assessing the impact of health technology assessment. *International Journal of Technology Assessment in Health Care* 13 (1): 68–80.

Johnston, S. C., J. D. Rootenberg, S. Katrak *et al.* 2006. Effects of a US National Institute of Health programme of clinical trials on public health and costs. *Lancet* 367: 1319–27.

Joint Economic Committee, US Senate 2000. *The benefits of medical research and the role of the NIH.* Available online at http://hsc.utoledo.edu/research/nih_research_benefits.pdf Accessed 20 February 2008.

Kavanagh, D. A. and G. Svehla 1998. Variation of salivary calcium, phosphate and buffering capacity in adolescents. *Archives of Oral Biology* 43 (12): 1023–7.

Kavanagh, D. A., D. M. O'Mullane *et al.* 1998. Variation of salivary flow rate in adolescents. *Archives of Oral Biology* 43 (5): 347–52.

Kettler, H. and R. Modi 2001. Building local research capacity for the prevention and cure of neglected diseases: the case of India. *Bulletin of the World Health Organization* 79 (8): 742.

Khor, C., S. O. Chapman, F. Vannberg *et al.* 2007. A MAL functional variant is associated with protection against invasive pneumococcal disease, bacteremia, malaria and tuberculosis. *Nature Genetics* 39: 523–8.

Kwan, P., J. Johnston, A.Y.K. Fung *et al.* 2007. A systematic evaluation of payback of publicly funded health and health services research in Hong Kong. *BMC Health Services Research*. 7: 121.

Lewison, G. and G. Dawson. 1998. The effect of funding on the outputs of biomedical research. *Scientometrics* 41: 17–27.

Lindgren, P., T. Kahan, N. Poulter *et al*. 2007. Utility loss and indirect costs following cardiovascular events in hypertensive patients: the ASCOT health economic sub-study. *European Journal of Health Economics* 8: 25–30.

MacGowan, G. A., D. O'Callaghan and J. H. Horgan 1991. Medical management of acute myocardial infarction in Ireland: information from the second international study of infarct survival (ISIS-2). *Irish Journal of Medical Science* 160: 347–9.

Mandel, I. 1974. Relation of saliva and plaque to caries. *Journal of Dental Research* 53 (2): 245–66.

Manning, D., K. Sheehan, M. Byrne *et al.* 2007. Cyclooxygenase-2 expression in chronic hepatitis C and the effect of interferon α treatment. *Journal of Gastroenterology and Hepatology* 22 (10): 1633–37.

Mant, D. 2006. *Primary care R&D in Ireland*. Dublin: HRB.

Matthews, J. and L. A. J. O'Neill 1999. Distinct roles for p42/p44 and p38 mitogen-activated protein kinases in the induction of IL-2 by IL-1. *Cytokine* 11: 643–55.

McGee, H. M., C. Browne, J. H. Horgan and the Council on Acute Coronary Care of the Irish Heart Foundation 1996. Presentation and management of acute myocardial infarction in Irish hospitals: a national census. Dublin: Council on Acute Coronary Care of the Irish Heart Foundation.

McGee, H. M., C. Browne, J. H. Horgan *et al.* 1995. Presentation and management of acute myocardial infarction in Irish hospitals: a national census. *British Heart Journal* 73 Supplement 3: 50.

McGee, H. M., O'Callaghan, D., MacGowan, G. A., Horgan, H. J. and the Irish ISIS-2 Collaborators. 1994. Factors associated with delay to treatment for acute myocardial infarction in Ireland. Irish Medical Journal 87 (6): 187.

McGee, H. M., F. Doyle, R. M. Conroy *et al.* 2006. Impact of briefly-assessed depression on secondary prevention outcomes after acute coronary syndrome: a one-year longitudinal survey. *BMC Health Services Research* 6: 9. Available online at http://www.biomedcentral.com/content/pdf/1472–6963–6-9.pdf Accessed 4 February 2008.

McGorry, P. 2005. Early intervention in psychotic disorders: beyond debate to solving problems. *British Journal of Psychiatry* 187 (48): 108–10.

McKeown, T. 1979. *The role of medicine*. Oxford: Basil Blackwell.

McWilliam, P., G. J. Farrar, P. Kenna *et al.* 1989. Autosomal dominant retinitis pigmentosa (ADRP): localization of an ADRP gene to the long arm of chromosome 3. *Genomics* 5 (3): 619–22.

Merck n.d. VIOXX (refecoxib) Information Center. Available online at http://www.merck.com/newsroom/vioxx/ Accessed 30 January 2008.

Mihalopolous, C., P. D. McGorry and R. C. Carter 1999. Is phase-specific, community-oriented treatment of early psychosis an economically viable method of improving outcome? *Acta Psychiatrica Scandinavica* 100 (1): 47–55.

Millington-Ward, S., B. O'Neill, G. Tuohy *et al.* 1997. Strategems in vitro for gene therapies directed to dominant mutations. *Human Molecular Genetics* 6 (9): 1415–26.

Moncayo, A. 2003. Chagas disease: current epidemiological trends in the Southern Cone countries. *Memorias do Instituto Oswaldo Cruz* 98: 577–91.

Morris, M. C., D. A. Evans, J. L. Bienias *et al.* 2003. Consumption of fish and n-3 fatty acids and risk of incident Alzheimer disease. *Archives of Neurology*, 60: 940–46.

Murphy, A. W., R. Power, D. M. Kinlen *et al.* 1994. MMR immunisation status among Dublin paediatric A&E attenders. *Irish Medical Journal* 87 (2): 40–2.

Murphy, K. and R. Topel, eds, 2003. *Measuring the gains from medical research. An economic approach.* Chicago, IL: University of Chicago Press.

Murray, C. A. and M. A. Lynch 1998. Evidence that increased hippocampal expression of the cytokine interleukin-1b is a common trigger for age and stress-induced impairments in long-term potentiation. *Journal of Neuroscience* 18 (8): 1974–2981.

Mushkin, S. 1979. *Biomedical research: costs and benefits.* Cambridge, MA: Ballinger.

National Heartwatch Programme 2006. Heartwatch clinical report of the national programme in general practice for the secondary prevention of cardiovascular disease in Ireland.

National Institutes of Health 1993. *Cost savings resulting from NIH research support*. 2nd edn. Bethesda, MD: US Dept. of Health and Human Services, NIH.

O'Callaghan, P. A., D. M. Comerford, I. M. Graham *et al.* 1995. National perspective of acute coronary care in the Republic of Ireland. *British Heart Journal* 73: 576–80.

OECD 2004. *OECD Review of higher education in Ireland, 2004*. Available online at http://www.hea.ie/uploads/pdf/OECD%20Review%20of%20Highe%20Education%202004.pdf Accessed 20 February 2008.

OECD 2007. OECD country statistical profile 2007: Ireland Available online at http://stats.oecd.org/wbos/viewhtml.aspx?queryname=319&querytype=view&lang=en Accessed 2 February 2008.

Oortwijn, W. J., S. Hanney, A. Ligtvoet, (In Press). Assessing the impact of Health Technology Assessment in the Netherlands. *International Journal of Technology Assessment in Health Care.*

Oral Health Services Research Centre 2004. *Report on activities: October 2002–September 2004.* Cork: University Dental School and Hospital.

Palsson, E., M. Popoff, M. Thelestam *et al.* 2000. Divergent roles for Ras and Rap in the activation of p38 MAPK by interleukin-1. *Journal of Biological Chemistry* 275: 7818–25.

Pang, T., R. Sadana, S. Hanney *et al.* 2003. Knowledge for better health — a conceptual framework and foundation for health research systems. *Bulletin of the World Health Organization* 81 (11) Available online at htttp://www.who.int/rpc/meetings/HRSAManuscript2003.pdf Accessed 20 February 2008.

Primary Health Care Research and Information Service 2006. Primary health care research impact assessment. Available online at http://www.phcris.org.au/activities/rip/index.php Accessed 3 February 2008.

Raiten, D. and S. Berman 1993. *Can the impact of basic biomedical research be measured? A case study approach*. Bethesda, ML: Life Sciences Research Office, FASEB.

Rosenberg, L. 2002. Exceptional economic returns on investments in medical research. *Medical Journal of Australia* 177: 368–37.

Royal Netherlands Academy of Arts and Sciences 2002. T*he societal impact of applied research towards a quality assessment system*. Amsterdam: Royal Netherlands Academy of Arts and Sciences.

Salter, A. and B. Martin 2001. The economic benefits of publicly funded basic research: a critical review. *Research Policy* 30: 509–32.

Science Foundation Ireland (SFI) n.d. About SFI. Available online at www.sfi.ie/content/content.asp?section_id=314&language_id=1 Accessed 4 February 2008.

Shelley, E. 2006. The changing pattern of cardiovascular disease in Ireland: achievements and challenges. HeartWise, Winter. Available online at http://www.heartwise.ie/heartwise/pdfs/HEARTWISE%20WIN.pdf Accessed 9 January 2008.

UK Evaluation Forum 2006. *Medical research: assessing the benefits to society*. Supported by the Academy of Medical Sciences, Medical Research Council and Wellcome Trust Available online at http://www.acmedsci.ac.uk/index.php?pid=48&prid=1 Accessed 20 February 2008.

Verhorn, C., J. Landerfeld and D. Wagner 1982. Measuring the contribution of biomedical research to the production of health. *Research Policy* 11: 3–13.

Warry, P. 2006. *Increasing the economic impact of research councils.* Research Council Economic Impact Group. (Warry Report). London: Department of Trade and Industry.

Wellcome Trust 2000. *Evaluation of the matching funds agreement.* London: Wellcome Trust

Whelton, H. P. 1997. Anatomy and physiology of the salivary glands, Ch 1. in Edgar, M. and D. M. O'Mullane, *Saliva and oral health*. 2nd edn. London: BDJ Press.

Whelton, H., E. Crowley, D. O'Mullane *et al*. 2003. *North–south survey of children's oral health 2002*. Cork: Oral Health Services Research Centre, University College Cork.

Williams, B., N. R. Poulter, M. J. Brown *et al.* 2004. The BHS guidelines working party guidelines for management of hypertension: report of the fourth working party of the British Hypertension Society. BHS IV. *Journal of Human Hypertension* 18: 139–85. Available online at http://www.bhsoc.org/Latest_BHS_management_Guidelines.stm Accessed 30 January 2008.

Winrow, V. R., P. G. Winyard, C. J. Morris, and D. R. Blake 1993. Free radicals in inflammation: second messengers and mediators of tissue destruction. *British Medical Bulletin* 49, 506–22.

Wooding, S., S. Hanney, M. Buxton and J. Grant 2004. *The returns from arthritis research. Vol. 1: approach, analysis and recommendations.* RAND Europe, Available online at http://www.rand.org/pubs/monographs/2004/RAND_MG251.pdf Accessed 20 February 2008.

Wooding, S., S. Hanney, M. Buxton and J. Grant 2005. Payback arising from research funding: evaluation of the Arthritis Research Campaign. *Rheumatology* 44: 1145–56.

World Health Organization: expanded Programme of Immunisation, Immunisation Policy. Geneva: WHO, 1986.

Worthington, L. M., P. J. Flynn and L. Strunin 1998. Death in the dental chair: an avoidable catastrophe? *British Journal of Anaesthesia* 80 (2): 131–2.

Wrigley n.d. Chewing gum helps improve oral health. Available online at http:// www.gumisgood.com/oral_health.html Accessed 2 February 2008.

Yin, R. 2003. *Case study research: design and methods*. 3rd edn. London: Sage.

APPENDICES

Appendix A: Methods used

As with previous payback studies, this project used a variety of research methods to triangulate research and strengthen findings. The initial part of the project aimed to generate an understanding of the context in which health research has progressed in Ireland and how this context has changed. This used a combination of KIIs and a context paper produced by the HRB . The second part of the project involved selecting case studies from HRB-funded projects. The final part was mainly made up of the case study research itself, together with an academic literature review of the methods for assessing economic benefits that can accrue from health research. The sections below describe these methodological steps in more detail.

Key informant interviews

With the help of the HRB we identified a range of stakeholders to consult over the methodology to be used in the study, to provide us with an understanding of the state of the Irish health research system over the last 15–20 years and today and to help identify high impact researchers and research areas to feed into the case study selection matrix. We identified eight key informants to interview across the range of stakeholders in the health research system of Ireland (Box 6). The interviews were recorded and the notes transcribed.

Ruth Barrington	Outgoing Chair of the HRB
Martin Shanagher	DETE
Tom Mooney	DoHC
Dermot Kelleher	Head of TCD Medical School
Tim O'Brien	Researcher and former HRB board member
Muiris Fitzgerald	Former HRB Chair; now at HSE
Leo Bishop	IDA of Ireland
Conor O'Caroll	Irish Universities Association

Box 6. Key informant interviewees

The outcome of these interviews complemented the perusal of HRB policy and strategy, providing a full contextual background in which to place the case studies; informed the selection matrix of the case study and aided the identification of what should be considered an economic output from Irish health research in the view of different stakeholders in the system.

HRB context review

In order to place the case study research in the fast changing context of Irish health research, we utilized the expertise of the HRB by asking it to provide a paper that surveyed this context. This paper covers the way that the health research context in Ireland has changed over the last 20 years or so, including funding body changes, policy decisions and the evolution of the HRB funding portfolio. It is built on the tacit knowledge of senior staff at the HRB and a number of key policy documents from government and key research funders. In combination with the findings from the KIIs, it forms the context section of the introduction to this report.

Case study selection

Selecting a suitable set of case studies was critical to the robustness and validity of this evaluation and was important for producing a quality research product. Since the payback on health research is not instantaneous, we needed to identify research grants that would have had adequate time for the research results to feed through to any wider impact. From previous studies we have estimated this time-lag to be between 10 and 15 years for health research. As we wished to identify case studies that would provide useful information on the activities of HRB-funded researchers, we purposively selected those researchers who had a high impact (Yin 2003), using a selection framework that took into account various proxies for research impact (Box 7). They also were split between basic/early clinical research (B/EC) and health services/public health/primary care research (HS/PH/PCR), as defined by the information about the HRB grants.

- Recommendations from KIIs
- Unit/programme funding
- Volume funding (IR£ and €)
- Number of HRB grants
- Additional SFI funding

Box 7. Proxies for research impact used in selecting case studies

Four studies were chosen in each area (B/EC or HSR/PH/PCR), and were selected to include researchers who had been funded recently, a breadth of research locations (not just in Dublin) and researchers of both genders.

The selection was performed at a meeting attended by the research team and representatives of the HRB in order to maximize knowledge about specific researchers and their respective fields of research, since the title of the grants was the only information held on a researcher's area and the topic was not always clear. A long list of candidate case studies was identified using the selection criteria and, with an input from the HRB we prioritized names to identify the eight case studies and two reserves for each group (B/EC and HSR/PH/PCR), should a case study PI refuse to participate. Selected case study PIs were approached by the HRB to test their ability and willingness to participate in the evaluation. All PIs in the eight selected studies agreed to participate.

It should be noted that the number of case studies (eight) limits the number of comparisons that can be made. As a general rule it is necessary to have a minimum of four

case studies of similar characteristics (e.g. B/EC) to make a comparison with another characteristic (e.g., HSR/PH/PCR research). However, since the focus of this report is on the economic impacts of the portfolio of HRB-funded research, it was more important to have a balance of the areas that were funded in order to show the different types of impact achieved than it was to have a balance to compare the characteristics of the research. In this project we have not compared case studies with one another, but simply collated evidence from all the studies to produce a representative array of impacts.

Case study methods

We carried out eight case studies as part of this project. Four of these investigated B/EC grants, four investigated HSR/PH/PCR. The case study research used a combination of interviews and desk research. The data sources used in the case studies are shown in Box 8.

The grant application and subsequent applications
Any peer review comments on the grant or on subsequent grants
End-of-grant reports (for the study grant and subsequent grants)
Papers and other publications attributed to the grants
Face to face interviews with the PI
Face to face or telephone interviews with other researchers associated with the grant
Face to face or telephone interviews with policy-makers, practitioners or industry collaborators associated with the grant and/or the PI
Review of relevant policy documents
Review of open source data related to the grant and/or PI (e.g. the company websites of collaborators)

Box 8. Data sources used in the case studies

The data identified through the case studies are presented as both a narrative of the research process and outcomes following the structure of the payback framework, and as a table of payback, based on the payback categories. This allows a reader to understand each case study in its context and full detail, while having an easy way to compare outputs and outcomes across case studies using the categorizations.

Case study analysis

The findings from the case studies were analysed and synthesized in a half-day workshop attended by the project team, including those not involved in the specific case studies. To begin the workshop, the study team discussed the need for a way to capture impacts that are specific to the case study grant (a narrow definition of impacts) and those related to further work by the PI that would not be possible without the support of the HRB (a wide definition of impacts). Each case study was presented in turn, noting the key outputs and outcomes at each stage of the payback framework. Throughout the day emerging findings were captured on a wall-sized whiteboard on repositionable notes. These notes were classified into where they fit into the payback framework. In the second part of the workshop the findings were reviewed and reclassified into particular payback categories, in

order to allow comparison across studies. The study team then discussed the ways in which outcomes can be classified as economic returns, agreeing to identify outcomes that can have an economic value and then to assign economic values to them where possible. The ways in which economic values can be assigned to outcomes are discussed in Appendix B.

Appendix B: Prior work on valuing economic returns on health research

The economic benefits that accrued through HRB funding must have a solid basis, both in terms of the attribution of outcomes to research findings and in terms of a sound methodological foundation for identifying economic benefits. The narratives of the case studies have made the case for attributing particular outputs and outcomes to HRB funding, individual researchers and specific research funding. This appendix explores the second concept: methodologies for identifying and quantifying the economic impacts of health research.

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 Academy of Medical Sciences (AMS), the MRC and the WT recently came together to form an Evaluation Forum to consider 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).

The report from the Evaluation Forum organized its analysis of the areas of economic benefits from health research around that developed by the Health Economics Research Group (HERG), Brunel University (Buxton *et al.* 2004). This review of previous assessments of economic benefits identified four main areas of economic benefits:

1. valuing direct cost savings to the health system,
2. valuing benefits to the economy from the a healthy workforce,
3. measuring the intrinsic value to society of the health gain,
4. valuing the benefits to the economy from commercial development.

1: 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' healthcare systems (Moncayo 2003).

Health technology assessments (HTAs) can also lead to cost savings. Jacob and McGregor (1997) explicitly looked at direct savings to the healthcare system from HTAs undertaken in Quebec, Canada, and found that several of these had directly influenced policy and contributed to healthcare cost savings.

Direct cost savings (or reduction on claims on resources) may accrue more widely than to the healthcare system alone. Research-based treatments that result in shorter and/or more effective treatments may also result in savings in non-medical direct costs such as custodial care, special diets, tutors, transportation, special equipment, government and voluntary community support programmes (National Institutes of Health 1993).

2: Benefits to the economy from a healthy workforce

It is too narrow to focus only on healthcare savings, 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 no longer lost, 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%. A series of case studies by the US National Institutes of Health (1993) that analysed particular pieces of research, included estimates of the saving from the lost production that had been avoided by the research results.

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

3: The intrinsic value to society of the health gain

This consists of more recent studies that attempt 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). 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 (Murphy and Topel, 2003).

The key support of this work is using economic evidence suggesting that individuals' willingness to pay for small reductions in the risk of death are equivalent to a value of around US$3m to prevent a fatality. This is then included in calculations of the economic value of the increasing longevity of the US population. They then consider what proportion of these gains can reasonably be attributed to medical research. In the area of cardiovascular disease, for example, it has been suggested 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 link between research findings and practice and behavioural changes are also emphasized. The importance of these contributions lies in their common use of a willingness to pay value of a statistical life (or life year), that enables the intrinsic 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 are obliged to make. For example they essentially treat the USA as a research island. Even if this is a reasonable approximation for the USA, this not easily be generalized to other countries.

4: Benefits to the economy from commercial development

A recent review identifies a range of categories of benefits to the economy but finds that none of the studies provided a simple and comprehensive model (Salter and Martin 2001). In its evidence to the US Congress, the National Institute of Health cites 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 public and privately funded research and made no attempt to calculate the social rate of return.

Many studies stress the employment benefits of research, but few link estimates of employment to specific (costed) bodies of research. Rosenberg (2002) observes that the estimated 500,000 jobs in the US biopharmaceutical industry "would not exist if industry wasn't standing on the shoulders of public funding and academic performance". There have, however, been some attempts to put a monetary value on such employment creation, including that occurring at a sub-national level (Davy, 1996).

Raiten and Berman (1993) studied the research that led to a methodology for producing monoclonal antibodies. In addition to tracing historically the developments that led to the discovery, they also conducted a cost benefit analysis from the perspective of the USA. They then applied a multiplier effect to estimate the employment and other benefits brought about by the manufacture and use of the products.

Various developing countries use R&D to help build a pharmaceutical industry to generate a range of economic benefits, including employment, import substitution and reduced drug costs. Examples include Brazil (Gadelha 2000) and India (Kettler and Modi 2001).

Several issues emerge from this grouping of benefits. First, it is clear that the second and third areas both in some way set a value on health gain. Therefore, they should not be added together in any analysis as this would amount to 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 healthcare system. The fact that the health gain is so central to these approaches to assessing economic benefit 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 of the) 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 second issue that emerges, and that might be particularly relevant in the Irish context, is the need to expand the final area so as to consider how the very existence of research capacity itself can generate economic benefits and might help a country to retain, as opposed to creating, a capacity for pharmaceutical manufacturing. The public funding of research has traditionally been seen as a transfer payment and does not in itself represent a benefit to the economy. However, where the public funding of research leads to the establishment of research capacity that is then able to attract further research funding from overseas public, charitable or pharmaceutical funders, then that is a boost to the domestic economy. Furthermore, there has been a major shift to Ireland of the manufacturing capacity of pharmaceutical industries (Advisory Council for Science, Technology and Innovation, 2006), and an expansion of research capacity might help make Ireland an attractive location in which to retain this capacity.

Turning to how these groupings of benefit described above should best be assessed, a range of techniques is available. The HERG review examined over 20 studies and found that various combinations of these areas were included in different studies. Some approaches are clearly alternatives to each other, so that the health gain can be evaluated either using the human capital approach or the intrinsic/monetary value of a life. The review suggested that there were two main issues of concern even before we get to the question of how we value the benefits.

The first concerns the inputs in question. A number of key science policy studies have emphasized 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 the HERG review the breadth of the research considered varies considerably. Some studies consider 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, about 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), suggested that during the 20th century much of the reduction in mortality was not due to medical advances and medical research, but to improvements in general living standards. Then there are difficulties establishing the link between specific research, its level of implementation and its impact. This means that while some studies attempt to assess the actual gain from research, reflecting the extent of uptake or absorption of the research findings, others provide an estimate of the potential economic benefit if the findings were implemented. A further problem is that we can observe events only given past research, but 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.

Ways of progressing in this field include working at a macro level and trying, as with the Funding First work in the USA, to consider the health gain in a society, making assumptions about the proportion that is linked to the research produced in the society and then setting a value to that health gain. There are enormous challenges in relation to

the availability of data and the assumptions that should be made in whatever society such a study is undertaken. Outside the USA, which does produce a sizable proportion of global health research, the challenges are even greater.

Another approach that is supported in the Warry Report is the use of case studies that attempt to identify benefits from specific pieces or programmes of research. The second issue listed above, i.e., attributing any 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 by the National Institutes of Health (1993; Johnston *et al.*, 2006) because they seem to have made assumptions about the level of implementation of National Institute of Health 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). Applying this framework, which is the most widely used approach (Hanney *et al.*, 2007), involves attempting to establish links between specific pieces of research and a range of possible benefits. The multidimensional categorization of benefits in the payback framework goes far beyond the economic benefits but, as we have seen above, there are now moves to consider a broad range of benefits as being economic impacts. Therefore, overlaps between the health sector benefits and the broader economic benefits are unlikely to cause major methodological problems.

design by **drawinginc**