PRELARE

Informing Policy with Evidence

Estimating the Economic Value of NIHR Biomedical Research Centres and Units

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Key points

- Since their establishment in 2007, Biomedical Research Centres (BRCs) and Biomedical Research Units (BRUs) have received over £1.4 billion from the National Institute of Health Research (NIHR). Given this scale of funding, it is useful to assess whether this investment is good value for money. A number of factors might influence this:
    - The existence of BRCs and BRUs may encourage further funding from charities and private companies, which might not have happened in the absence of NIHR investment.
    - BRC and BRU investment (with or without further funds) may improve population health, following the translation of their scientific discoveries into practical treatments.
    - BRC and BRU investment may create improvements in the local economies in which they are located, through employment, salaries and a 'multiplier effect' of local spending.
- Previous studies have estimated the 'value' of biomedical research using economic models to determine how much charity and private sector funding is associated with NIHR investment, and assessing health gains and local wealth creation resulting from medical research. In this fast-response report we strive to update these earlier studies, although the time constraints on this project mean that our estimates are often tentative.
- **NIHR expenditure on biomedical research appears to provide a good return on investment:**
    - Populating a microeconomic model developed by DHSC with values identified by this project suggests the annual rate of return from an increase in NIHR investment in BRCs is around 29%. This includes the net gain from improved health outcomes and is a conservative estimate.
    - Adopting a macroeconomic approach, using input-output analysis, to estimate the value of NIHR investment on BRCs, suggests the 'internal rate of return' is around 57%, rising to 58% when the net health gains are included.
    - Both values are excess of the expected from public or private investment.
    - Focusing only on the health gain gave an internal rate of return of 16%.
- **NIHR investment also appears to attract further funds from charitable and private sector sources**: alongside the £1.4 billion of NIHR funding, the centres raised further funds from other public and private sources such that total funds received to 31 March 2019 were £7.86 billion. This is not all clearly linked to the NIHR funding and, in the absence of a 'counterfactual', it is difficult to estimate what investment would have been obtained without the NIHR funds.
    - A previous study (Sussex et al 2016) estimated that a 1 % increase in public sector expenditure is associated with a 0.81 % increase in private sector expenditure. We found a similar complementary relationship between public and private R&D expenditure.
- BRCs exist across England, but **funding is highly skewed towards Oxford, Cambridge and London**. These areas realise the economic benefits – particularly from employment and other spillovers to local economies. They may also benefit disproportionately from innovation, if uptake is faster in areas local to where the research takes place. These create the potential to perpetuate geographic inequalities in both health and productivity.
- We have some concerns about the 'return on investment' methodology as it may overestimate the value of biomedical research compared with other NIHR priority areas such as (for example) public health, where societal benefits may be more difficult to value in financial terms.

Executive Summary

Background

Biomedical research centres (BRCs) and biomedical research units (BRUs) were established in 2007 by the National Institute of Health Research (NIHR). NIHR currently funds 20 Biomedical Research Centres (BRCs),[1] which are collaborations between world-leading universities and NHS organisations that bring together academics and clinicians to translate laboratory-based scientific breakthroughs into potential new treatments, diagnostics and medical technologies.[2] Through employment and spending they contribute to their local economies, and they may also attract investment from other national and international funders, furthering the nation's economic growth.

Together, BRCs and BRUs have received over £1.4bn of funding from National Institute of Health Research (NIHR), and raised further funds from other public and private sources such that total funds received to 31 March 2019 were £7.86bn.

Previous studies have attempted to quantify the economic impact of government and charity funding on medical research, using different methods. Sussex (2016) used an economic model to estimate the complementary relationship between public/charity and private pharmaceutical research and development expenditure. Smith (2019) estimate the impact of Oxford's NIHR Biomedical Research Centre on income and job creation using a macroeconomic approach, building on earlier studies of the economic and financial impact of medical research (e.g. HERG 2008).

In this fast-response report we strive to update previous estimates of the 'value' of biomedical research, specifically the impact of NIHR investment in Biomedical Research Centres (BRCs), using both these approaches. DHSC also asked that we review evidence on related topics such as depreciation rates and cost of capital. Time constraints on this project mean that our estimates are often tentative.

Findings

This project has estimated the economic returns attributable to NIHR funding of the BRCs/BRUs from:

- Health gains, net of the health care costs of delivering them.
- Gains to the local and national economy, in particular the income that results directly and indirectly from the research and the further activity stimulated by it.

[1] BRU funding ceased in 2016/17

[2] https://www.nihr.ac.uk/explore-nihr/support/experimental-medicine.htm

The health gains, valued at £60,000 per quality adjusted life year as recommended by the Treasury, are estimated to generate an internal rate of return (IRR) [3] of around 16% (range 13% to 17.5%) for four disease groups.[4]

Applying national ONS type 1 multipliers to the direct output and staff employed by BRCs/BRUs reported additional output valued at £0.65bn, attributable to the original direct investment of £1.14bn, giving a total economic impact of £1.79bn. The BRCs and BRUs have created over 7,400 full-time equivalent (FTE) staff, which generated employment opportunities for a further 5,788 FTEs, resulting in a total of 13,190 FTE staff employed over the time period.

The combined economic and health IRR from NIHR's investment is estimated to total 58%. This is much higher than the hurdle rates applying in the private sector for new investment (around 12%) and the annual discount rate of 3.5% in real terms, which is set for public sector investments. This supports continued Government investment in biomedical research, as the gains are well in excess of its opportunity cost of capital.

Adopting a different approach, as advised by DHSC, which uses the concept of spillover and applies values for the parameters identified in later sections of this report, produced an annual rate of return of 29%. The parameters considered and the findings on each include:

- Updating the analysis by Sussex et al (2016) quantifying the relationship between public funding of medical research and private R&D expenditure proved problematic, and our findings are currently tentative. Like Sussex et al, we found a statistically significant complementary relationship between public and private R&D expenditure, but our baseline model, and many other specifications tested, had problems of dynamic specification, which complicated our analysis. Exploring different lag structures and excluding some of the disease areas resulted in a variety of coefficient estimates, all demonstrating a statistically significant complementarity between public and private sector expenditure but with a wide range of numerical values. The most plausible model specification that passed our dynamic specification tests generated estimates of the main parameter of interest between 0.8 and 1.07, which is consistent with Sussex et al (2016), but in other respects the estimates are quite different; our findings are thus extremely sensitive to the model specification and we are not confident of these estimates.
- Our updated literature review found limited new empirical evidence for a value of spillover (being externalities accruing to organisations other than the one making the initial investment), consistent with the 50% rate used by Sussex (2016). These findings are from the USA and from unrelated industries so there is still insufficient evidence to provide a robust value of the spillover associated with UK private or public sector investment in biomedical research. Such externalities contribute to the social rate of return and ideally will be captured.
- Updating a literature review by Hanney (2015) found empirical evidence from two large studies that time lags are about 14 years from patent to launch for new drugs marketed in the UK and

[3] The IRR is the interest rate at which the net present value of all the cash flows (both positive and negative) from a project or investment equal zero. It is used to evaluate the attractiveness of a project or investment.

[4] Musculoskeletal diseases, cancer, mental ill-health and cardiovascular diseases.

USA. The lag has increased by about 1.3 years since 2010 due to longer duration of the clinical trials phase. Recent USA data suggests the lags have started to fall. Further progress is anticipated as EU and US regulators have each introduced new regulations designed to improve the efficiency of trials, and both now engage with pharmaceutical companies at an earlier stage. Reducing time lags improves the IRR from investment in new drugs and are an important driver to encourage new innovation.

- These lags are somewhat shorter than the lags observed by the studies calculating the IRRs for the four diseases, which used between 12 and 17 years. The differences can be attributed to different start and stop periods, with the disease specific interventions extending beyond regulatory approval to include a measure of the time associated with adoption activities. The inclusion of a period for adoption is appropriate for the IRR calculations.
- The cost of capital to the private sector (as an opportunity cost) and to the public sector (as a discount rate) are relevant to estimating the return to NIHR funds. The cost of private sector capital was found to be around 6.5% post-tax and 8% pre-tax (both nominal). The cost of capital for the pharmaceutical sector seems to be similar to or slightly higher than the market overall, possibly reflecting the risky nature of the spend on research and development (R&D). The private sector rates are about 1% higher than the nominal rates of 5.5% implied by HM Treasury's annual discount rate of 3.5% in real terms.
- An understanding of the expected profile of decline in the value of innovative biomedical products is required to ensure their capital value is amortised appropriately. We found that differences in the depreciation/amortisation of R&D expenditures are a function of geography (USA vs the rest of the world) and between the NHS and universities due to their differing accounting standards. The USA standards and those applying to UK universities apply more stringent rules to capitalising R&D spend than the international standards followed by the NHS. Under all accounting standards, BRC funded investment and indeed most biomedical research expenditure should be expended in the year it is incurred.
- The pharmaceutical industry has longer average asset lives than many other sectors. Observers have noted factors that impact on asset lives include the long-term nature of its research, effective patent protection and other entry barriers.
- The Office for Life Sciences reported that in 2018, companies with overseas owners accounted for around 65% of the turnover in the life sciences sector, with UK owned companies accounting for 32% and ownership of the remaining 3% unknown. Overseas owned companies also employed 52% of all staff, with UK companies employing 42% and 'unknowns' 6%. The 2017 statistics reported that 59% of all companies with ownership information were UK owned but that statistic is not reported for 2018. The earliest value reported by The Office for Life Sciences is for 2011, where 43% of companies in that sector were UK owned, similar to the value in 2017 of 41%. The impact of BRCs/BRUs on this value is unknown.

Two other topics have been also explored. Firstly, whilst BRCs exist across England, funding is highly skewed towards the 'golden triangle': Oxford, Cambridge and London. Funding is directed to academic-NHS partnerships based on levels of existing world-class biomedical research, and therefore an even geographic distribution is unlikely. Nevertheless, it is important to note that returns on this investment – particularly in terms of spillovers to the local economy, but also potentially in terms of health gains if

innovation is more likely to be adopted in the area it is developed - are likely to be highly unevenly spread.

Secondly, the cost per publication for each BRC is provided. The results show a strong relationship between the level of funding and cost per publication, with BRCs receiving above average funding having a higher than average cost per publication. The potential for double-counting and the attribution problem means there is material uncertainty about the absolute cost per publication derived using the NIHR figures.

Further Research

Our original proposal planned to explore several topics with a range of interviewees, but this was not possible due to the COVID-19 outbreak. We see merit in conducting these qualitative analyses at a later date. Our analysis of the relationship between public and private investment in medical research is tentative and may benefit from further investigation. In addition, there may be opportunities to refine the cost per publication approach to use a less crude measure such as field-weighted citation indices.

Limitations

This is a fast-response analysis which of necessity mean that our estimates are often tentative. This applies particularly to the results from the economic model. The updated literature reviews are also pragmatic and not necessarily to the quality of a full systematic review.

The project has used NIHR collated data provided by the sites, the quality of which has improved over time, but we suspect there was under-reporting in some early returns, particularly of staffing levels. Data quality issues have also limited the usefulness of crude productivity measures such as cost per publication.

A major limitation with the multiplier approach in calculating the indirect benefits accruing to NIHR funding is there is no measure of the output of the BRCs/BRUs. We assumed that the output value was the same as the value of the NIHR funds. This limitation does not apply to the estimated indirect gross value added, employment costs and staff numbers generated using NIHR funding. It is also not possible to unpick the component parts of the output multiplier to establish the weight given to commercialising intellectual property rights. Indeed, it is not known if the multiplier captures such benefits. We did not include the value of spin-out companies, in order to avoid any double counting.

Finally, there is a major conceptual problem with the multiplier approach in that it does not adopt a marginal approach. Thus, one cannot estimate the value of the next or last £1m of investment in biomedical research. A marginal analysis would be more informative when developing future strategy/policy.

Recommendations

We recommend strengthening the current approach to monitoring and evaluation of BRCs, particularly to enhance the guidance to BRCs on the annual returns and to gain more transparency of the research agenda being pursued by each BRC to help in understanding the expected outcomes.

Conclusions

We adopted two different approaches to estimating the rate of return to NIHR investment in BRCs. In each case we included the net benefit from health gains. Populating a model developed by DHSC suggested the total rate of return was about 29%, whilst an input-output analysis reported such investment generated a return to the national economy of about 58%. These returns are well in excess of the cost of capital set for the public sector and that adopted by private sector companies.

We have also been able to confirm the value of spillover used by Sussex (2016) is reasonable and that the time lags assumed to calculate the IRR from net health gains are valid. Overall, our results suggest that there is a statistically significant complementary relationship in the long run between public and private pharmaceutical expenditure in biomedical research. A 1 % increase in public sector expenditure was associated with a 0.75% increase in private sector expenditure, which is of a similar order of magnitude to that proposed by Sussex (2016). Hence, public sector expenditure and private sector expenditure are complements.

While we are convinced of the economic and health benefits of investment in biomedical research, it is clear that this financial estimate is a partial measure of benefit. Other factors should (and do) influence decisions about the allocation of research funds. Reflecting on the overall approach taken in this project, we have some concerns about the 'return on investment' methodology if reported in isolation. First, it may overestimate the value of biomedical research compared with other areas of clear priority for NIHR, for which societal benefits may be more difficult to value in financial terms. In addition, we have concerns that funding allocation decisions made on return on investment information alone may continue the circle of public and private investment directed towards the 'golden triangle', which has potential to perpetuate geographic inequalities in health and productivity. Balancing the dual objectives of scientific endeavour with the fairer distribution of the benefits of research investment may be furthered by further consideration of 'place based' health research and 'levelling up' currently disadvantaged regions.

Glossary and Abbreviations

ABPI Association of the British Pharmaceutical Industry
AMRC Association of Medical Research Charities
AZ AstraZeneca
BRC Biomedical Research Centre
BRU Biomedical Research Unit
CAR-T Chimeric antigen receptor T-cell
CEA Cost-effectiveness analysis
CTP Computed tomography perfusion
CVD Cardiovascular disease
DHSC Department of Health and Social Care
EMA European Medicines Agency
FDA Food and Drug Administration
FTE Full time equivalent
GAAP Generally Accepted Accounting Principles
GAM Group accounting manual
GDHI Gross disposable household income
GDP Gross domestic product
HERG Health Economics Research Group
GVA Gross value added – this is a measure of the goods and services produced in a sector and is the total of wages & salaries, dividends, savings (profits, depreciation) and indirect taxes
IAS International Accounting Standard
IFRS International Financial Reporting Standards
IP Intellectual property
IQR Interquartile range
IRR Internal rate of return. This is the interest rate at which the net present value of all the cash flows (both positive and negative) from a project or investment equal zero. It is used to evaluate the attractiveness of a project or investment.
MRC Medical Research Council
MSK Musculoskeletal
NICE National Institute for Health and Care Excellence
NIHR National Institute of Health Research
NIST National Institute of Standards and Technology
ONS Office of National Statistics
PIP Paediatric Investigation Plans
QALY Quality Adjusted Life Year
R&D Research and development
RoR Rate of return
SBIR Small Business Innovation Research

SORP Statement of Recommended Practice

Spillover - a measure of the gain to other organisations from investment in medical research by one organisation; the other organisations may be other organisations in the medical sector, in other sectors, public and private sector and also in other countries. These benefits should be measured as they contribute to the total social rate of return from investment.

WACC Weighted average cost of capital

1 Evaluating the economic value of BRCs and BRUs: background and approach

1.1 Background

In 2007, the National Institute of Health Research (NIHR) created biomedical research centres (BRCs) and biomedical research units (BRUs), within leading NHS/university partnerships, to enable researchers to develop clinical applications from early research into new treatments for patients. Now there are 20 BRCs, with BRUs disbanded in 2017. Together these partnerships have received over £1.4bn of NIHR funding in the 11 years to 31 March 2019.

The aims of the NIHR BRCs are to:

- bring together academics and clinicians to translate lab-based scientific breakthroughs into potential new treatments, diagnostics and medical technologies.
- create an environment where experimental medicine can thrive.
- develop innovative research ideas that can attract investment from other funders, furthering the nation's economic growth. [5]

They have been successful in attracting public, charity and industry funding. In 2018/19, these funders provided almost £1.07bn, six times more than the funding from NIHR (£0.18bn).

No studies have evaluated the impact of NIHR funding on the national economy. Rather, previous studies have attempted to quantify the economic impact of government and charity funding on medical research, using different methods. Sussex (2016) used an economic model to estimate the complementary relationship between public/charity and private pharmaceutical research and development (R&D) expenditure. Smith (2019) estimated the impact of Oxford's NIHR BRC on income and job creation using a macroeconomic approach, building on earlier studies of the economic and financial impact of medical research (e.g. HERG 2008).

In this fast-response report we strive to update previous estimates of the 'value' of biomedical research, specifically the impact of NIHR investment in BRCs, although the time constraints on this project mean that our estimates are often tentative.

[5] nihr.ac.uk/explore-nihr/support/experimental-medicine.htm

1.2 Our Approach

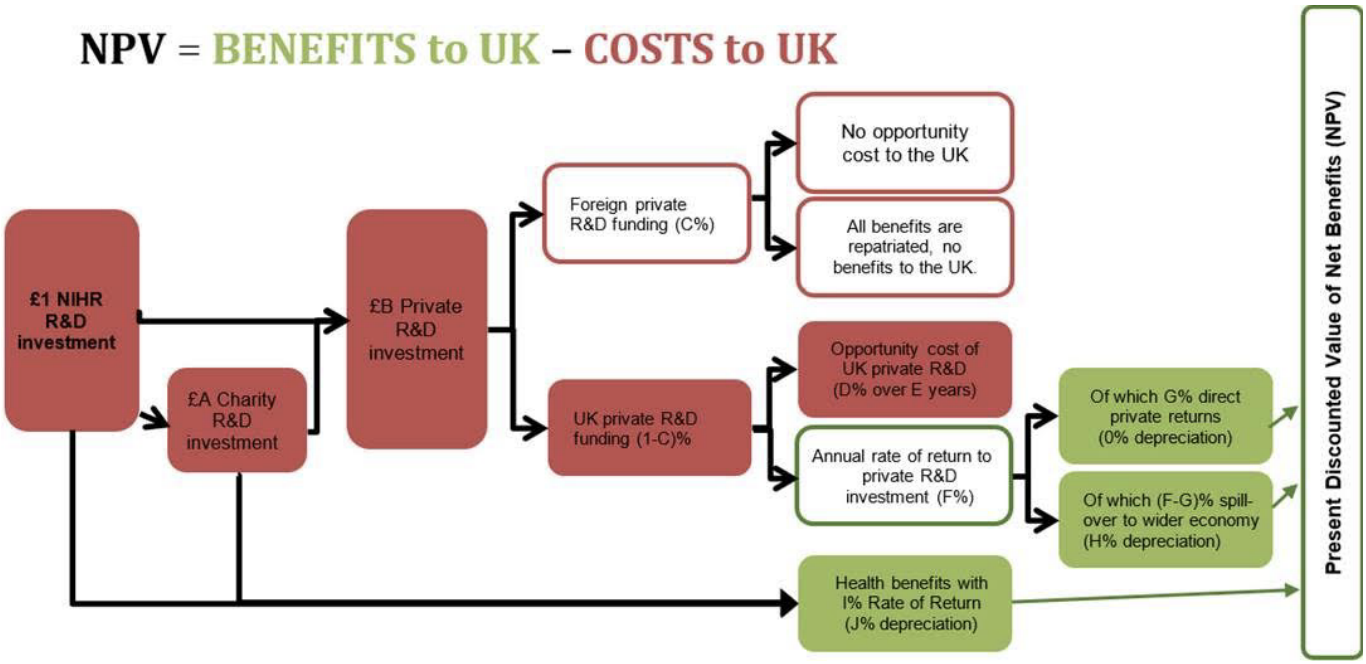
This paper is a contribution to inform the value of BRCs and biomedical research units (BRUs) nationally. Specifically, it takes forward the work of several researchers in this area by:

a. Updating the data to re-run the model developed by Sussex (2016) to inform the level of private sector research funding crowded in by public sector spend (Section 2).
b. Updating the internal rates of return arising from the increase in quality adjusted life years (QALYs) associated with innovative therapies adopted in four disease areas, using funds provided by the UK public and charity sectors (Section 3). The value per QALY was increased from £25,000 to £60,000 to be consistent with HM Treasury's societal value of a QALY (HM Treasury, 2018).
c. Calculating the contribution from NIHR funds to the BRCs and BRUs in terms of direct and indirect staff employed, gross value added and contribution to national output (Section 4). This uses the ONS type I multipliers and builds on the case study reported by Smith (2019).
d. Updating two existing literature reviews on:
    - The value of spillovers generated from publicly funded R&D (Section 5). The original review, reported in HERG (2008), was previously updated by Sussex (2016).
    - Time lags between the conduct of biomedical research and NHS adoption of the resulting medicine or device (Section 6). The original review was reported in Hanney (2015).
e. Conducting a geographical analysis of the funds received by BRCs and BRUs, comparing this regional distribution with analyses of regional populations and income levels (Section 7).
f. Summarising the cost of capital faced by public and private sector organisations and pharmaceutical companies (Section 8).
g. Advising on the depreciation policies adopted by UK public and private sector entities and internationally (Section 9).
h. Addressing the ownership of biomedical companies operating in England (Section 10).
i. Comparing of the cost of publications and citations generated by BRCs/BRUs (Section 11).
j. Calculating the net benefit of marginal spend on BRCs using a model developed by the Department of Health and Social Care (DHSC) (Section 12).

Each section is self-contained with its own summary, strengths, limitations and conclusions.

The rationale for each topic can be explained using a diagram of the net benefit of £1 of NIHR investment in biomedical research, developed by DHSC (See Figure 1.1).

Figure 1.1 Net Present Value to UK Economy from Marginal Spend by NIHR on BRCs



(Source DHSC 8th November 2020, personal communication).

This approach is discussed further in Section 12.

1.3 Potential Future Research

Exploring the effects of public funding on future investments from the private sector in R&D requires a long time series (more than 30 data points), which means that changes in the quality and quantity of data reported over time affect the reliability of the estimates. For future research, the development of more robust methods to allocate funding to specific disease areas could help to improve the reliability of estimates of the relationships between these sources of funding.

Our earlier plans, agreed with DHSC, included addressing a number of topics using interviews with various stakeholders, which were curtailed due to the COVID-19 outbreak. These plans included:

1 Interviews with BRCs, to explore:

- The 'counterfactual' - what would have happened if the BRCs had not been created?
- Attribution of outputs to NIHR funded initiatives compared to those funded by other monies given there is no ring-fencing of the projects or people benefiting from NIHR funds.
- Whether the BRCs have affected time lags between knowledge generation and its translation into health improvement and economic gain.
- Human capital benefits, including impact on future earnings potential from employment on BRC/BRU projects.
- The value to patients from participating in BRC projects.

- The value to clinicians from participating in BRC projects.
- The value of the BRC/BRU activities in respect of:
    - Patents granted and spin-off companies.
    - Conducting clinical trials and recruiting patients.
    - Collaborations.
    - Exploitation of intellectual property (IP) generated within centres.[6]

2 Interviews with other stakeholders

We also planned to explore the benefits of BRCs and their collaborations with the private sector from a charity sector perspective (The Wellcome Trust, Association of Medical Research Charities AMRC and MRC). This would have also explored any externalities that charities gain from the additional research capacity, infrastructure, networks and patients provided by the BRCs.

We had also hoped to interview ABPI to get a private sector perspective on the direct benefits from the BRCs, together with related externalities.

3 Interviews with other experts

Finally, we had planned a round table discussion of the potential social costs and benefits associated with BRC funding with leading experts in this field.

Two other aspects that were in the original proposal and not taken forward are:

- Changing research agendas over time

Time and resources have precluded us from addressing this question. We note MRC and Wellcome provide regular reports identifying the themes driving their research programmes and how these change over time. We are not aware of a similar level of transparency in respect of how BRCs develop their research portfolios over time.

- This weakness impacts on the effective monitoring and evaluation of BRCs. As the Green Book notes: '*The first step in appraisal is to provide the rationale for intervention*' (HM Treasury, 2018). Without an understanding of the high-level aims for the research portfolio of a BRC, selecting valid measures to monitor the conduct of the research effectively is likely to be hindered. Moreover, evaluation is a relative process requiring an understanding of what was planned. Hence we see value in exploring these aspects with BRCs and with NIHR, given their on-going role in evaluating the BRCs.

[6] The BRCs do state a value of the IP generated but the basis of the valuation is neither defined nor reported.

- The value added from citations using a field-weighted citation impact measure,[7] together with cost data.

We have not been able to use this measure because there is insufficient information on the publications attributable to BRCs; rather the information is only available for the parent organisations. We explored potential for mapping BRC themes to SciVal categories in order to permit a field-weighted citation impact comparison, but are not confident of this comparison. In Section 11 we provide a cost per publication but note the limitations with this crude measure of productivity rather than using a measure of impact. The results suggest there are major data quality issues, which limit the usefulness of even this crude benchmark.

Whilst we were conducting the evaluation we identified areas where ideally more information would be available to give a fuller assessment of the impact of BRCs. These areas include:

- The value and nature of infrastructure investment, including the services it is delivering, to whom and over what time periods, and the reason for this being funded through a BRC route.
- The attributes of BRCs that have been able to leverage funds from external sources most successfully.
- The perceived synergies from the collaboration between academia and the hospital sectors and between these parties and other stakeholders.

If further work is commissioned we propose these aspects are also explored through interviews.

1.4 Recommendations for Future Monitoring and Evaluation

As the Green Book notes, effective monitoring requires robust data collection (HM Treasury 2018). This work has identified some deficiencies in the data collected by NIHR. For example:

- In every year except 2018/19 the sum of salaries and other revenue costs exceeded the level of NIHR funding.
- The number of FTEs is not always reported against a job title, suggesting under-reporting of the number of FTEs attributable to NIHR funding.
- Values are reported for intellectual property rights but no advice seems to be provided to centres on how such assets should be valued, and so we cannot interpret the figures reported.
- Several centres report costs per publication of under £5,000 which suggest double counting of NIHR-related publications, incorrect attribution, or that these are all the publications and so the measure we use is wrong.[8]

7 See https://www.elsevier.com/solutions/scopus/how-scopus-works/metrics

8 We have calculated total cost per publication if this is more relevant.

Data quality has undoubtedly improved over time but in many areas we were not confident we were comparing like with like (for example the average salaries per employee in 2013/14 varied from over £250,000 at Cambridge, to under £100,000 for the London centres). Hence we recommend improving the guidance to centres to address aspects including attribution, approach to counting projects or other measures which span several years, describing the valuation concepts to be adopted, plus applying rules so that total funding aligns to total spend. We recognise this will require more central resource to set up and monitor the annual returns plus dialogue with each BRC.

The second recommendation is around evaluation. Standard methodology involves comparing what happened with the original plan to gain insights into how well a project achieved its objectives and to inform lessons learned (HM Treasury, 2018). This is more difficult to do for a portfolio of projects, but, in this case, it is further hindered because there was no insight available into what the BRCs intended to happen. Greater transparency of the research agenda being pursued by each BRC over time may help in understanding the expected outcomes and a comparison with actual outcomes. We recognise this is challenging and suggest it may be useful to explore whether there are lessons to learn from how the MRC and Wellcome conduct evaluations of their portfolios.

2 Quantifying the magnitude of the effect of public medical research expenditure on private investment in R&D.

2.1 Summary

Sussex et al (2016) conducted a time series analysis to measure the complementarity of government and charity funded medical research and private sector research and development. To estimate the relationship, these authors fitted an econometric vector error correction model (VECM) to time series of biomedical and health R&D expenditure in the UK for ten disease areas for the government, charity and private sectors. Sussex's time series on R&D spend spanned 1982 to 2012. They found a statistically significant complementary relationship between public and private biomedical R&D expenditure, with their best-fit model showing that a 1% increase in public (i.e. government plus charity) sector expenditure is associated with a 0.81% increase in private sector expenditure.

We attempt here to update the Sussex analysis, extending the time series to explore any change in the relationship. Time and other constraints of a rapid-response project mean that we could not replicate the data sources exactly for some of the variables, so our findings must be viewed with a high degree of caution. Like Sussex et al, we found a statistically significant complementary relationship between public and private R&D expenditure, but our baseline model, and many other specifications tested, had problems of dynamic specification, which complicated our analysis. Exploring different lag structures and excluding some of the disease areas resulted in a variety of coefficient estimates, all demonstrating a statistically significant complementarity between public and private sector expenditure but with a wide range of numerical values. The most plausible model specification that passed our dynamic specification tests generated estimates of the main parameter of interest between 0.8 and 1.07, which is consistent with Sussex et al (2016), but in other respects the estimates are quite different; our findings are thus extremely sensitive to the model specification.

2.2 Background

NIHR BRCs and BRUs were intended to address the 'gap in translation' (Cooksey 2006), realising benefits of medical research in terms of preventing and treating illness. Such translation, and associated improvements in science and economic benefits, involve partnerships as one of, but not the only, transmission mechanism for spillovers from public research to the private sector. Private industry, particularly the pharmaceutical industry, "builds on and interacts with government- and charity-funded research and researchers; it conducts its own further research and develops and commercialises medicines and other technologies for use in healthcare" (Sussex et al 2016). There is a general belief, supported by economic theory and some applied research, that public funding of medical research (by

government and charities) 'crowds in' private sector investment. Sussex et al (2016) attempted to measure the magnitude of this effect, quantifying the complementarity of public and private R&D investment in medical research. Using the framework summarised in Figure 1 above, if NIHR invests £1 and charities invest £A, how much will be invested by private industry (£B)?

2.3 Methods

We replicated the study conducted by Sussex et al. (2016) and added data for the period 2012 to 2018 (in some cases 2008 to 2018 as the Sussex model included a 4-year lag) to obtain an updated estimate of the relationship between private and public funding of biomedical research. We are grateful to the authors of the study for providing the original dataset.

2.3.1 Updating funding data

Government funding

Sussex et al. (2016) included the Medical Research Council (MRC), Department of Health (now DHSC) and Higher Education Funding Council for England (HEFCE) within its Government spend group. We compared the data obtained from different sources (specified below) to data reported in Sussex et al (2016) for 2012, which was the last year available. Table 2.1 provides the data extracted for 2012, the value provided in Sussex's dataset and the projected values to 2017.

Table 2.1 Actual and projected Government spend on R&D (£m in nominal terms.)

Year	MRC [a)]	DHSC	NHS [a)]	HEFCE	Forecast Totals	Total in model	Difference
2012	£600	£1,142.71	£948	£465.25	£2,207.96 b)	£,2207.53	£0.43
2013	£790	£499.46	£984	£496.25	£2,769.71		
2014	£716	£462.07	£1,036	£517.00	£2,731.07		
2015	£817	£496.77	£1,036	£521.96	£2,871.72		
2016	£649	£674.12	£1,043	£531.58	£2,897.70		
2017	£716	£585.97	£1,126	£551.72	£2,979.69		

a) Data reported as £m, with no decimal places
b) In 2012 NHS spend is included in DHSC spend but excluded in subsequent years

Using the values for each component gives a total for 2012 of £2,208m, which is very close to £2,207.5m used by Sussex et al. (2016) in their model.

The MRC value used is that reported in Table 3 of the latest ONS report 'R&D expenditure by the UK Government'.[9] In comparison, Sussex used MRC reported data on grant funding under the 'exclusive'

[9] https://www.ons.gov.uk/economy/governmentpublicsectorandtaxes/researchanddevelopmentexpenditure/datasets/scienceengineeringandtechnologystatisticsreferencetables

measure. The data identified from the MRC's annual accounts were lower than the ONS data. For example, in 2017 the MRC reported £652m spend on grants compared with £716m in ONS. We used the ONS data for consistency with the other sources (i.e. for NHS and HEFCE data)

DHSC data were taken from the annual accounts. In 2013/14, Department of Health changed the methods used to allocate intercompany eliminations. It was assumed that the 2012/13 value included NHS R&D spend but excluded that in subsequent years. The value of NHS and HEFCE spend was taken from Table 3.[7]

The UK Health Research Analysis 2018 report[10] noted that '*Research England (formerly HEFCE, now part of UKRI) had a total budget of £3.6bn, of which £1.4bn was allocated to research. Of this, a total of £432.1m (30.6%) was coded to units of assessment relevant to health and biomedicine*.' Earlier reports from HEFCE noted that spend on medical science was increasing relative to other spend but no absolute value of its contribution was identified. Assuming it was 26.8% in 2012 allowed us to obtain totals from these sources which sum to a similar value to that used by Sussex et al. (2016) in their model. This value also seemed consistent with the statement that funding in this area had increased over time. Hence, it was assumed the share of biomedical and health spend increased from 26.8% by 1.027% annually to reach 30.6% in 2017. This is a simplification and source of uncertainty.

Charity funding

Charity sector funding on R&D in Sussex et al. (2016) included annual spend on R&D grants by Wellcome from the Wellcome grants database and annual expenditure provided by the Association of Medical Research Charities (AMRC) (excluding Wellcome). The values modelled by Sussex et al. (2016) for this sector from 2009 are shown in Table 2.2 below, together with estimated values for the two elements.

Table 2.2 Charity funding: values adopted in model and estimated for 2013 to 2017 (£m in nominal terms)

	Total in model	Wellcome	AMRC balance	Forecast total
2009	£1,209.38	£377.31	£832.07	
2010	£1,094.45	£345.28	£749.17	
2011	£1,156.14	£326.50	£829.64	
2012	£1,221.54	£375.34	£846.21	
2013		£400.69	£873.29	£1,273.98
2014		£375.74	£901.23	£1,276.97
2015		£501.80	£898.53	£1,400.33
2016		£510.13	£895.83	£1,405.96
2017		£595.46	£893.15	£1,488.61

[10] https://hrcsonline.net/reports/analysis-reports/uk-health-research-analysis-2018/

The values for the Wellcome element were calculated as follows:

a) The annual value of grants awarded by Wellcome from 2009 were extracted from Table 6 of the Annual Report and Accounts for 2009 to 2013 and Table 7 thereafter.
b) The value of Wellcome spend on medical research in 2009 and 2014 was extracted from the UK Health Research Analysis (HRA) for those years.
c) The key difference between the values for 2009 and 2014 from the Accounts and UK HRA is that the former measures the total value of grants awarded in the year whilst the latter measures the within year expenditure. The latter is not reported in the Accounts. The ratio of within year spend to total grants was 62% in 2009 and 63% in 2014. In the absence of a better estimate, we used the mean value (62.6%) to the total grants awarded from 2013 to 2017, except 2014, to estimate the annual Wellcome within year R&D spend. For 2014, the value reported by the UK HRA for that year was used.

The values for the balance of AMRC annual spend were calculated as follows:

d) The values estimated for the Wellcome within year spend for 2009 to 2012 (from step c above) were subtracted from the total values of charity spend included in the Sussex et al. (2016) data. The values obtained were £832.07m in 2009, rising to £846.21m in 2012 as shown in Table 2.
e) Values were extracted from UK HRA 2009, 2014 and 2018 datasets for the original 12 organisations minus the spends of DH, MRC and Wellcome. The annual rate of change across the two periods (2009 to 2014 and 2014 to 2018) were calculated.
f) The estimated value for 2013 was the value for 2012 (£846.21) multiplied by the relevant annual growth rate (from e). In subsequent years the annual growth rates (from step e) were applied.

There are two uncertainties about these estimates. We have used the value of grants awarded each year by Wellcome after adjustment for exchange rate fluctuations and other items. The values excluded direct payments made to science and all allocated support costs, but included grants on cultural and societal activities. We have also included all grants thereby including infrastructure and activities such as student grants. We cannot establish if this basis is consistent with that adopted by Sussex et al (2016).

Additionally, Sussex et al. (2016) appears to have included R&D spend by the Scottish, Welsh and Northern Irish Governments who are members of AMRC, but not funding made by their Higher Education Funding Councils. Thus, these estimates are not consistently applicable to English or UK-wide expenditure.

Private sector expenditure

Sussex et al. (2016) used data published by The Association of the British Pharmaceutical Industry (ABPI) to estimate private R&D expenditure in the UK. We have instead used ONS data on private sector

investment by the pharmaceutical industry.[11] The two sources are similar other than for 2017. We decided to use the ONS data because the values were published more recently; therefore, the difference observed may reflect the ONS revising its data. However, neither are consistent with the data used in the model for 2011 (see Table 2.3), presumably due to later data revisions.

Table 2.3 Private expenditure on biomedical and health R&D UK (£m in nominal terms).

Year	ONS	ABPI	Total in model
2011	£4,914	£4,914	£5,016
2012	£4,208	£4,208	£4,207
2013	£4,039	£4,039	
2014	£3,855	£3,855	
2015	£4,165	£4,165	
2016	£4,090	£4,090	
2017	£4,320	£4,337	

Global pharmaceutical sales

Sussex et al. (2016) used data provided by IMS Health (now IQVIA) for global pharmaceutical sales. IQVIA publishes an annual report on the global use of medicines but it does not provide the annual sales value. For example, its presentations are often graphical presentation, in constant prices, with adjustments for exchange rate movements but no absolute values or discussion of the adjustments made. We therefore used the data from EvaluatePharma who collect and aggregate data from the world's pharmaceutical companies. EvaluatePharma publishes annual reports detailing the total value worldwide of prescription drug sales. The total in 2012 was $721bn. No conversion to pounds sterling was made. Rather the annual change in total worldwide sales was calculated and applied to the values used in the model for 2012 onwards (see Table 2.4). EvaluatePharma also publish annually an analysis of spend by 20 top therapy areas, which was used for allocating expenditure to each disease area (see Section 2.1.2.3).

Table 2.4 Global pharmaceutical sales (£m in nominal terms)

	Total in model	Extrapolated values	Annual change %
2009	£515,855.50m		
2010	£532,312.60m		
2011	£549,132.30m		
2012	£540,527.10m		
2013		£547,274.32m	101%
2014		£566,016.59m	103%
2015		£560,019.06m	99%
2016		£579,511.02m	103%
2017		£591506.08m	102%

[11] https://www.ons.gov.uk/economy/governmentpublicsectorandtaxes/researchanddevelopmentexpenditure/timeseries/dlcd/berd

2.3.2 Allocations across disease areas

Sussex et al. (2016) used data aggregated at disease area level to increase the robustness of the estimates from the Vector Error Correction model. They were able to retrieve data at disease area level for global pharmaceutical sales and Charity funding. However, for private and government funding, they used a bibliographic analysis to allocate funding to each disease area. Given that there is a delay between receiving funding and publishing the results of that research, they tested for the different lags between funding and publication. The model that provided the best fit used a 4-year lag. That meant that, although they had data up to 2012, their final model included data only up to 2008.

Government and Charity funding

The UK Health Research Analysis (UKHRA)[12] provides an overview of health research activity across different areas of health and disease in the UK. It details the largest government and charity funders. There have been four reports, each report contains a year worth of data. The reports cover data for 2004, 2009, 2014 and 2018. We used the ten health categories from Sussex et al. (2016) to re-classify the health categories found within UKHRA (see

[12] https://hrcsonline.net/reports/analysis-reports/uk-health-research-analysis-2018

Table 2.5).

For government funding, we selected for each year of data provided those organisations classed as "Other government and public bodies". We then calculated the total funding provided by these organisations, and the proportion allocated to each disease area. In the case of charity funding, we selected the data for charities and not for profit organisations. The percentage of funding going to each health category was then calculated. For government and charity funding, the data for missing years were estimated using simple interpolation.

Private sector expenditure

Sussex et al. (2016) used a bibliographic analysis to allocate private funding to each disease area. We replicated this analysis for the year 2008 onwards. We searched in Web of Science, in the Science Citation Index Expanded and the Conference Proceedings Citation Index for Science. Sussex et al. (2016) used the address of the corresponding author to determine how many publications were UK-funded. Instead, we searched for all publication reporting the UK or any of their constituent countries as country of origin.

Table 2.5 Mapping HRCS to Sussex Disease Areas.

HRCS code	Categories in Sussex et al. (2016)
Blood	Blood
Cancer & neoplasms	Cancer
CVD	Cardiovascular diseases
Stroke	Cardiovascular diseases
Neurological	Central Nervous System
Mental health	Central Nervous System
Oral & GI	Gastroenterology
Infection	Infectious diseases
Respiratory	Respiratory
Skin	Skin
Eye	Vision
Congenital disorders	Other
Disputed aetiology & other	Other
Generic health	Other
Ear	Other
Inflammation & immunity	Other
Injuries & accidents	Other
Metabolic & Endocrine	Other
MSK	Other
Renal & Urogenital	Other
Reproductive health & child	Other

To determine the number of publications with private funding, we filtered our search by the following companies:

- AstraZeneca
- Pfizer
- Boehringer
- Janssen
- Gilead
- Eli Lily
- Schering Plough
- Bristol Myers
- Novo Nordisk
- Merck Novartis
- Abbott

- Takeda
- Amgen
- Johnson & Johnson
- Wyeth
- Roche
- Bayer

These were amongst the 100 most common private research funders between 2008 and 2020. For the disease area classification, we followed the taxonomy presented in Sussex et al. (2016) (see Table 2.6)

Table 2.6 Mapping of Sussex et al. (2016) Disease Areas to Thomson Reuters classification

Sussex et al (2016)	**Thomson Reuters JSC**
Blood	Haematology
Cancer	Oncology
Cardiovascular diseases	Cardiac and Cardiovascular systems
Central Nervous System	Neurosciences
Gastrointestinal	Gastroenterology and Hepatology
Infectious diseases	Infectious diseases
Respiratory	Respiratory system
Skin	Dermatology
Vision	Ophthalmology
Others	

We assumed that research that did not fall within the other nine categories could be classified as "other". The percentage change year-on-year obtained from this analysis was used to estimate how funding allocation changed between 2008 and 2020, using 2008 as a base year.

Global pharmaceutical sales

The annual EvaluatePharma World Preview[13] publication analyses sales across therapeutic areas. We first mapped the therapeutic areas into Sussex et al. (2016) disease categories (see Table 2.7). These data were then aggregated to produce Table 2.8.

Global pharmaceutical sales data were incomplete for two areas: gastroenterology and CNS. To complete the time series, we estimated the proportion for the other disease areas using absolute percentage change with 2012 as index year. For gastrointestinal, we modelled a time series using a moving average with 3 lags and 1 lead data point, adding one data point from global pharmaceutical R&D investment (source ABPI). For neurology, we used the remaining proportion (1-sum of all other areas) for the missing years.

[13] https://info.evaluate.com/rs/607-YGS-364/images/EvaluatePharma_World_Preview_2019.pdf

Table 2.7 Mapping of Sussex et al. (2016) Disease Areas to EvaluatePharma Therapeutic areas

Therapeutic area EvaluatePharma	Sussex et al. (2016) disease areas
Anti-coagulants	Blood
Anti-fibrinolytics	Blood
Oncology	Cancer
Anti-psychotics	Central Nervous System
Anti-hypertensives	Cardiovascular diseases
Anti-hyperlipidaemic	Cardiovascular diseases
Antacid/ulcer	Gastrointestinal
Anti-bacterial	Infectious diseases
Anti-viral	Infectious diseases
Immunosuppressants	Infectious diseases
Vaccines	Infectious diseases
Bronchodilators	Respiratory
Dermatological	Skin
Sensory Organs	Vision represents 70%
Anti-diabetics	Other
Anti-rheumatics	Other
Antianemia	Other
Bone calcium regulators	Other
MS therapies	Other
Sera & gamma globulins	Other
Others	Other

Table 2.8 Trends in global sales by disease area from 2012 up to 2018

	2012	2013	2014	2015	2016	2017	2018
Blood	2.4%	2.7%	1.5%	2.9%	2.9%	3.5%	3.8%
Central Nervous System	0.0%	1.8%	1.6%	0.0%	0.0%	0.0%	0.0%
Cardiovascular diseases	8.2%	7.1%	6.2%	5.3%	5.3%	4.2%	3.7%
Cancer	9.1%	9.7%	10.1%	10.7%	10.7%	12.6%	14.3%
Gastrointestinal	0.0%	1.7%	1.5%	0.0%	0.0%	0.0%	0.0%
Infectious diseases	8.9%	10.1%	10.6%	12.8%	12.8%	10.2%	9.6%
Skin	1.8%	1.8%	1.6%	1.6%	1.6%	1.6%	1.8%
Respiratory	4.6%	4.3%	4.2%	3.9%	3.9%	3.3%	3.2%
Vision	2.1%	2.3%	2.4%	2.6%	2.6%	2.6%	2.6%
Other	63.0%	58.5%	60.3%	60.2%	60.2%	62.0%	61.0%

Data Limitations

The key limitation is assuming straight line changes in expenditure by disease area for each organisation over the years between HRA analyses (2018, 2014 and 2009). However, more detailed data from Wellcome suggest the changes between years are relatively minor and, therefore, the spend by disease area is reasonably constant.

2.3.3 Vector error correction model (VECM)

Several assumptions need to be met before a VECM can be fitted. The first assumption is that data is non-stationary, which is verified using an Augmented Dickey Fuller (ADF) unit root test. This test was applied to all the time series (i.e. public and private funding and global sales). The ADF test is applied to the levels and first differences, with and without taking logarithms, of all variables. In the finally chosen VECM we use variables in log form, which allows estimated coefficients to be interpreted as elasticities. In the best-fit model, government expenditure and charity sector expenditure are combined into a single measure of public expenditure.

Model

The VECM treats all variables as endogenous. The model details are chosen by a specification search. First, the number (0, 1 or 2) of cointegration relationships (long-term equilibrium relations) between public sector research expenditure, private sector R&D expenditure and global pharmaceutical sales is determined. Second, the number of time lags needed to properly account for the short-term movements of each of the three variables is determined. Third, the presence or absence of a deterministic trend for both the long-term and short-term effects must be decided. Since the cointegration test outcomes are in general affected by the number of lags included for the short-term effect and specification of the deterministic trend, the three model features must be determined simultaneously.

The model was estimated with one, two, or three lags in the short-term dynamics. For each short-term specification, we tested four deterministic trends:

1. No intercept or trend in the cointegration equation (CE) and the vector autoregression (VAR)
2. No trend in the CE or the VAR, but there is an intercept in the CE.
3. Intercept in the CE and both an intercept and a trend in the VAR.
4. Trend and intercept in the CE, and an intercept but no trend in the VAR.

After estimating the twelve options, we used the Pantula principle to select the preferred model. The selection accounts for the number of cointegration relationships, autocorrelation of the VECM residuals, number of insignificant coefficients in the VECM and statistics that measure the relative quality of models (Akaike Information Criterion, Schwarz Criterion and log likelihood ratios). Our chosen model yielded an implausible coefficient; therefore, we explored potential causes behind that result.

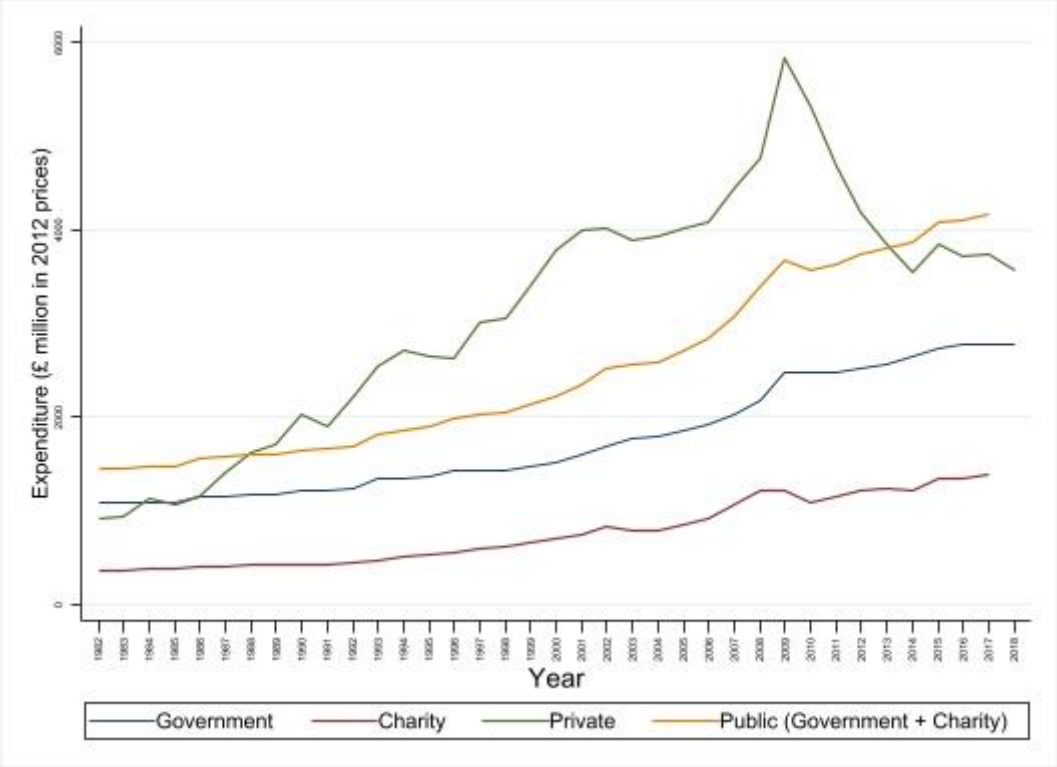
Given that we used several assumptions to allocate funding to each disease area, we re-ran the models excluding those disease areas where we thought the reliability of the data was lower. We used the same principles outlined above to choose the best fit model.

2.4 Results

2.4.1 Government, charity and private expenditure in biomedical research

Total expenditure in biomedical research from public, charity and private sectors between 1982 and 2018 is shown in Figure 2.1. There has been a gradual increase in public expenditure from £1.09bn in 1982 to £2.78bn in 2017. Between 2008 and 2011, there was a decrease in charity expenditure from £1.22bn to £1.09bn, probably associated with the economic downturn. A sharper reduction in R&D expenditure is observed for private investment, which went from £4.78bn to £3.56bn between 2008 and 2014. Part of this decrease is explained by Pfizer closing their R&D operations in Sandwich, East Kent, in 2011.

Figure 2.1 Total UK research and development expenditure (government, charity, and private), 1982-2018, in constant 2012 prices



2.4.2 Public and private expenditure by disease areas

Public and private expenditure by disease area between 1982 and 2018 is shown in Figure 2.2 and Figure 2.3, expressed in their logarithmic form, which is how they are entered into the model. Overall,

public expenditure had an upward trend up to 2008 for all disease areas, but then it started falling for blood, skin and respiratory conditions. In the case of private funding, the trends are more erratic, but tend to go upward up to 2005. For cancer and central nervous system diseases expenditure stagnated after 2008, and now it is falling slightly. For gastrointestinal, vision and infectious diseases, funding is decreasing. For example, in 2008 infectious diseases received £218.5m while in 2017, £64.9m were allocated to that area of research. Gastrointestinal and vision have a much sharper decrease in funding after 2013.

2.4.3 Global pharmaceutical sales

Global pharmaceutical sales between 1982 and 2018 by disease areas are shown in Figure 2.4. Overall, the expenditure patterns in the figure reveal an upward trend in global medicine sales in all the disease areas. However, looking at specific disease areas we observe some variation. For instance, in 'Blood', there is a decrease in sales from 1988 to 1989, followed by a steady upward trend thereafter. The 'Cancer' medicines global sales series somewhat interrupts in 1993, with a decrease in sales between 1993 and 1994, but is followed by a steady increase thereafter. Interestingly, the global pharmaceutical sales series shows a particularly strong rise in sales starting in 1999 in most disease areas. Around 2010, global sales seem to be decreasing in areas such as neurological, cardiovascular and respiratory diseases.

Figure 2.2 Public (government and charity) research and development (log) expenditure by disease area, 1982-2018, in constant 2012 prices

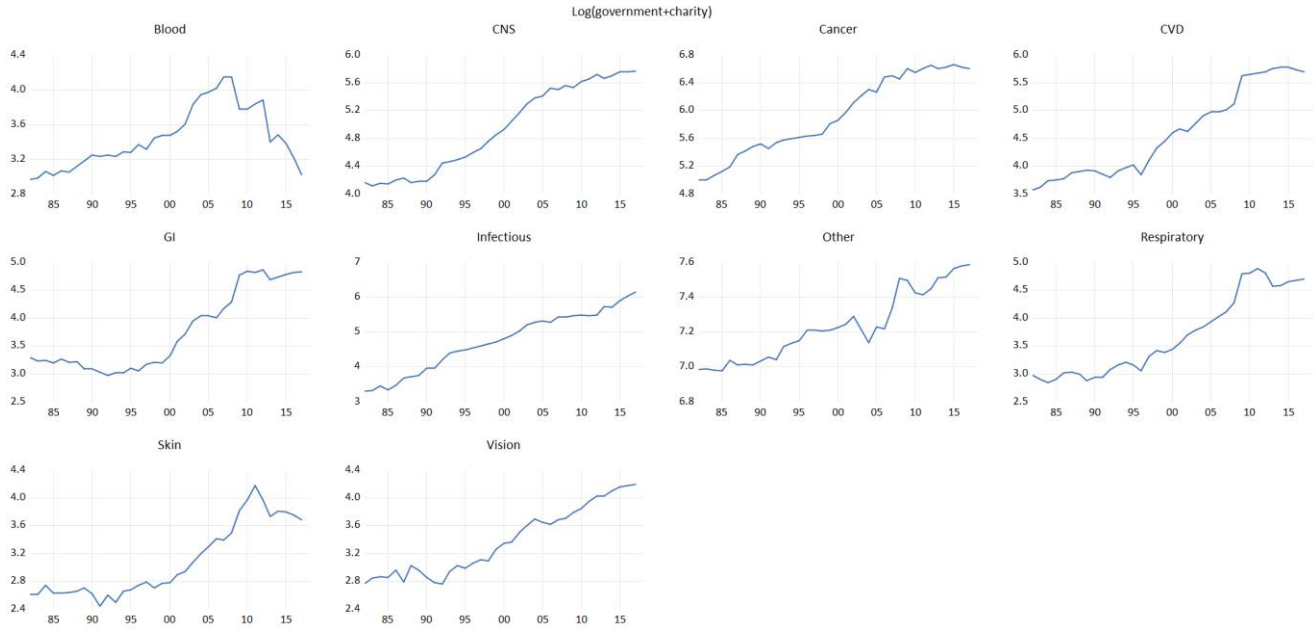
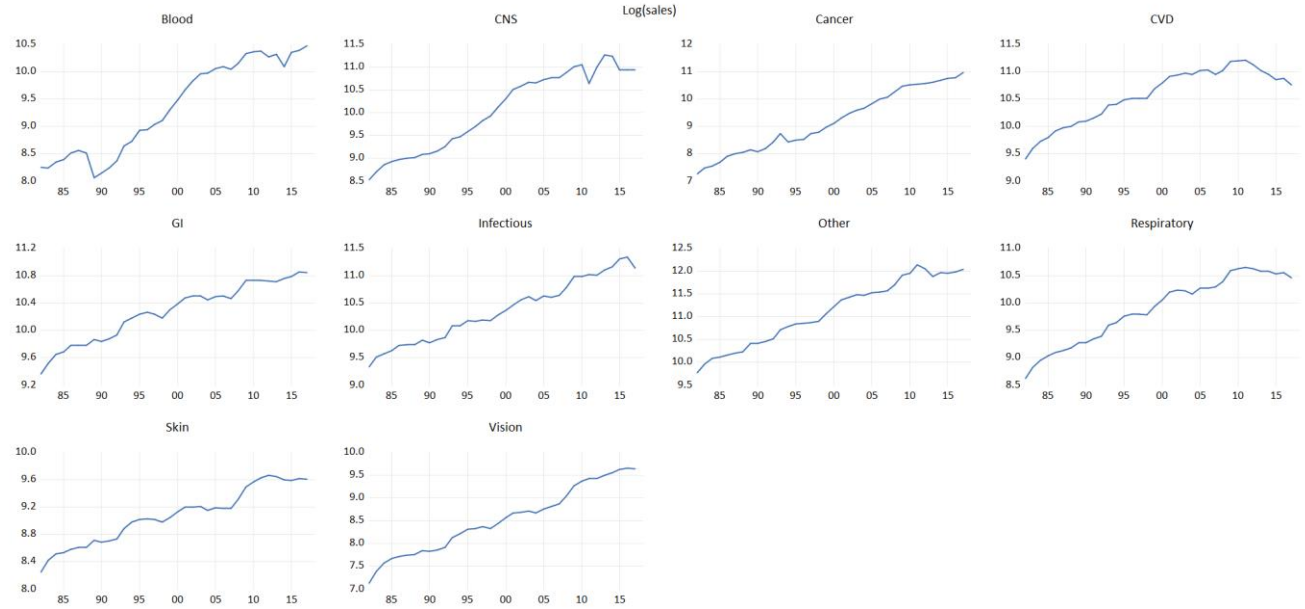


Figure 2.3 Private research and development (log) expenditure by disease area, 1982-2018, in constant 2012 prices

Figure 2.4 Global pharmaceutical (log) sales by disease area, 1982-2018, in constant 2012 prices



2.4.4 Econometric modelling

After testing several model specifications (see Appendix A2), the best fit model was the one excluding data from haematological conditions. Therefore, our final model includes nine disease areas. Overall, our results suggest that there is a statistically significant complementary relationship between public

and private pharmaceutical expenditure in biomedical research. A 1 % increase in public sector expenditure is associated with a 0.75% increase in private sector expenditure (see Table 2.9), which is of a similar order of magnitude to that proposed by Sussex (2016).

The results suggest that there is one cointegration relationship between the three variables. In the long run, public sector expenditure and private sector expenditure are complements.

Table 2.9 Estimations from the best fit VECM model

Cointegrating Equation	Cointegration equation 1		
LNPRIVATE(-1)	1		
LNPUBLIC(-1)	-0.75		
	-0.15		
	-5.02		
LNSALE(-1)	0.54		
	-0.23		
	2.31		
Intercept	-7.03		
Error Correction:	D(LNPRIVATE)	D(LNPUBLIC)	D(LNSALE)
Cointegration equation 1	-0.17	0.02	-0.01
	(0.03)	(0.01)	(0.01)
	-5.24	1.75	-0.92
D(LNPRIVATE(-1))	-0.26	-0.01	0.03
	(0.06)	(0.02)	(0.02)
	-4.19	-0.58	1.75
D(LNPRIVATE(-2))	-0.21	0.02	0.01
	(0.06)	(0.02)	(0.02)
	-3.36	1.18	0.61
D(LNPRIVATE(-3))	-0.06	0.004	0.02
	(0.06)	(0.02)	(0.02)
	-1.12	-0.23	1.43
D(LNPUBLIC(-1))	0.30	0.06	0.01
	(0.20)	(0.06)	(0.05)
	1.50	0.94	0.28
D(LNPUBLIC(-2))	0.15	-0.01	0.08
	(0.20)	(0.06)	(0.05)
	0.75	-0.12	1.49
D(LNPUBLIC(-3))	-0.01	-0.03	-0.05
	(0.20)	(0.06)	(0.05)
	-0.07	-0.51	-0.88
D(LNSALE(-1))	0.34	0.10	0.06
	(0.23)	(0.07)	(0.06)
	1.45	1.35	1.02

D(LNSALE(-2))	0.08	0.03	-0.11
	(0.24)	(0.07)	(0.06)
	0.32	0.43	-1.75
D(LNSALE(-3))	-0.36	-0.06	-0.17
	(0.23)	(0.07)	(0.06)
	-1.54	-0.88	-2.79
Error Correction:	D(LNPRIVATE)	D(LNPUBLIC)	D(LNSALE)
Intercept	0.21	0.02	0.08
	(0.05)	(0.02)	(0.01)
	4.25	1.56	5.87
Gastrointestinal*2013	-0.32	-0.07	0.00
	(0.17)	(0.05)	(0.05)
	-1.84	-1.37	-0.09
Vision*2013	-0.39	-0.02	-0.01
	(0.17)	(0.05)	(0.05)
	-2.30	-0.41	-0.15
Cancer	-0.27	0.03	0.03
	(0.09)	(0.03)	(0.02)
	-3.22	1.16	1.54
CVD	-0.18	0.04	-0.03
	(0.07)	(0.02)	(0.02)
	-2.51	1.68	-1.78
Gastrointestinal	-0.06	0.03	-0.03
	(0.07)	(0.02)	(0.02)
	-0.87	1.22	-1.57
Infectious	-0.24	0.06	-0.01
	(0.07)	(0.02)	(0.02)
	-3.27	2.55	-0.70
Skin	-0.15	0.01	-0.04
	(0.07)	(0.02)	(0.02)
	-2.05	0.57	-1.94
Vision	-0.46	0.05	-0.02
	(0.12)	(0.04)	(0.03)
	-4.00	1.40	-0.51
R-squared	0.24	0.07	0.12
Adj. R-squared	0.18	0.01	0.06
Sum sq. resids	25.82	2.47	1.83
S.E. equation	0.32	0.10	0.08
F-statistic	4.46	1.10	1.91
Log likelihood	-63.87	263.47	305.71
IC	0.59	-1.75	-2.06
Schwarz SC	0.84	-1.51	-1.81
Mean dependent	0.04	0.05	0.06
S.D. dependent	0.35	0.10	0.09

Determinant resid covariance (dof adj.)	6.15E-06
Determinant resid covariance	4.98E-06
Log likelihood	515.71
Akaike information criterion	-3.27
Schwarz criterion	-2.49

These findings were, however, extremely sensitive to inclusion or exclusion of different disease areas, and many of the model specifications had serial correlation problems. The range of elasticity coefficients found by Sussex (2016) was 0.68 to 1.07, while the range of estimates from our model search was 0.38 to 1.64. The results for this model estimating a separate long-term relationship for government and charity funding with private R&D are reported in Table 2.10. The results suggest that in the long term, a 1% increase in government expenditure is associated with 0.68% increase in private R&D investment. In the case of charity funding, a 1% increase in charity funding is associated with a non-significant increase of 0.09% of private R&D expenditure. If government and charity funding remained in fixed proportions in the long run, the two elasticities would sum to 0.75, which is the case in our model.

Table 2.10 Estimations from the best fit VECM model entering government and charity expenditure separately

Cointegrating Equation	Cointegration equation 1			
LNPRIVATE(-1)	1			
LNGOVERNMENT(-1)	-0.68			
	-0.14			
	-4.86			
LNCHARITY(-1)	-0.09			
	-0.09			
	-0.96			
LNSALE(-1)	0.47			
	-0.23			
	2.02			
Intercept	-6.63			
Error Correction:	D(LNPRIVATE)	D(LNGOVERNMENT)	D(LNCHARITY)	D(LNSALE)
Cointegration equation 1	-0.16	0.03	0.14	-0.004
	(-0.04)	(0.01)	(0.06)	(0.01)
	-4.54	2.49	2.48	-0.44
D(LNPRIVATE(-1))	-0.25	-0.01	-0.13	0.03
	(-0.06)	(0.02)	(0.10)	(0.02)
	-3.93	-0.47	-1.32	1.96
D(LNPRIVATE(-2))	-0.19	0.01	0.003	0.02
	(-0.06)	(0.02)	(0.10)	(0.02)
	-2.99	0.59	0.03	0.94
D(LNPRIVATE(-3))	-0.04	-0.002	0.02	0.03

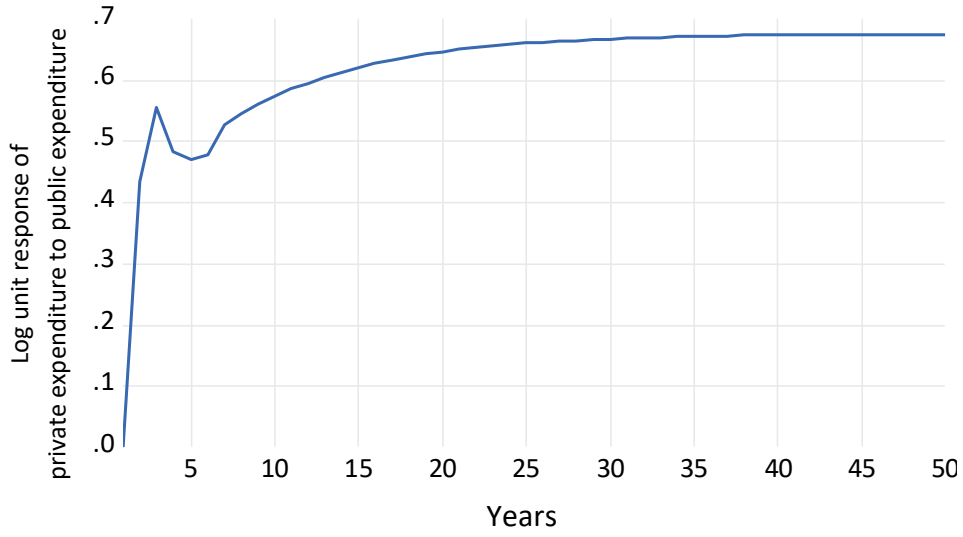
	(-0.06)	(0.02)	(0.09)	(0.02)
	-0.70	-0.09	0.20	1.81
D(LNGOVERNMENT(-1))	0.16	0.01	-0.10	-0.05
	(-0.18)	(0.06)	(0.27)	(0.05)
	0.91	0.08	-0.35	-1.08
Error Correction:	D(LNPRIVATE)	D(LNGOVERNMENT)	D(LNCHARITY)	D(LNSALE)
D(LNGOVERNMENT(-2))	0.01	0.004	-0.25	0.01
	(-0.18)	(0.06)	(0.27)	(0.05)
	0.04	0.06	-0.92	0.28
D(LNGOVERNMENT(-3))	-0.17	-0.01	-0.47	-0.07
	(-0.18)	(0.06)	(0.27)	(0.05)
	-0.95	-0.14	-1.72	-1.50
D(LNCHARITY(-1))	0.01	0.001	-0.02	0.02
	(-0.04)	(0.01)	(0.06)	(0.01)
	0.27	0.11	-0.35	1.67
D(LNCHARITY(-2))	0.03	-0.01	-0.003	0.02
	(-0.04)	(0.01)	(0.06)	(0.01)
	0.71	-0.44	-0.05	1.86
D(LNCHARITY(-3))	0.01	0.01	-0.23	0.01
	(-0.04)	(0.01)	(0.06)	(0.01)
	0.32	0.86	-3.82	0.95
D(LNSALE(-1))	0.32	0.14	-0.01	0.06
	(-0.24)	(0.09)	(0.37)	(0.06)
	1.33	1.58	-0.02	0.94
D(LNSALE(-2))	0.07	-0.11	0.55	-0.11
	(-0.25)	(0.09)	(0.38)	(0.06)
	0.28	-1.25	1.44	-1.69
D(LNSALE(-3))	-0.28	-0.02	-0.20	-0.17
	(-0.24)	(0.09)	(0.37)	(0.06)
	-1.19	-0.26	-0.54	-2.70
Intercept	0.19	0.02	0.03	0.07
	(-0.05)	(0.02)	(0.07)	(0.01)
	3.87	0.98	0.38	5.88
Cancer	-0.15	0.04	0.07	0.05
	(-0.08)	(0.03)	(0.12)	(0.02)
	-1.94	1.43	0.63	2.39
CVD	-0.14	0.04	0.12	-0.03
	(-0.07)	(0.03)	(0.11)	(0.02)
	-1.96	1.51	1.06	-1.42
Gastrointestinal	-0.05	0.03	0.07	-0.03
	(-0.07)	(0.03)	(0.11)	(0.02)
	-0.65	1.07	0.62	-1.37
Infectious	-0.22	0.06	0.23	-0.01

	(-0.08)	(0.03)	(0.12)	(0.02)
	-2.87	2.26	1.95	-0.43
Error Correction:	D(LNPRIVATE)	D(LNGOVERNMENT)	D(LNCHARITY)	D(LNSALE)
Skin	-0.12	0.02	0.13	-0.03
	(-0.07)	(0.03)	(0.11)	(0.02)
	-1.59	0.78	1.12	-1.81
Vision	-0.41	0.08	0.42	-0.01
	(-0.12)	(0.04)	(0.18)	(0.03)
	-3.49	1.85	2.31	-0.24
Gastrointestinal*2013	-0.34	-0.003	-0.48	0.01
	(-0.17)	(0.06)	(0.27)	(0.05)
	-1.92	-0.06	-1.76	0.23
Vision*2013	-0.41	-0.01	-0.24	-0.001
	(-0.17)	(0.06)	(0.27)	(0.05)
	-2.34	-0.09	-0.90	-0.01
R-squared	0.22	0.06	0.10	0.14
Adj. R-squared	0.16	-0.01	0.03	0.07
Sum sq. resids	26.24	3.42	62.83	1.77
S.E. equation	0.32	0.12	0.49	0.08
F-statistic	3.52	0.83	1.35	2.03
Log likelihood	-66.13	218.05	-187.93	309.79
IC	0.63	-1.41	1.50	-2.06
Schwarz SC	0.92	-1.12	1.79	-1.78
Mean dependent	0.04	0.05	0.09	0.06
S.D. dependent	0.35	0.11	0.50	0.09
Determinant resid covariance (dof adj.)		2.03E-06		
Determinant resid covariance		1.46E-06		
Log likelihood		290.55		
Akaike information criterion		-1.42		
Schwarz criterion		-0.22		

2.4.5 Impulse response function

Figure 2.5 shows that more than half of the response from private sector investment in R&D as the result of a long-run shock to public sector expenditure will happen within the first five years. One unit increase in the log public sector expenditure leads to 0.44 unit increase in the log private sector expenditure in R&D within the first five years. In the long run it will reach 0.68 unit increase in the log private sector expenditure.

Figure 2.5 Impulse response of an increase of public research expenditure on private sector R&D investment.



2.4.6 Economic rate of return implied by the model

Sussex (2016) used the results from their model, together with assuming a 50% social rate of return (RoR), to estimate that the economic RoR (excluding health gains to patients) to public biomedical and health research was 17% (real, per annum). Using the same methodology but applying the latest estimates of public and private sector investment in such research and the 0.75% relationship between public sector funding and the resulting private sector funds (Table 2.9) we find the RoR remains 17%.

2.5 Discussion

Sussex et al. (2016) are extremely open about the limitations of the extent and quality of the data that underpins their model, particularly the use of publications as a proxy for disease area, which is far from perfect. The authors were also concerned about the small number of observations (less than 30 years, which is relatively short for a VECM analysis). Additionally, there were concerns about pooling heterogeneous data from different sources and different disease areas. All of these limitations are also pertinent to our analysis, but we have further concerns. We were not always able to replicate the time series data exactly, and some of our data, despite best efforts to match or approximate the earlier information, appeared inconsistent with that in Sussex et al. (2016). Our models were more prone to serial correlation and more sensitive to changes in specification and variables included. One potential explanation is that trends were more heterogeneous after 2008, which might be related to the economic crisis, Pfizer closing operations in Sandwich in 2011, and differing responses from research funders. As Figure 2.2 shows, private investment in R&D declined steadily between 2008 and 2013; while government funding kept increasing and charity funding dropped slightly between 2008 and 2010. For a VECM model, this means that the long-term equilibrium after 2008 does not hold.

To address these issues, we added variables to the model that allow for separate short-term dynamics for some disease areas with trends departing from the average trend. We also added terms to account for the dramatic decrease in funding for gastrointestinal and vision conditions after 2013. One caveat of adding more variables into the model is that more coefficients make the model erratic and unstable. This impacts on the ability to find a significant relationship between charity and private funding once government and charity expenditures are entered separately. Despite all these issues, however, our estimates are of the same order of magnitude as those reported by Sussex et al. (2016).

3 Economic Value of Health Benefits from Medical Research

3.1 Summary

Existing estimates of the internal rates of return (IRRs) measuring the value of health gains associated with UK investment in medical research range from 7% to 10%. These values have been updated by adopting a value of £60,000 per quality adjusted life year (QALY), in line with the HM Treasury Green Book (2018). The resulting mean IRR is 16%, ranging from 13% for musculoskeletal (MSK) therapies to 17.5% for cancer drugs.

3.2 Background

Several studies (Glover, 2014 and 2018; HERG, 2008) have estimated the economic returns generated by public and charitable investment in UK medical research, using four diseases as exemplars: MSK, cancer, mental health and cardiovascular diseases (CVD).

In 2018, Wellcome, NIHR, The Academy of Medical Sciences, Medical Research Council (MRC) and Arthritis Research UK published a report synthesising the findings from the individual studies for each disease area, setting out the underlying assumptions, methodology and the costs and benefits for each disease (Wellcome, 2018).

These studies all valued a QALY at £25,000, being the mid-point of the 'threshold range' used by the National Institute for Health and Care Excellence (NICE). The NICE threshold is a measure of what the NHS is willing to pay for a QALY generated by innovative technologies. Claxton and colleagues have argued that the NICE threshold is considerably higher than the average cost of a QALY in the NHS, which they estimate to be £13,000. For this project, however, both of these estimated values of a QALY are arguably inappropriate. Rather the relevant value is society's willingness to pay for a QALY. Government estimates of this willingness to pay (drawing on survey-based estimates of public willingness to pay to avoid road traffic accidents) implies a societal valuation of £60,000 per QALY, as advised in the Green Book. (HM Treasury, 2018).

We therefore re-calculated the existing internal rates of return (IRRs) for health gains by adopting a value of £60,000 per quality adjusted life year (QALY) in line with the Treasury Green Book (2018), assuming these IRRs apply across all health care investments, irrespective of disease area.

3.3 Methodology

The gross values of the QALYs and other inputs to the IRR calculations were extracted from the individual studies (Glover, 2014 and 2018; HERG, 2008). The value of the gross QALY benefit was uprated using £60,000 per QALY. For each disease area, the costs to the NHS of delivering the associated interventions were deducted from the uprated QALY benefits to give a net benefit to the NHS. The same assumptions as those used in the original studies were made about research costs, attribution of benefit to UK patients and time lags, and updated IRRs calculated.

The original and uprated IRRs are shown in Table 3.1. The IRRs range from 12.9% for MSK treatments to 17.5% for cancer drugs. Using the average UK annual research investment values which informed the calculations to weight the relative impact of each disease, gives a mean IRR of 16.0%. The impact of the change varies slightly across the disease areas because of the different inputs, particularly the ratio of NHS costs to QALY gains.

Table 3.1: Original and uprated IRRs by disease

Disease area	MSK	Cancer	Mental health	CVD
Original IRR	6.8%	10.1%	7.0%	9.2%
Updated IRR	12.9%	17.5%	14.8%	15.7%
% change	+90%	+73%	+112%	+70%

In addition, each study added a value for the return from spillover [14] associated with the original public sector research. The most recent calculation estimated a rate of return from spillover of 15% to 18% (Sussex, 2016). This project takes a different approach to measuring the gain in national income by using a multiplier approach. The sum of the IRRs from the health gains and from national income are added to give the total economic benefit of medical research. This work is reported in Section 4.

This method builds on existing values, which were calculated using a detailed bottom-up approach. Updating the inputs and extending the existing analyses to other disease areas were beyond the scope of this project.

[14] Spillover is a measure of the gain to other organisations from investment in medical research by one organisation; the other organisations may be other organisations in the medical sector, in other sectors, public and private sector and also in other countries. These benefits should be measured as they contribute to the total social rate of return from investment.

The main limitations are we could not update the costs and benefits parameter values for more recent interventions in each disease area, or extend the coverage beyond the four disease areas. Moreover, we retained the same time lags between the conduct of the research and the implementation of the technology into NHS practice as used in the original calculations. These were 12 years for new mental health interventions, 15 years for cancer drugs, 16 years for MSK and 17 years for CVD interventions. The IRRs are sensitive to the assumed time lags. This topic is explored in Section 6.

3.4 Conclusion

The monetary value of the improved health (QALYs generated) derived from UK investment in medical research is estimated as an internal rate of return of 16% per year, ranging from 12.9% for MSK therapies to 17.5% for cancer drugs.

4 Impact of NIHR Funded Research on Employees, Staff Costs and National Output

4.1 Summary

Applying Office of National Statistics (ONS) multipliers suggests that, since their inception, NIHR funding has enabled the BRCs and BRUs to generate:

- Direct output with a value of £1.14bn, together with indirect outputs, (as measured by type 1 input-output multipliers), equivalent to £0.65bn, giving a total economic impact of £1.79bn.
- Gross value added (GVA)[15] of £0.98bn, together with associated indirect GVA of £0.57bn, giving a total GVA impact of £1.55bn.
- Payments to their staff of £0.98bn, together with associated indirect employee payments of £0.49bn, giving a boost to earnings across the economy of £1.47bn.
- Directly employed over 7,400 full-time equivalent (FTE) years of employment which generated employment opportunities for a further 5,788 FTEs, giving 13,190 FTE years of employment.

Applying the relevant type 1 multiplier suggested additional indirect national economic output associated with NIHR funding for BRCs/BRUs averaged about £0.57 for each £1 invested. The combined IRR, summing the economic and health gains from the NIHR investment, is 58%. This is well in excess of the annual discount rate set by HM Treasury of 3.5% in real terms.

Applying the same type 1 multiplier to the total funding received by BRCs and BRUs indicates they generated a total output valued at £7,861m, together with indirect outputs equivalent to £4,473m, giving a total economic impact of £12,334m.

There are several limitations including data for the early periods following the establishment of the BRCs and the 'black box' nature of the multiplier value.

4.2 Background

Health gain, however measured and valued, is not the only economic return on investment in medical research. The local economies of each BRC, as well as the overall UK economy, benefit from government investment, through employment, earnings and spending power and wider increases in economic output, generally referred to as a multiplier effect.

[15] Gross value added is a measure of the goods and services produced in a sector and is the total of wages & salaries, dividends, savings (profits, depreciation), and indirect taxes. In this case it is output less the value of bought in goods and services.

In order to estimate gains to the local and national economy that result indirectly from NIHR funding of the BRCs and BRUs, we use ONS multipliers for employment, gross value added (GVA) and output to estimate the value of the medical research at national level.

In this section we seek to quantify the economic value to the national economy from the NIHR funded clinical research activity delivered by BRCs and BRUs, focusing on the direct and indirect economic effects of this funding. A combined internal rate of return (IRR) is also calculated by adding the internal rate of return from net health benefits (Section 3). Finally, we estimate the direct and indirect impact of the total funding received by BRCs and BRUs.

Limited regional analyses of FTEs, staff costs per employee and funding were also carried out. The analyses were undertaken to check the internal validity of the data, with the lower granulation affording the opportunity to spot data gaps or inconsistencies.

4.3 Methodology

The economic contribution associated with NIHR funding is measured in terms of increased output, GVA and employment (salaries and full-time equivalents FTEs). Multipliers which apply to each measure are calculated and published by the ONS.[16]

This methodology has been checked to ensure it is consistent with the Green Book requirements. The Green Book (HM Treasury, 2018) notes that the multiplier effects '*are likely to have limited additionality and the effects are generally already accounted for at a macro level by aggregate decisions to spend at a particular leve*l.' Adding '*With robust, objective evidence supply chain effects may be used for local level analysis (see Annex 3 for the approach to local level effects in distributional analysis)*.'

To align with this requirement, we judged there was evidence of a supply chain impact from the cited literature, particularly the Annex to chapter six of HERG (2008). However, to be consistent with the Green Book we excluded any benefit from induced effects and hence did not apply type 2 multipliers.

The most recent values for each multiplier were obtained from ONS 2015 Detailed Input-Output Analytical Tables (multipliers and effects (product)[17] for code 72n being 'Non-profit scientific research and development services'. Multipliers for this industry group are not produced annually, with the most recent data being for 2015.[18] Earlier values of the sector's multipliers were published in 2014, 2013 and 2010. Their values, and the years these were applied to the direct impact are shown in Table 4.1.

[16] https://www.ons.gov.uk/economy/nationalaccounts/supplyandusetables/datasets/ukinputoutputanalyticaltablesdetailed

[17] https://www.ons.gov.uk/releases/ukinputoutputanalyticaltables2015detailed

[18] The 2015 data were published in April 2019, with no information on the next release date.

Each output multiplier was applied to the relevant annual NIHR funding to BRCs and BRUs, (assuming NIHR funds were spent within the year received) in accordance with the last column of Table 4.1. The GVA multiplier was applied to the estimated direct GVA created by the BRCs/BRUs as a consequence of the funding. The employment effects multiplier was applied to the estimated direct employment costs[19] for the BRCs/BRUs. The employment multiplier (impact on full time equivalent employees FTEs) was applied to the estimated direct FTEs employed by the BRCs/BRUs.

Table 4.1 Value of multipliers

Values for	Output	GVA	Employment costs	FTEs	Applied to direct impact in years:
2015	1.575	1.547	1.569	1.96	2015 and later years
2014	1.615	1.607	1.753	1.93	2014
2013	1.406	1.320	1.430	1.66	FTEs 2007 to 2013; others 2013
2010	1.675	1.801	1.41	N/A	From 2007 to 2013
Mean (a)	1.569	1.580	1.497	1.782	

(a) Mean is shown for information only.

Using these multipliers is straightforward. For example, if 300 FTE staff are employed directly by the BRCs/BRUs using NIHR funding, then applying the employment multiplier of 1.96 (300*1.96) gives 588 direct and indirect FTE jobs created. Subtracting the initial direct job increase (300) gives the additional indirect number of jobs supported throughout the economy of 288 FTEs.

The data used to estimate staff numbers, costs, GVA and output for the BRCs and BRUs are now considered. Analysis by region (Cambridge, London, Oxford and other) are provided in Appendix A4. These areas were chosen to identify the uneven geographic distribution. The lower level data were also helpful to quality assure the data.

4.4 Data from the Annual Reports for 2007/08 to 2018/19 for BRCs and BRUs

The NIHR Programme Manager provided summaries of published data and copies of the annual reports for each BRU and BRC. These included for each BRC and BRU, annual data on:

- Employees (from 2012/13 onwards).
- Salaries and other revenue costs.
- External funding including funding from NIHR.

We also received a copy of NIHR's Guidance to BRCs on completing the annual returns.

[19] The relevant employment costs are total compensation related costs including pension and national insurance. It was assumed this definition is consistent with the basis reported by the BRCs/BRUs to NIHR

These data were cleaned, any inconsistencies checked and verified where possible using additional data provided by NIHR colleagues. The resulting values for each parameter are now presented.

4.5 Number of Employees: 2013/14 to 2018/19

The data from DHSC provided numbers of FTEs by centre from 2012/13. The data from 2012/13 could not be used as no number of FTEs were entered and only descriptive analyses of the post and staff type were provided for all records. In later years, several hundred records recorded 'null' values for the number of FTEs. The use of this entry reduced over time (e.g. from 557 records in 2013/14 to under 20 by 2017/18). We set these records to equal the mean value of FTEs recorded across all the records with the FTE field completed. The mean number of employees per completed record with FTEs recorded was 0.17. In the early years centres also recorded values of '0.0' against some records, with 57 such records in 2013/14, falling to 10 in 2017/18. These values were retained as the value may be correct in that the FTE input was less than 0.05 but do suggest under-recording in earlier years and hence there is uncertainty about trend analyses.

The amended dataset was used to analyse the FTEs by region (Cambridge, London, Oxford and other) and by staff group.

Table 4.2 provides the estimated total number of employees by region. Of note, the total number of FTEs across the BRCs reduced by almost 50% between 2013/14 and 2014/15. Some of the gap is accounted for by the failure of Oxford BRC to record any FTEs. [20] But even adding in say 100 for that BRC still suggests a 40% drop in FTEs from 657 to under 400. In 2017 the number of FTEs recorded at BRCs increased by 185 (40%), with some of the increase possibly being accounted for by the demise of BRUs. The 2014/15 data are definitely incomplete which confirms concerns about data quality.

The regional analysis for BRCs shows a dynamic picture, with London accounting for 75% (495) of FTEs in 2013/14, falling to 36% (243) in 2018/19, averaging 57% over the 6 years. FTEs outside Oxford, Cambridge and London rose from 4% (29 FTEs) to 28% (190 FTEs) by 2018/19, but only accounted for an average of 14% of FTE over the period. Cambridge's share of FTEs ranged from 6% in 2013/14 to 19% the following year (but its absolute numbers were more stable with 42 increasing to 56), averaging 11% over the 6 years. FTEs at Oxford were stable around 100 (except 2014/15) for the first few years, before increasing to 149, giving it an average of 18% of all FTEs.

The numbers of reported FTEs at the BRUs declined steadily from 161 in 2013/14 to 116 in 2016/17. The majority of staff, averaging 68% over the 4 years were deployed outside the Oxford, Cambridge and London region.

Table 4.2 Estimated FTEs by year and centre

Year	BRC									BRU									Grand Total	
	Cambridge		London		Other		Oxford		BRC Total	Cambridge		London		Other		Oxford		BRU Total		
	No	%	No	%	No	%	No	%	No	No	%	No	%	No	%	No	%	No	No	% change pa
2013/14	42	6%	495	75%	29	4%	91	14%	657	0	0%	40	25%	102	63%	19	12%	161	818	
2014/15	56	19%	213	74%	20	7%		0%	289	0	0%	17	12%	117	81%	11	8%	145	434	-47%
2015/16	55	11%	300	61%	27	6%	108	22%	490	1	1%	28	24%	76	64%	13	11%	118	608	40%
2016/17	62	13%	267	58%	30	6%	105	23%	464	1	1%	28	24%	76	66%	11	9%	116	580	-5%
2017/18	58	9%	316	49%	159	24%	116	18%	649										649	12%
2018/19	86	13%	243	36%	190	28%	149	22%	668										668	3%
Total	359	11%	1,834	57%	455	14%	569	18%	3,217	3	1%	114	21%	370	68%	54	10%	541	3,757	

Note rounding affects totals

4.6 Number of Employees: 2007/08 to 2012/13

NIHR had no data on FTEs before 2013/14 but had total salary costs for these years. Hence we were able to estimate the number of FTEs for the first five years using the following methodology:

a. Calculate the average staff costs per employee in 2013/14, using the salary information shown in Table 4.5 and the staff numbers from Table 4.2.
b. Reduce the average staff costs per employee in each year prior to 2013/14 by ONS earnings data.[21]
c. Divide the annual salary information by the calculated annual average staff costs.

The resulting estimates total are provided at Table 4.3.

Data quality issues are flagged up by some of the values and some values look wrong. For example, average 2013/14 salaries per employee varied across BRCs, ranging from £251,308 at Cambridge, £158,717 at Oxford, £98,374 in London and £114,675 at the other centres. The equivalent figures for BRUs are £85,825 at London, £56,846 at Oxford and £81,507 at the other centres. Cambridge BRU only recorded 0.06 FTE, with salaries of £723,280. Given concerns about data quality no attempt is made to allocate the staff numbers estimated for 2007/08 to 2012/13 across centres. The differences may arise because different centres have adopted different approaches to overheads within their charge-out rates. However, given these issues the estimates of FTEs, salaries and GVA are subject to material uncertainty.

Table 4.3 Estimated FTEs 2007/08 to 2012/3

	BRCs	BRUs	Total
2007/8	226		
2008/9	491	36	**527**
2009/10	577	105	**683**
2010/11	594	141	**735**
2011/12	521	133	**653**
2012/13	540	129	**668**
Total	**2,948**	**544**	**3,492**

Note rounding applied impacting on totals

4.7 Analysis by Staff Group

Table 4.4 and Figure 4.1 provides an analysis by staff group, by year for the period from 2013/14. These analyses are not available for earlier years.

[21] EARN02 Average Weekly Earnings - Decomposition (Public Sector)

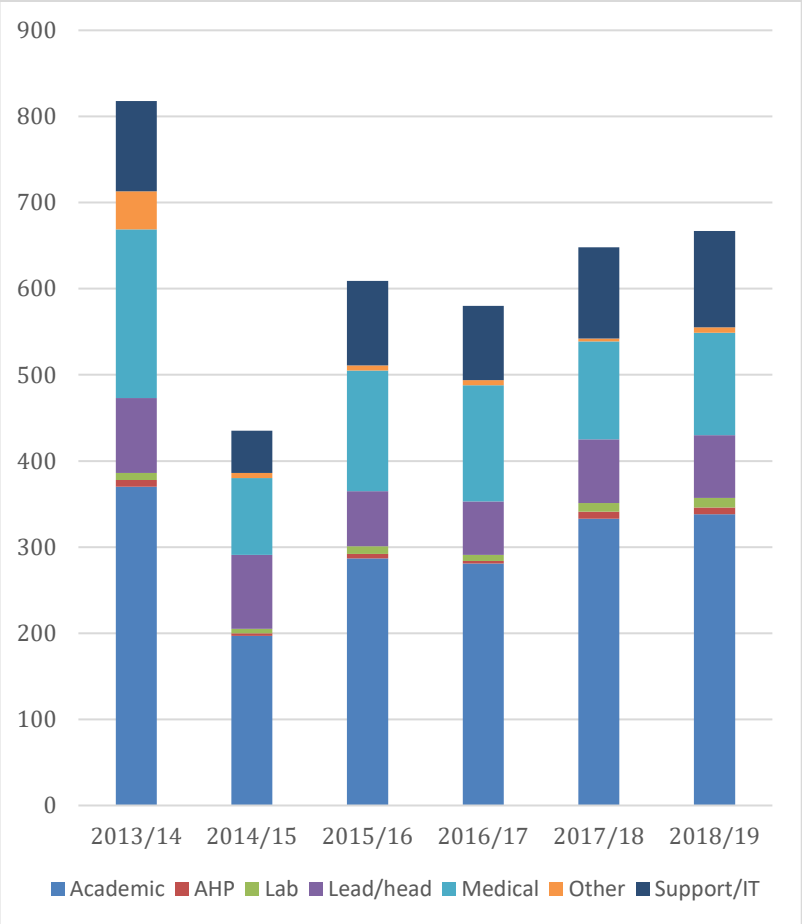
Table 4.4 FTEs by staff group and year

Staff Group	Year	BRC		BRU		Grand Total	
		No	%	No	%	No	%
Academic	2013/14	293	45%	77	48%	370	45%
	2014/15	134	46%	63	43%	197	45%
	2015/16	225	46%	62	53%	287	47%
	2016/17	216	46%	65	56%	281	48%
	2017/18	333	51%			333	51%
	2018/19	338	51%			338	51%
	Total	1,539	48%	267	49%	1,806	48%
Allied Healthcare professional	2013/14	6	1%	2	1%	8	1%
	2014/15	1	0%	2	1%	3	1%
	2015/16	5	1%	0	0%	5	1%
	2016/17	3	1%	0	0%	3	1%
	2017/18	8	1%			8	1%
	2018/19	8	1%			8	1%
	Total	31	1%	4	1%	35	1%
Laboratory	2013/14	8	1%	0	0%	8	1%
	2014/15	4	1%	1	1%	5	1%
	2015/16	6	1%	3	3%	9	1%
	2016/17	5	1%	2	2%	7	1%
	2017/18	10	2%			10	2%
	2018/19	11	2%			11	2%
	Total	44	1%	5	1%	50	1%
Lead/Head	2013/14	54	8%	32	20%	87	11%
	2014/15	39	13%	47	32%	86	20%
	2015/16	51	10%	12	10%	64	11%
	2016/17	52	11%	11	9%	62	11%
	2017/18	74	11%			74	11%
	2018/19	73	11%			73	11%
	Total	344	11%	102	19%	446	12%
Medical	2013/14	175	27%	21	13%	196	24%
	2014/15	74	26%	15	10%	89	21%
	2015/16	120	24%	20	17%	140	23%
	2016/17	116	25%	20	17%	135	23%
	2017/18	114	18%			114	18%
	2018/19	119	18%			119	18%
	Total	719	22%	75	14%	793	21%
Other	2013/14	40	6%	4	2%	44	5%
	2014/15	2	1%	4	3%	6	1%
	2015/16	6	1%	0	0%	6	1%
	2016/17	6	1%	0	0%	6	1%
	2017/18	3	0%			3	0%
	2018/19	6	1%			6	1%
	Total	61	2%	9	2%	70	2%
Support/IT	2013/14	80	12%	25	16%	105	13%
	2014/15	35	12%	13	9%	49	11%
	2015/16	77	16%	21	18%	98	16%
	2016/17	68	15%	18	16%	86	15%

Staff Group	Year	BRC		BRU		Grand Total	
		No	%	No	%	No	%
	2017/18	106	16%			106	16%
	2018/19	112	17%			112	17%
	Total	479	15%	77	14%	556	15%

Note rounding affects totals.

Figure 4.1 FTEs at BRCs and BRUs by Function and Year



Academics consistently were the largest staff group, forming almost 50% of FTEs employed by BRCs and BRUs on NIHR funded work over the 6-year period.[22] For BRCs the second largest group was medical staff forming 22% of the workforce (14% for BRUs), and support/IT staff were a further 15% of the workforce in BRCs (14% in BRUs). These relativities were reasonably stable over the period. Thus, most of the employment opportunities afforded by BRC and BRU funding benefited university researchers, with medics following in the ratio of about 1 to 2. Total support staff have averaged around 90 to 110.

[22] All FTEs coded as researchers, PhD, analysts, lecturers, statisticians, health economists, systematic reviewers were grouped under this heading.

4.8 Salary Costs and Other Revenue Spend

Salary data were extracted by year and by BRC/BRU.[23] These were compared with the total revenue spend for each year (see Table 4.5). Over the period, salaries have accounted for about 55% of revenue spend, slightly higher for BRUs than BRCs. Given the data quality issues with the earlier years a better guide is likely to be the 66% reported in 2018/19.

Table 4.5 Salaries and as % total revenue, by year for BRUs and BRCs

	BRU £m	BRC £m	Total £m	As % total revenue spend		
				BRU	BRC	Total
2007/8	0	£22.39a	£22.39		50%	50%
2008/9	2.99	£50.62	£53.61	57%	48%	48%
2009/10	9.01	£61.90	£70.91	47%	52%	52%
2010/11	12.44	£65.59	£78.03	49%	51%	50%
2011/12	12.00	£58.98	£70.98	46%	50%	49%
2012/13	11.91	£62.62	£74.53	56%	41%	43%
2013/14	15.07	£77.02	£92.09	59%	48%	50%
2014/15	16.01	£80.80	£96.81	74%	53%	56%
2015/16	17.08	£82.14	£99.22	62%	57%	58%
2016/17	16.25	£81.19	£97.44	60%	56%	56%
2017/18	0	£107.74	£107.74		60%	60%
2018/19	0	£115.65	£115.65		66%	66%
Total	£112.75	£866.66	£979.40	57%	53%	54%

a) £2.6m were added to salary costs in 2007 as 1 centre reported total revenue costs only. The total was assumed to be salaries.
b) Note rounding applied impacting on totals

4.9 Output: External Funding from NIHR

BRCs and BRUs do not have a conventional measure of output. There are two options to use as a surrogate for output being:

- NIHR annual funding (total £1,141.1m).
- Reported total revenue costs (total £1,822.0m).

[23] The Treasury Green Book (2018) defines the relevant staff costs to adopt in economic evaluation as basic salary, pension costs, National Insurance, allowances and benefits. The NIHR Guidance does not define the salary information required other than noting it can include 'support costs' such as training, so we cannot ascertain if the reported salaries align with this definition. As noted mean BRU salaries vary from over £250k at Cambridge to under £100k at the London centres.

BRCs account for almost 90% of the total revenue costs being £1,622.9m. These are the sum of salaries (£866.7m) plus research costs[24] (£370.8m) plus NHS service costs[25] (£214.4m), indirect costs (£163.0m), revenue consequences of capital spend (£7.1m) and other costs (£0.9m). We cannot explain why the total revenue costs exceeded NIHR funding by 60%, (£681m). The differences are greatest across the BRCs, particularly in the earlier years. In 2018/19 NIHR funding exactly matched revenue costs (both were £176.3m).

Given these interpretation issues, we have used NIHR funding as the better surrogate for output (see Table 4.6).

Table 4.6 Funding from NIHR and % change year on year

	BRU		BRC		Total	
	£m	% change	£m	% change	£m	% change
2007/8			34.72		34.72	
2008/9	3.81		25.21	-27%	29.02	-16%
2009/10	3.29	-14%	41.77	+66%	45.06	+55%
2010/11	6.05	+84%	52.29	+25%	58.34	+29%
2011/12	13.21	+118%	74.90	+43%	88.11	+51%
2012/13	21.57	+63%	63.63	-15%	85.20	-3%
2013/14	22.61	+5%	119.68	+88%	142.29	+67%
2014/15	31.90	+41%	91.25	-24%	123.15	-13%
2015/16	18.46	-42%	84.36	-8%	102.82	-17%
2016/17	25.25	+37%	74.77	-11%	100.02	-3%
2017/18			156.02	+109%	156.02	+56%
2018/19			176.30	+13%	176.30	+13%
Total	146.15		994.90		1,141.05	

Note rounding applied impacting on totals

The funding of BRUs increased steadily until 2014/15 before dropping back to pre-2012/13 levels; funding ceased in 2016/17. In contrast, BRCs experienced greater annual fluctuations in funding, but on a rising trend, with annual funding now over five times the average level of the first three years.

The regional distribution of this spend is presented in

[24] Described as non-pay before 2012

[25] Described as service costs before 2012

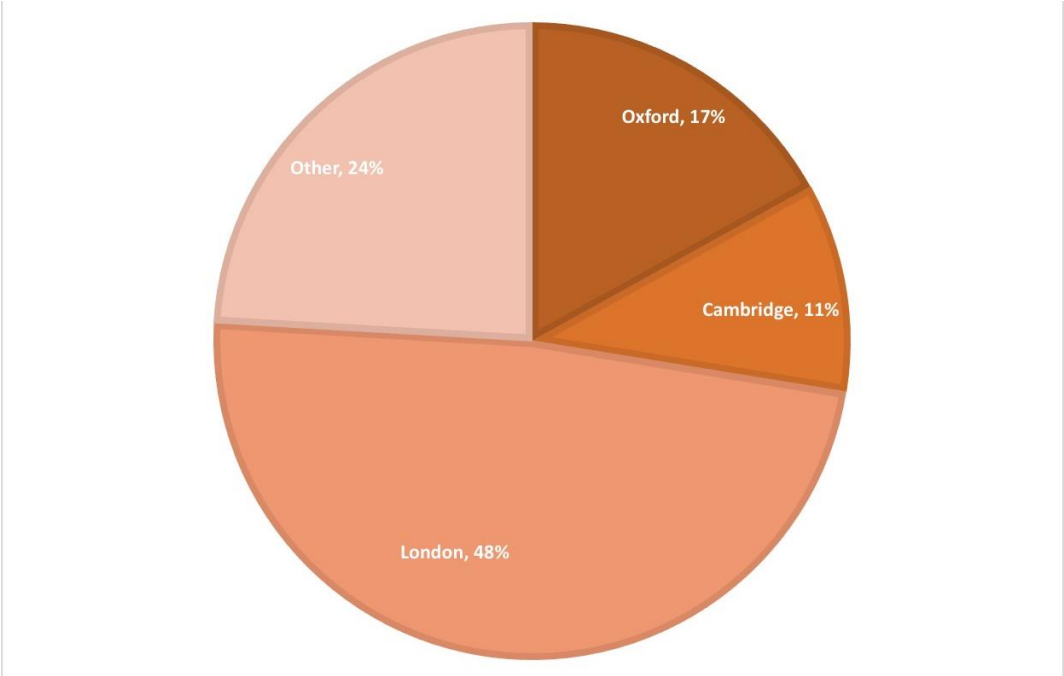
Table 4.7 and Figure 4.2 for BRCs and BRUs. Overall, Cambridge, Oxford and London BRCs and BRUs received 76% of all NIHR funding, with London receiving almost half the funding.

Table 4.7 Regional distribution of NIHR funding for BRCs and BRUs (£m and %)

BRC NIHR	Cambridge		London		Other		Oxford	
2007/08	£0.94m	3%	£21.69m	62%	£7.57m	22%	£4.51m	13%
2008/09	£4.51m	16%	£14.94m	51%	£4.70m	16%	£4.88m	17%
2009/10	£14.46m	32%	£17.36m	39%	£6.15m	14%	£7.09m	16%
2010/11	£8.79m	15%	£20.28m	35%	£11.79m	20%	£17.49m	30%
2011/12	£15.92m	18%	£39.81m	45%	£26.98m	31%	£5.40m	6%
2012/13	£11.50m	13%	£45.62m	54%	£15.55m	18%	£12.53m	15%
2013/14	£14.68m	10%	£48.21m	34%	£21.26m	15%	£58.15m	41%
2014/15	£8.31m	7%	£65.20m	53%	£29.23m	24%	£20.40m	17%
2015/16	£7.84m	8%	£65.91m	64%	£20.70m	20%	£8.38m	8%
2016/17	£9.44m	9%	£51.13m	51%	£23.77m	24%	£15.68m	16%
2017/18	£10.27m	7%	£74.71m	48%	£53.78m	34%	£17.26m	11%
2018/19	£14.32m	8%	£86.89m	49%	£53.39m	30%	£21.70m	12%
Total	£120.97m	11%	£551.76m	48%	£274.85m	24%	£193.46m	17%

Note rounding applied impacting on totals

Figure 4.2 Regional distribution of NIHR funding for BRCs and BRUs



Tables 4.8 and 4.9 report on NIHR funding per employee for BRCs and BRUs respectively. Only data from 2013/14 that use the self-reported employees are shown, as uncertainties about the employee numbers in earlier years limits their usefulness. The data presented also look questionable for Oxford BRC in the 2013/14 and 2014/15. BRCs outside Oxford, Cambridge and London have about a 30% higher capital to labour ratio than elsewhere. Interpreting the BRU data for Cambridge is also challenging because it only reported 3 FTEs in total. For London and centres outside London the BRUs required materially lower capital per FTE than BRCs. These tables indicate data quality issues prevent robust comparisons of the usage of capital and labour.

Table 4.8 NIHR funding per employee for BRCs

	Cambridge	London	Other	Oxford	Total
2013/14	£337,214	£95,933	£114,527	£601,537	£182,118
2014/15	£148,516	£291,921	£223,606		£315,315
2015/16	£142,548	£206,607	£344,290	£48,426	£172,323
2016/17	£152,847	£178,590	£223,393	£104,008	£161,158
2017/18	£177,065	£236,033	£338,427	£149,117	£240,339
2018/19	£167,431	£358,143	£280,567	£145,479	£264,081
Mean	£179,632	£207,686	**£280,567**	£221,492	£218,346

Table 4.9 NIHR funding per employee for BRUs

	Cambridge	London	Other	Oxford	Total
2012/13	£8,782,817	£16,306	£177,473	£180,519	**£140,573**
2013/14	£500,000	£160,388	£212,154	£387,236	**£219,361**
2014/15	£27,291	£138,169	£150,862	£250,573	**£156,991**
2015/16		£125,309	£223,813	£432,266	**£217,106**
Mean	£197,148	£95,154	£192,561	£290,952	£181,834

4.10 Gross Value Added

Gross value added measures the contribution made to the national economy by one individual producer or industrial sector or region. It quantifies the value of goods and services produced minus the cost of inputs and materials used in the production process. ONS uses an income approach to measure GVA[26] comprising: *'compensation of employees, plus gross operating surplus, plus mixed income, plus taxes on production, less subsidies on production*.' For BRCs and BRUs this reduces to salaries plus depreciation as these entities do not pay corporation tax and medical research expenditure is usually exempt from VAT.

Estimating a value for depreciation is not straightforward as we have no information on capital spend by BRCs and BRUs. As previously noted, the revenue spend reported in the annual returns made by centres exceed the funding received from NIHR by about 60%. However, in order to recognise that the funds received are used to build new facilities we have assumed that:

- 10% of NIHR funding is spent on new capital assets.
- The expenditure creates 3 types of assets being IT/software, plant and building in a ratio: 7:26:67.[27]
- Relevant assets lives are 8, 15 and 50 years for IT, plant and buildings.[28]

[26] https://www.ons.gov.uk/economy/grossvalueaddedgva/datasets/regionalgrossvalueaddedincomeapproach

[27] This is the average over 2 years for the transfer of assets in the course of construction to fixed assets. Source: Guy's and St Thomas' NHS Foundation Trust Annual Report and Accounts 2018/19.

[28] These rates are consistent with asset lives across the NHS sector including at Guys & St Thomas'.

Table 4.10 reports the associated depreciation consistent with these assumptions plus salaries, giving total GVA.

4.11 Contribution to National Economy

Table 4.11 shows the results of applying the output, employment costs, GVA and FTE multipliers to the direct values for each. The direct values are those reported earlier and the indirect are the additional value created as a result of the multiplier effect. Using data from the centres and applying the type 1 multipliers produced by ONS suggests that over the 12 years from 2007/08, the investment by NIHR of £1,141m has led to the creation of additional indirect national output of almost £650m, additional indirect GVA of £571m, additional indirect salaries of £487m and 5,788 additional years of full-time employment across the economy.

4.12 Combined IRR

The combined economic returns to medical research conducted by BRCs/BRUs comprise:

- Net health gains.
- Direct and indirect output gains.

Section 3 calculated that the IRR from net health benefits was 16%, with the health gains occurring after a time lag of 17 years from the initial investment. The value of the indirect gain is a marginal 57% but for one year only and with no time lags (that is an investment by the BRC generates wider economic benefits of £157 in year 2, giving an IRR of 57%). The combined IRR is 58% over the total lifetime of the project (see Appendix A4).[29]

HM Treasury (2018) advises public sector bodies on the long terms discount rates to be applied when discounting future cash flows in policies, programmes and projects. The current annual discount rate of 3.5% in real terms has been applied since 2003. The rate of return achieved from investment medical research exceeds this opportunity cost of capital.

4.13 Value of National Output Gain from all Funding Provided to BRCs/BRUs

In addition to NIHR funding, BRCs and BRUs have received funds from other organisations in the public sector, charities and industry. Since their start in 2007 to 2018/19 the centres report receiving funding totaling £7,861m. Applying the mean output type 1 multiplier of 1.569, gives an indirect benefit to the national economy of £4,473m, giving a total benefit of £12,334m. No measure of the FTEs or staff costs associated with this total funding is available.

[29] The IRR is not the sum of 16% and 57% but the discount rate that makes the net present value (NPV) of all cash flows from a particular project equal to zero. The value of the health gain in year 18 when discounted at 57% a year is equal to about £1 in year 1. Hence the increase in the IRR is small.

Table 4.10 Depreciation, salaries and GVA

	Depreciation £m			Salaries £m			GVA £m		
	BRC	BRU	Total	BRC	BRU	Total	BRC	BRU	Total
2007/8	£0.14	£0.00	£0.14	£22.39	0	£22.39	£22.53	£0.00	£22.53
2008/9	£0.10	£0.01	£0.11	£50.62	2.99	£53.61	£50.72	£3.00	£53.72
2009/10	£0.16	£0.01	£0.18	£61.90	9.01	£70.91	£62.06	£9.02	£71.09
2010/11	£0.21	£0.02	£0.23	£65.59	12.44	£78.03	£65.80	£12.46	£78.26
2011/12	£0.30	£0.05	£0.35	£58.98	12.00	£70.98	£59.28	£12.05	£71.33
2012/13	£0.25	£0.08	£0.33	£62.62	11.91	£74.53	£62.87	£11.99	£74.86
2013/14	£0.47	£0.09	£0.56	£77.02	15.07	£92.09	£77.49	£15.16	£92.65
2014/15	£0.36	£0.13	£0.48	£80.80	16.01	£96.81	£81.16	£16.14	£97.29
2015/16	£0.34	£0.07	£0.41	£82.14	17.08	£99.22	£82.48	£17.15	£99.63
2016/17	£0.29	£0.10	£0.39	£81.19	16.25	£97.44	£81.48	£16.35	£97.83
2017/18	£0.61	£0.00	£0.61	£107.74	0	£107.74	£108.35		£108.35
2018/19	£0.69	£0.00	£0.69	£115.65	0	£115.65	£116.34		£116.34
Total	£3.92	£0.58	£4.50	£866.64	£112.75	£979.40	£870.56	£113.33	£983.90

Table 4.11 Impact of BRC and BRUs on national output, GVA, employment costs and FTEs

	Output £m			**GVA £m**			**Employment costs £m**			**FTEs**		
	BRC	**BRU**	**Total**	**BRC**	**BRU**	**Total**	**BRC**	**BRU**	**Total**	**BRC**	**BRU**	**Total**
Direct	£994.90	£146.15	**£1,141.05**	£870.56	£113.33	**£983.90**	£866.64	£112.75	**£979.40**	6,319	1,084	**7,402**
Indirect	£566.10	£83.16	**£649.26**	£504.92	£65.73	**£570.66**	£430.72	£56.04	**£486.76**	4,941	848	**5,788**
Total	**£1,561.00**	**£229.31**	**£1,790.31**	**£1,375.48**	**£179.06**	**£1,554.56**	**£1,297.36**	**£168.79**	**£1,466.16**	**11,260**	**1,932**	**13,190**

4.14 Strengths and Limitations

The strength of this methodology is it uses ONS data specific to the non-profit scientific research and development services sector to calculate the impact of NIHR funding of BRC/BRU activity on the national economy. The alternative spillover approach uses values that are neither UK based nor derived from medical research activities.

The major limitation is the inability to measure the output of BRCs and hence the use of NIHR funding as a surrogate measure. A second limitation was the quality of the data. We found inconsistencies across centres with some submitting incomplete entries, null values or not reporting any values. The problems were greater in the earlier years. Hence 'rules' were devised to clean the data and, for employee numbers, to extrapolate back from 2013, before which no data were available.

There are also limitations with the multiplier approach itself in this context. The benefits from externalities associated with the R&D are at best partially captured. For example, the benefit from the creation of a more skilled labour force is partially captured through the employment cost multiplier but it does not measure the full value (e.g. the discounted value of the earnings accruing after receiving training from a BRC in comparison to the counterfactual). There is also no attempt to measure aspects such as the value of new knowledge generated which can then be exploited by other organisations.

It is also not possible to unpick the component parts of the output multiplier to establish the weight given to commercialising intellectual property rights. Indeed, it is not known if the multiplier captures such benefits. We did not include the value of spin-out companies or other intellectual property in order to avoid any double count.

Input-output tables assume the same relative impact of any additional spend, irrespective of its magnitude. Thus, an extra £100m investment has 100 times the impact of £1m extra spend. Moreover input-output tables assume constant returns to scale and a constant production function. These simplifying assumptions limit the applicability of the technique to sectors subject to rapid technological development or when there are major step changes in inputs or outputs.

4.15 Conclusion

The additional national economic output associated with the NIHR funding of biomedical research has averaged about £0.57 for each £1 invested with no time lag. In addition, the value of the health gain associated with the resultant increase in quality of life is equivalent to a 16% internal rate of return. The combined annual IRR is 58%.

5 Spillover Effects of Biomedical Research: Review Update

5.1 Summary

An updated literature search using the same terms and sources as adopted by Sussex (2016) was conducted. Seven papers met the inclusion criteria. Three of these included some measure of spillover.

The most developed methodology was adopted by Link and Scott (2019) who applied it to several R&D projects funded by the public sector in the USA. They concluded that the value of spillover was of the order of 50% and well in excess of the opportunity cost of 7% for government funded research. The rate of return (RoR) from spillover also exceeded the expected return to the private sector (19%) and the hurdle rate for new investment (25%). If only the private sector funded R&D then there would be underinvestment in R&D. The externalities giving rise to spillover arose because of market failure. Governments should fund R&D to capture the value of these externalities.

Three papers with shared authorship developed the case for regulators and governments to consider including the value of spillover (together with other elements) when assessing the value of investment in medical devices. The final paper measured inter-firm spillover for two cardiac interventions.

No other studies provided new empirical evidence of the rate of return from spillover. Thus the only new empirical evidence identified a value of spillover consistent with the 50% rate used by Sussex (2016). However, these findings are from the USA and from unrelated industries, so there is still insufficient evidence to inform on the value of spillover associated with UK private or public sector investment in biomedical research.

5.2 Background

This project starts from the premise that the economic returns to medical research comprise two, additive, elements:

- Health and social care gains, net of the health and social care costs of delivering them.
- Gains to the local and national economy, in particular the income that results directly and indirectly from the research and the further activity stimulated by it.

This approach was first adopted by Health Economics Research Group (HERG, 2008) and has been taken forward by some of the authors seeking to estimate the RoR from biomedical research, for example Sussex (2016).

HERG (2008) distinguished between two types of economic return:

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

The difference between the social and the private RoR represents the value of R&D spillover. A literature review on spillover in general and as applied specifically to medical research was also conducted by the HERG. The 2008 review was updated by Sussex (2016) and we also updated this review to include any recent estimates of the spillover effects of biomedical research.

This section summarises the findings from the 2008 and 2016 reviews, and our review update.

5.3 Findings from HERG 2008 review

The search strategy adopted by HERG members is reported sparsely, with very limited information about results and studies identified and included. A synthesis of the included studies was provided, reporting that one study estimated that the RoR generated by investment in R&D by two UK private sector pharmaceutical companies in the UK was 51%, of which 14% was captured by the investing firm, 26% was captured by other firms in the same sector, and 11% was captured in other non-pharmaceutical sectors of the UK economy (Garau and Sussex 2007). The authors highlighted their results were highly uncertain owing to the paucity of empirical data.

HERG also reported that the 'total social returns' to private R&D spending (all sectors) were typically around 50%, with the value of spillover exceeding the typical private sector return of 20% (being that captured by the investing organisation).

The HERG search returned no empirical studies estimating the social return to public investment in biomedical research but only for agricultural research in the USA. The returns ranged from 20% to 67%.

The evidence supported the concept that spillover from private and public R&D spending arose from the:

- Production of new knowledge which was exploited by other organisations.
- Creation of a more skilled labour force.
- Dissemination of knowledge and technology transfer.

The quantified spillover effects and the mechanisms enabling its transfer could not be evidenced.

5.4 Update Reported by Sussex (2016)

Sussex (2016) updated the literature review undertaken by the HERG group, identifying two additional papers. Frontier Economics (2014) reviewed the literature on return on investment from science and innovation, concluding that the social returns to publicly-funded R&D investments were around 30 to 40%, but this was largely based on the agricultural sector and international evidence.

Haskel (2014) focused on the UK and looked at how different industrial sectors, but not biomedical and health research, interacted with publicly funded R&D. This estimated social returns of around 20% for UK public R&D investments.

Sussex concluded these studies supported an estimated social return of around 30% from publicly funded R&D but that there was no evidence on the return to UK biomedical research.

5.5 Methods of our Review Update

Our initial aim was to update the reviews using the same search methods as those used by HERG (see *Annex to Chapter Six: Literature review on R&D spillovers, 2008),* but insufficient information was available to enable these to be reproduced. Developing a *de novo* search methodology was considered but ruled out as inappropriate within the context of this project's aims, resources and timelines. Hence an informed estimate of the search methods used by HERG (2008) was developed. This was based on an interpretation of the reported methods, and adapted as appropriate to the project context.[30]

The resulting search strategy is shown in Figure 5.1. Date and language restrictions were applied to identify papers published in English from 2015 to date. That year was chosen to ensure no gaps between this update and the previous update by Sussex (2016).

Figure 5.1 Search strategy (not database-specific)

medical AND (R&D OR research) AND (spillover OR spillovers OR spill-over OR spill-overs OR externalities OR synergies OR rate of return OR rates of return)

[30] The search methods used do not represent YHEC de novo search methods. The aim was not to conduct an optimal search but update the HERG searches using a methodology adapted from those methods reported by HERG (2008). No quality assurance of the original HERG search methods or their adaptation as used for this search was undertaken. No attempt was made to 'enhance' the HERG (2008) search methods.

The databases and information resources used are shown in Table 5.1. The search resources reflect those used by HERG (2008) with one difference. HERG (2008) report searching the 'British Library Integrated Catalogue'. The British Library main catalogue was judged to be the most likely equivalent to this resource, so was used instead.

Table 5.1 Databases and information sources searched

Resource	Interface / URL
PubMed	https://www.ncbi.nlm.nih.gov/pubmed/
EconPapers	https://econpapers.repec.org/
Econlit	OvidSP
British Library main catalogue	http://explore.bl.uk/

Appendix A5 contains the full strategies (including search dates) for all the sources searched.

The results of searches were downloaded in a tagged format and loaded into bibliographic software (EndNote). They were deduplicated using several algorithms. Results from resources that did not allow export in a format compatible with EndNote were saved in Word or PDF documents as appropriate.

5.5.1 Literature Search Results

The searches were conducted on the 31 March 2020 and retrieved 1,113 records (Table 5.2). Following deduplication, 1,107 records were assessed for relevance.

Table 5.2 Literature search results

Resource	Number of records identified
PubMed	696
EconPapers	123
Econlit	13
British Library main catalogue	281
Total number of records retrieved	1,113
Total number of records after deduplication	1,107

Following review of titles and abstracts, full papers were obtained for 10 references. Of these, seven are included for review.

5.6 Description of Included Studies

This section provides a brief overview of the seven papers and their funders, with a fuller commentary on each paper provided in the next section.

Link and Scott (2019) edited a book comprising 15 related papers, all authored by one or both or the authors plus colleagues. The two Professors have developed and applied a methodology to estimate the value of spillover from public-sector R&D projects. This estimated the RoRs from spillover for a number of US funded R&D projects but these were not specific to the biomedical or health sectors.

Várnai (2018) reported the spillover benefits from the EU's regulation of paediatric medicines. The report was prepared for the European Commission.

Farahati (2017) estimated the potential economic spillover benefits from US Federal Government's investment in a burn debridement product. Farahati is a public health economist at the University of Maryland, whist the co-authors are from the US Department of Health and Human Services.

A fourth paper was a Working Group Paper by Grennan (2018), published by the National Bureau of Economic Research, a nonprofit economic research organization in the USA. The paper measured the spillover benefits derived by medical device manufacturers from selling a range of products across a key market, with these benefits not available to firms which only had one product to sell in that market. No rate of return (RoR) was calculated, rather Grennan (2018) used a metric of increased sales. No spillover outside the investing firm was considered.

The paper by Lakdawalla (2018) was produced by a Special Task Force set up by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) (2018). This identified spillover as one of 10 elements to consider when conducting value assessments of medical technologies. The Task Force developed themes first set out in two earlier position papers (Garrison 2016 and 2017). Both were supported by The Office of Health Economics and the pharmaceutical industry.

Hence, we identified:

- Three papers (Link and Scott 2019, Varnai 2018 and Farahati 2018) reporting some measure of spillover from externalities.
- Three (ISPOR 2018 and Garrison 2016 and 2017) develop the case for regulators and governments to consider including the value of spillover (together with other elements) when assessing the value of investment in medical devices.
- One measuring inter-firm spillover (Grennan 2018).

The range of authorships show interest spanning regulators, the industry and academics.

5.7 Quantification of Spillover

5.7.1 Link and Scott

Link and Scott (2019) calculated the value of spillover accruing to publicly funded, privately performed research and compared this rate with the opportunity cost of government funded research. They also calculated the private sector RoR and compared that to its 'hurdle rate' and the social rate of return being the sum of the spillover RoR and the private RoR.

The context for their work was the existence of market failure giving rise to underinvestment in R&D. Market failure was associated with eight factors:

1) High technical risk associated with underlying R&D.
2) High capital cost to undertake R&D.
3) Long time to complete the R&D and commercialise the project.
4) Underlying R&D spills over to other markets and is not appropriable.
5) Market success of the technology depends on technologies in different industries.
6) Property rights cannot be assigned to the underlying R&D.
7) Resulting technologies must be compatible and interoperable with other technologies.
8) High risk of opportunistic behaviour when sharing information about the technology.

The authors concluded publicly funded R&D was necessary to correct market failure.

The intellectual basis for their analyses was Arrow (1962)[31] and various publications by Schumpeter on why large firms dominate certain markets, with access to funds for R&D being a key factor.

Detail was provided on 8 projects selected from 10 projects funded by the National Institute of Standards and Technology (NIST). Each project was designed to stimulate early-stage advanced technology development that would otherwise not be funded by the private sector. None was in biomedical research. The methods used were interview-based to obtain values for parameters that were used in quite complex equations.

Findings included that:

- The average expected private rate of return from the 8 projects, in the absence of NIST funding, was 19%.
- This is less than the average private hurdle rate of 25%.
- In the absence of NIST funding the firms would not have undertaken this research (which is also the counterfactual).

[31] Arrow K, 1962. "Economic Welfare and the Allocation of Resources for Invention," NBER Chapters, in: The Rate and Direction of Inventive Activity: Economic and Social Factors, pages 609-626, National Bureau of Economic Research, Inc.

- The average expected social rate of return was 72%, with the minimum being 63%.
- The spillover return was at least 43% and averaged 53%.
- The opportunity cost of Government R&D funding was 7% in real terms.
- The NIST funding was socially valuable.
- The estimated achieved rate of return to firms with NIST funding from their own private funding was 33%.

Various other evaluations were also summarised, including findings from an evaluation of 14 New England Small Business Innovation Research (SBIR) projects. This work concluded that the private RoR with no SBIR funding was 30%, compared with a lower bound of the social RoR of 60%. This was judged conservative as it excluded any measure of consumer surplus.

Of 12 SBIR projects in south-eastern states:

- Six fast track companies had a private RoR of 28% and social RoR of 132%
- Six others had private RoR of 21% and 104% social RoRs.

The average private sector return for a further 44 SBIR projects was 25%, compared with a social return of 84%.

A high resolution wavelength calibration project was estimated to have a social RoR of 4,400%, rising to 5,500% when consumer surplus was added in.

The same authors also calculated the net social benefits associated with the Baldrige National Quality Award Program,[32] established within the National Institute of Standards and Technology in 1987. Using survey data extrapolated to the economy as a whole, they found that the ratio of economy-wide benefits to social costs probably exceeded 207:1. Even higher benefits of 351:1 and 820:1 were identified from projects funded after 2006 for the same Program.

The Canadian Institute of Health Research analysed the impact of investments in computed tomography perfusion (CTP) research over a 14-year period. The net social benefits-to-cost ratio were estimated at between 6.66-to-1 and 9.99-to-1. This group also found a consensus among 15 neuroradiologists and stroke neurologists that the Government research and the licensing of the algorithms and protocols to GE Healthcare accelerated the clinical use of CTP by between 5 and 7 years, adding that without the public funds the software that would have emerged would likely have been inferior in the accuracy and precision of measurement.

[32] https://www.nist.gov/baldrige

Taken together these empirical findings led the authors to conclude that the private sector will underinvest in R&D because of market failures and that it was worthwhile for Government to fund R&D.

5.7.2 Farahati

Farahati (2017) modelled the potential economic spillover effects for a federal investment in a burn debridement product for responding to an improvised nuclear device. The study results reported that, if approved for use in the USA, the burn debridement product had potential economic spillover benefits that exceeded the federal government's initial investment of $24 million within a few years of its implementation. No RoR was provided. The paper concluded that estimating the value of spillover can help to inform the prioritisation of scarce government resources for R&D in medical products.

This paper also started from the premise that market failure leads to underinvestment in R&D, concluding that government should invest in such R&D or provide subsidies to private firms so that the socially optimum outcome is reached.

5.7.3 Varnai

Varnai (2018) measured the benefit from R&D investment in Paediatric Investigation Plans (PIPs). The pharmaceutical industry is required to prepare PIPs as part of the EU paediatric regulatory framework. Spillover benefits were judged to accrue from job creation, growth and innovative activity across EU and non-EU sectors. The spillover effects were estimated based on published RoRs. A conservative estimate of the social RoR was €6bn after 10 years from an annual €2bn investment in PIPs R&D. This comprised of:

- Private rate of return to the organisation of 14%.
- Return to the pharma sector, including to generic companies.
- Return to other sectors in the economy.

A literature search identified two sources of the estimated private sector return being:

- The Annual Reports by GSK in 2013 and 2015 which quoted achieved internal rate of returns (IRRs) on R&D investments of 13% and that its long-term target was set at 14%.
- Garau and Sussex (2007) who also adopted a 14% private RoR.

No estimates of intra-industry and across industry RoR related to R&D investment in the pharmaceutical industry were identified. Hence Varnai (2018) used the HERG (2008) estimated total social RoR from private investment of around 50%, and that the social RoR from public investment was at least 20% and could be as high as 67%, with a best estimate of 30%.

The intra-industry and across industry RoRs were assumed to be 16% (30% minus 14%). Hence an extra €1 invested in cardiovascular research this year, was assumed to increase GDP by €0.30 annually for 10 years.

5.7.4 Grennan

Grennan (2018) estimated the magnitude of spillovers for three categories of interventional cardiology devices: stents, balloons, and guidewires. The authors used manufacturers' monthly market share within each device category in hospitals in the USA for 2005 to 2013. In this context the spillover is from externalities across product lines within one firm and does not relate to externalities arising outside the firm. Hence it is not directly relevant to this project.

The analyses concluded spillovers from stent sales provided the average multi-category firm with an advantage equivalent to a 25% increase in its balloon share in US hospitals relative to a single-category firm selling only balloons. This was associated with a 4% increase in sales revenue relative to a single-product manufacturer with no such spillover benefit. No similar benefit was identified for sales of guidewires, suggesting that familiarity with a manufacturer's other products was not associated with a spillover benefit for that product line.

5.8 The Value of Spillover Relevant to Cost-Effectiveness Analysis

5.8.1 Lakdawalla (2018)

The ISPOR Special Task Force report by Lakdawalla (2018) argued that new research would be encouraged if regulators incorporated 12 additional elements of value into cost-effectiveness analysis (CEA). They advocated that the concept of value should move beyond quality-adjusted life-years (QALYS) and net costs to consider wider aspects including productivity, adherence-improving factors, and reduction in uncertainty, and scientific spillover. The authors noted that the majority of the concepts were well understood. Scientific spillover was one of two exceptions, requiring more theoretical development and consensus on its measurement before it could be included in decision-making.

Scientific spillover was defined as: "when the benefit of scientific advances cannot be entirely appropriated by those making them''. The chief example discussed is a first-in-class drug with a new, unique mechanism of action. The new drug might not in itself be valuable but the knowledge of the mechanism may lead to other, more valuable drugs, being developed. The first drug hence may unlock the value of the later innovations but the value of that externality is not currently captured in a cost/QALY framework.

The authors noted that the patent system requires the innovating company to share the science underpinning their invention to enable others to learn from and build upon it. They assert this system is

likely to lead to underinvestment and that healthcare commissioners may wish to reward developers with higher prices to encourage knowledge generation. No relevant empirical studies were identified and further research on the measurement and valuation of spillover was recommended.

5.8.2 Garrison (2017) and (2016)

Garrison (2017) similarly argued that spillover is one of five elements that is not captured by the cost/QALY decision rule. It also concluded further research is required before the value of these externalities can be adopted by regulators. In the meantime, ignoring the value of knowledge is likely to result in underinvestment in healthcare R&D.

Garrison (2016) undertook a systematic literature review which identified spillover as one of five elements related to the value of information. Scientific spillover was judged as adding value, through externalities. The paper exampled the first hepatitis C subtype genotype which enabled other manufactures to define more sub-genotype categories and develop more effective antiviral therapies. The initial R&D investment enabled rival firms to undertake their own randomized controlled trials more efficiently and more productively.

Spillover was also judged to accrue beyond the initial clinical trials as real-world evidence was gathered on the use of new therapies, alone and in combination with others, by clinicians treating patients.

Other scientific spillovers identified included the recruitment and retention of scientific staff, and the creation of organisational and physical infrastructures for health and social care. The authors argued that by taking a narrow perspective based on cost/QALY such elements of value are not explicitly recognised or valued by regulators

5.9 Summary and Conclusions

Link and Scott (2019) calculated the value of spillover accruing to publicly funded, privately performed research and concluded these were in the order of 50% and well in excess of the opportunity cost of 7% for government-funded research. The RoR from spillover also exceeded the return to the private sector. If only the private sector funded R&D then there would be underinvestment in R&D because of market failure. The authors concluded that governments should fund R&D to capture the value of these externalities.

No other studies provided new empirical evidence of the RoR from public or private sector R&D. Varnai (2018) used reported values to conclude the social benefits from investment in PIPs exceeded their costs to the private sector. A model by Farahati (2017) concluded there were potential spillover benefits from a federal investment in a burn debridement product, with these benefits forecast to exceed the initial investment.

The ISPOR Special Task Force (Lakdawalla 2018) and Garrison (2017 and 2016) note spillover is an important source of value arising from private sector R&D. Each paper concluded further research into measuring spillover was required before it could be included in CEA decision-making.

Thus the only new empirical evidence identified that there was net economic benefit from a range of public sector investments in new technologies. However, these findings cannot be generalised beyond the programmes and settings. There is still insufficient evidence to inform on the value of spillover associated with UK private or public sector investment in biomedical research.

6 Time Lags Between Investment and New Therapies: A Review Update

6.1 Summary

The literature search conducted by Hanney (2015) was updated to identify studies reporting time lags for new therapies published from 2014. Fifteen papers were identified and the information on lags synthesised into an evidence table. Five reviewed multiple drugs in a range of indications, one measured the lags associated with medical devices, with the remaining eight addressing the lags associated with a single drug. One study by The Institute of Cancer Research (2018) was of all new cancer drugs licensed in Europe since 2000 and a second by IQVIA (2019) of all new drugs licensed by the US Food and Drug Administration (FDA) over time. These provided a rich data set to inform the analyses.

The absolute lags reported in these papers were similar, averaging 14.1 years from patent to NICE approval (for the period 2009 to 2016) and 13.6 years from patent to launch for new drugs coming to the US market in 2018. Both sources reported that total time lags had increased, with companies taking longer between the start of phase 1 trials and the regulatory submission. This is despite the European Medicines Agency (EMA) and FDA offering accelerated pathways for drugs addressing unmet need. The causes were attributed to increased trial complexity and increased bureaucracy necessitated by regulations governing clinical trials. At the same time the success rates for new drugs has fallen.

Data from IQVIA for the most recent three years to 2018 suggest that in the USA time lags from patent to launch have started to fall gradually. This group see several reasons to anticipate that this trend will continue. This more optimistic outlook is echoed by The Institute of Cancer Research which hopes that a recent new EU clinical trials directive will achieve its aim of reducing the time and cost to conduct clinical trials. Other authors encouraged regulators to engage with pharmaceutical companies at an earlier stage so they could influence the design and outcomes measured in phase III and later trials. This is already happening to some extent, with NICE starting appraisals ahead of the final EMA decision.

Many of the single drug studies were for new indications for existing chemical entities. The time lags reported were often short being from the start of phase II trials to FDA approval. However, these time periods will not generalise to developing new compounds, requiring as they do basic research and phase I studies.

These lags are somewhat shorter than the lags observed by the studies calculating the IRRs for the four diseases (see Section 3). These lags were 12 years for new mental health interventions, 15 years for cancer drugs, 16 years for MSK and 17 years for coronary vascular disease interventions. The differences can be attributed to different start and stop periods, with the disease specific interventions extending beyond regulatory approval to include a measure of the time associated with adoption activities. The inclusion of a period for adoption is appropriate for the IRR calculations.

6.2 Background

One objective of this project is to estimate the internal rate of return (IRR) to the national economy and from health gains as a result of funding provided by the NIHR to BRCs. Time lags between the research expenditure and health gain are an important, but under researched, input into calculating these IRRs (HERG, 2008). In 2015, Hanney et al. published evidence on the time lags from undertaking basic research activities to implementing a new medicine. In this section, we report an update of Hanney's 2015 review.

The original proposal suggested updating the literature search conducted by Hanney (2015). This section reports the findings from the updated search.

The timing of this review seems fortuitous. The UK Clinical Research Collaboration (2020) reported a 'noticeable' additional investment in translational research activities funded predominantly by DHSC via the NIHR, citing the additional funding for BRCs. However, other funders are also investing heavily in translational research. For example, the MRC's annual budget for directed translational research has risen from under £10m per annum in 2008/09 to over £70m in 2017/18. The genesis of these changes can be traced back to the Cooksey Review in 2006.

6.3 Findings from Hanney (2015) on Time Lags

Hanney (2015) investigated time lags between biomedical research and the translation of this research into products, policy and practice. The authors updated an earlier literature review by Morris (2011) into such time lags. This earlier study concluded that understanding lags first required agreeing models, definitions and measures to apply in practice.

Hanney's paper updated the Morris (2011) literature search, identifying studies which quantified time lags in the health research translation process before developing a conceptual model. They applied the model to data collected consistently for seven case studies. Finally, they sought to identify reasons for the lags, together with any policy measures that had been taken to reduce excessive lags.

A key finding from both Hanney (2015) and Morris (2011) was the included papers did not measure time lags in a comparable way, thereby limiting the usefulness of the findings. Both found evidence that time lags varied with therapeutic area. For example, Hanney (2015) found that the mean lag ranged from 8.5 years for anti-infectives to 15 years for immunological medicines. Morris (2011) also found that anti-infective drugs addressing acquired immunodeficiency syndrome had shorter lags than average. The driver here seemed to be high level of unmet need. Regulators had adopted accelerated processes in such cases.

The findings from Hanney's literature search informed a "process marker model". This defined specific research translation milestones or events as process markers enabling the duration between these markers to be assessed. The model had four 'tracks' being discovery research, human research, regulatory approvals and clinical practice. The model was applied to seven case studies of interventions to manage cardiovascular or mental health disorders.

Many of the time lags identified by the seven case studies were substantially longer than the lags reported in other literature. Lags ranged from 18 years for an early intervention in schizophrenia to 49 years for cognitive behaviour therapy for depression and 54 years for a smoking cessation intervention. Indeed, the mean duration was more than double Morris's 17 years, being 34.6 years. The main reason for the difference is likely to be that Hanney (2015) started from a time point called 'discovery', whilst most published studies used patent date or date of first in human studies. However, due to limitations with the data, Hanney (2015) advised that it was difficult to generalise from the results of these seven case studies.

6.4 Strategy to update the Hanney (2015) search

Our initial aim was to update the searches conducted by Hanney et al. using the same search methods as described in a supplement to the original paper (Hanney, 2015a.) It was not however possible to ascertain the exact search methods used and thus not possible to reproduce the original searches.

Developing a de novo search methodology was not feasible within the project scope and timelines. Hence an informed estimate of the search methods used by Hanney (2015) was made, based on an interpretation of the reported methods, and adapted as appropriate to the project context.

After running several iterative search strategies, we decided to adopt a targeted strategy which focused on records that explicitly included the terms "bench to bedside" or "time lag". In addition, plural forms of some terms were added to the strategy. No attempt was made to 'enhance' the Hanney (2015) strategy. The search strategy resulting from this process is shown in Figure 6.1.

Figure 6.1 Search strategy (not database-specific)

(bench to bedside OR time lag OR time lags) AND (research OR development) AND (medical device OR medical devices OR health intervention OR health interventions OR pharmaceutical OR pharmaceuticals OR drug OR drugs OR medical technology OR medical technologies)

The Hanney (2015) searches were conducted using "Google Scholar, Web of Science, PubMed and EBSCO". It was not possible to be certain from this information which databases were searched (Web of Science is an interface, rather than a database; EBSCO is a company that provides research databases, rather than a database). The research team decided to conduct the update searches using PubMed and Embase as shown in Table 6.1. The strategy shown in Figure 6.1 was translated appropriately for each database.

Table 6.1 Databases and information sources searched

Resource	Interface / URL
PubMed	https://www.ncbi.nlm.nih.gov/pubmed/
Embase	OvidSP

Hanney (2015) stated no restrictions on the searched field were applied. This was interpreted as meaning that the search terms were simply entered into the search interface with no field restrictions applied (either through built in database limiters or through the addition of field-related syntax), with the database interface allowed to interpret the entered terms through its default algorithms. The same approach was therefore used in the update searches.

The Hanney paper was published in 2015. The updated search was hence restricted to identify papers published in English from 2014 to date. Appendix A6 contains the full strategies (including search dates) for all the sources searched.

The results of searches were downloaded in a tagged format and loaded onto bibliographic software (EndNote). The results were deduplicated using several algorithms and the duplicate references held in a separate EndNote database for checking if required.

6.5 Literature Search Results

The searches were conducted on 27 March 2020 and retrieved 1,293 records (Table 6.2). Following deduplication, 959 records were assessed for relevance.

Table 6.2 Literature search results

Resource	Number of records identified
PubMed	608
Embase	685
Total number of records retrieved	1,293
Total number of records after deduplication	959

In addition, reports from some leading bodies in the research field were included (Association of Medical Research Charities AMRC, UK Clinical Research Collaboration, IQVIA and EvaluatePharma).[33]

Following review of titles and abstracts, we obtained full papers obtained for 35 references. Of these, 16 are included in the review, one of which, UK Clinical Research Collaboration (2020), is used only for background information on translational research.

6.5.1 Description of included studies

This section provides a brief overview of the 15 papers, with a fuller commentary on each paper provided in the next section. Data were extracted from each study and are reported in Table 6.3.

[33] IQVIA and Evaluate Pharma are global providers of research services to the life sciences industry.

Table 6.3 Overview of the 15 included papers

Study (Year)	Context	Country	Dates	Start of time lag	End of time lag	Time lag (years)	Reasons for time lag	Policy measures to address
Studies of multiple drug interventions								
Institute of Cancer Research (2018)	97 drugs, 177 indications for cancer drugs licensed by the EMA from January 2000 to December 2016.	UK, Europe	2000 to 2016	Patent date Phase 1 trial launch	NICE final appraisal determination EMA authorisation	Mean time lag 12.7 (for 36 indications between 2000 and 2008) 14.1 (for 71 indications between 2009 and 2016) 7.8 (for indications authorised between 2000 and 2008) 9.1 (for indications authorised between 2009 and 2016)	Delays arising in setting up and running clinical trials, progressing from one trial to the next and gaining authorisation. Delays in taking drugs through clinical trials and licensing. Could be due to researchers facing bureaucracy and high expenses in setting up and gaining approval for clinical trials.	Monitoring the impact of the recently introduced EU Clinical Trials Regulation to ensure the process is not more onerous than the previous regulations. Innovative trial designs to be encouraged as can generate findings more quickly and cheaply. Use biomarker tests to select patients for treatment based on the genetics and biology of their tumours. EMA and NICE should help speed up access for new drugs to the market and into NHS using best practice from bodies such as the FDA.

Study (Year)	Context	Country	Dates	Start of time lag	End of time lag	Time lag (years)	Reasons for time lag	Policy measures to address
Horgan (2018)	Overview of issues around bringing personalised medicines to market	Europe	NA	Three general phases Phase 1: Lab Phase 2: Industrial application Phase 3: Market and adoption in healthcare system	End of each phase	Total time lag Phase 1+2 combined: 5-10 Phase 3: 5-10	There is a lack of collaboration between the industry and the assessor and decision-maker/payer which results in a longer timeframe for a medicine to get from bench to bedside.	A framework should be developed which tackles issues at the organisation and firm-level which are blocking effective, efficient and timely integration of genome-based technologies for personalised medicine in healthcare.
Uygur (2017)	97 drugs from 130 licensed indications for breast, lung and prostrate cancer34	USA and UK	To 2016	Patent priority date or initial publication date	Regulatory approval date for drug	Mean time lag Breast cancer 11 Lung cancer 10 Prostate cancer 10.4	Challenges in reproducible data generation. Human patient samples. Public-private partnership challenges. Intellectual property challenges	

[34] There was insufficient information to inform time lags on the remaining 33 studies.

Study (Year)	Context	Country	Dates	Start of time lag	End of time lag	Time lag (years)	Reasons for time lag	Policy measures to address
							for sharing research tools.	
Putera (2015)	15 medicines for acute coronary syndrome (ACS)	USA	1986 to 2012	Publication of first pivotal clinical trial	First mention of therapy as a recommendation in clinical guideline(s) 90% uptake of therapy in clinical practice from recommendation in clinical guideline(s)	Median time lag 2 14	Challenges in adopting clinical evidence into routine practice, include slow adoption of clinical guideline recommendations because of the tendency to wait for early adopters to share their experience, the lack of experience with new agents and indications, etc.	More effective quality improvement initiatives (e.g. pay for performance incentives; developing decision support tools to embed clinical guidance into electronic health systems. Better tools and platforms to deliver continuing education for physicians.
Ward (2015)	48 antiviral drugs licensed for use in UK	UK	1981 to 2014	Initiation of studies in humans (clinical trial)	Receipt of a Marketing Authorisation (MA or 'license')	Mean time lag All new drugs 6.4 Drugs licensed between:	The increases were due to longer development and trials phase (41.7 months for drugs	Regulators are developing initiatives such as MHRA's early access schemes & EU's adaptive licensing pilot. Also, welcome is new EU trials directive. All regulators must engage with pharmaceutical companies

Study (Year)	Context	Country	Dates	Start of time lag	End of time lag	Time lag (years)	Reasons for time lag	Policy measures to address
						1981-92 4.8 1993-2003 6.2 2004-14 7.6	licensed 1981–1992 but 91.7 months for drugs licensed 2004–2014). The regulatory approval phase reduced slightly from 16 to 13 months.	earlier to influence late trials and inclusion of patient outcomes.
Studies of multiple devices interventions								
Farkas (2016)	61 Medical devices	Germany	2004 to 2014	Priority date of the patent	Registration date of CE Mark approval of product	Median time lag Risk class 1 (lowest) 5.77 Risk class 2 6.11 Risk class 3 10.44	Increase is due to greater regulatory requirements for class 3-products and the greater complexity of the device. Results may not generalise to all devices as sample is limited to patented devices.	

Study (Year)	Context	Country	Dates	Start of time lag	End of time lag	Time lag (years)	Reasons for time lag	Policy measures to address
Studies of single drug interventions								
Capozzi (2019)	Lenvatinib in anti-cancer treatment	Italy	2006 to 2015	Enrolment for first phase 1 clinical trial	FDA approval for thyroid cancer	Total time lag 9		
Ittershagen (2019)	Chimeric antigen receptor T-cell (CAR-T) for acute lymphoblastic leukaemia (ALL) and lymphoma	USA, Switzerland	1989 to 2017 2011 to 2017	Initial research into 1rst generation CAR-T First case study published	FDA approval with initial indication for paediatric and young adult patients	Total time lag 28 6		
Locke (2019)	Anti-CD19 CAR-T therapy axicabtagene ciliileucel in large B-cell lymphoma	USA	1989 to 2017 2015 to 2017	Initial research into 1rst generation CAR-T First patient enrolled to Phase 1 study	FDA approval for use in relapsed/refractory large B-cell lymphoma	Total time lag 28 2		

Study (Year)	Context	Country	Dates	Start of time lag	End of time lag	Time lag (years)	Reasons for time lag	Policy measures to address
Goel (2018)	Regorafenib for refractory colorectal cancer	USA	Drug discovery programme 2010 to 2012	1990's Start date of phase I German study	FDA approval	Total time lag Approx. 17 years 2		
Rodriguez-Cartagena (2018)	CAR-T for ALL	USA	1989 to 2017 2015	Initial research into 1rst generation CAR-T Phase II trial	FDA approval	Total time lag 28 2		
Shirani (2018)	Natalizumab for multiple sclerosis	USA	1960s to 2006	Initial research	Initial FDA approval in 2005 but withdrawn 3 months later due to 3 serious adverse events; FDA re-approved in 2006	Total time lag: 40		

Study (Year)	Context	Country	Dates	Start of time lag	End of time lag	Time lag (years)	Reasons for time lag	Policy measures to address
			1998 to 2006	First phase 1 trial	FDA re-approval	8		
Lee (2015)	Sunitinib for renal cell carcinoma	USA	2001 to 2007	Launch date of phase I clinical trial	Accelerated FDA approval Regular FDA approval to allow use in the first-line setting	Total time lag 5 6		
Harrison (2014)	Rituximab for Non-Hodgkin's Lymphoma	USA	1980 to 1997	First molecule tested on a human	FDA approval	Total time lag 17	Challenges to translation from clinical trial to uptake include the cost of the antibody therapy.	
IQVIA 2019	In 2018 59 new active substances took a median of 13.6 years from the time of first patent filing to the launch of the medicine in the USA. This was two years faster than those in the prior two years and almost 6 months faster than the median of the past five years. The cumulative time from the start of Phase 1 trials to the end of development has increased over the past 10 years.							

Study (Year)	Context	Country	Dates	Start of time lag	End of time lag	Time lag (years)	Reasons for time lag	Policy measures to address
	Over the past 3 years, the drugs with accelerated approval designation and breakthrough status have had shorter times (by 15% to 19%) from patent filing to launch than those without. For a number of reasons including use of biomarkers to identify patients with a disease and as intermediate endpoints, availability of registries to provide standard care long-term data and aid recruitment, use of patient reported outcomes, availability of real world data, using AI to identify potential indications to test, use of wearables to collect higher quality data, regulatory support for adaptive, iterative and pragmatic trial designs, expanding phase 1 trials to efficacy within the same trial, increasing number of niched drugs and orphan drugs with fewer included patients, the organisations estimates there is an 85% likelihood that time lags will reduce over the next four years.							

Four of the papers reviewed multiple drugs in a range of indications. The largest disease specific study was by the Institute of Cancer Research (2018) which measured the time lags associated with 97 drugs in 177 cancer indications all licensed by the European Medicines Agency (EMA) since 2000. Uygur (2017) measured time lags for 97 drugs with data available to measure time lags. No indication restrictions were applied. IQVIA (2019) reported time lags for 59 new drugs approved by the FDA in the USA in 2018. Ward (2015) considered 48 anti-viral drugs licensed in the UK since 1981. This also had the earliest start date for records. Putera (2015) looked at 11 acute coronary syndrome (ACS) drugs.

Farkas (2015) was the only paper considering devices, 61 in total.

Horgan (2018) considered time lags associated with personalised medicines, but did not measure time lags associated with individual therapies.

These 7 studies also provided more reflective observations on the barriers giving rise to time lags and some had policy recommendations.

The remaining 8 studies all measured time lags for a single chemical entity, with 7 being for cancer indications Capozzi (2019); Goel (2018); Ittershagen (2019) Rodriguez-Cartagena (2018); Locke (2019); Harrison (2014); Lee (2015) and 1 for multiple sclerosis (Shirani (2018). Of the cancer drugs, 3 of the 7 addressed time lags associated with the introduction of chimeric antigen receptor T-cell (CAR-T) for acute lymphoblastic leukaemia (ALL) and/or lymphoma Ittershagen (2019) Rodriguez-Cartagena (2018) and Locke (2019). Hence we have 4 drugs but 7 indications.

All of the single drug studies had an end date associated with FDA approvals. Uygur (2017) also used FDA approval dates as their end point, whilst Putera (2015) measured a time period associated with introduction into American clinical practice. In contrast, the Institute of Cancer (2018), Farkas (2016), Ward (2015) and Horgan (2018) all adopted a European regulatory stance.

Most authors were from different non-profit making institutions or universities, other than two papers where the authors were employees of the US National Institute of Health Rodriguez-Cartagena (2018) and Uygur (2017). Exceptions were Ittershagen (2019) who were employees of Novartis and IVQIA which is a USA private quoted company.

6.6 Mean Length of Time Lags for Single Drug Studies

This section presents the average length of time lags for the single drug studies. None of these studies discussed reasons for the lags or offered policy insights. Rather the studies focused on the processes as they related to the drug of interest. Shirani (2018) did report a novel approach adopted by FDA. This study examined time lags associated with the introduction of natalizumab to manage multiple sclerosis. In February 2005, about 3 months after its first approval, natalizumab was voluntarily withdrawn by the

manufacturer due to the occurrence of three serious adverse events. It was later reintroduced to the market in June 2006, with a black box warning regarding the risk of the adverse event and requirements concerning its distribution. These steps were designed by the FDA to minimise risk whist still facilitating market entry. This is an area of unmet need and the FDA addressed the balance of harm and benefit in an innovative and timely way. This study also reported that research in rats to identify the target molecule had begun in the mid-1960s. Thus, under the Hanney (2015) model, the time lag would have been 40 years.

For the 7 studies considering single drug interventions in oncology Capozzi (2019); Ittershagen (2019); Locke (2019); Goel (2018); Rodriguez-Cartagena (2018); Lee (2015); Harrison (2014), the mean time lag from clinical trial to approval for a specific indication was 4.3 years, range 2 years to 9 years. However, the lags from the discovery period for the 4 drugs was materially longer at about 15 years.

The average time lag from clinical trial to approval for the three CAR-T indications was 3.3 years. Each drug/indication benefited from one or more of the accelerated processes offered by the FDA. The original research that identified the molecule started in 1989, giving a time lag of 28 years if one adopts that as the start date.

As Hanney and Morris note interpreting these dates with no agreed definitions for the start and end periods is fraught and potentially misleading. At best we can say the average of 3.3 years will not generalise to new chemical entities - rather these are time lags associated with extensions to current indications and under accelerated processes.

There is also likely to be selection bias in the studies in that authors are seeking to demonstrate what they believe are shorter than average time lags.

Section 6.7 reports the time lags extracted from the remaining studies, together with the reasons for the lags.

6.7 Reasons for Time Lags and Policy Measures

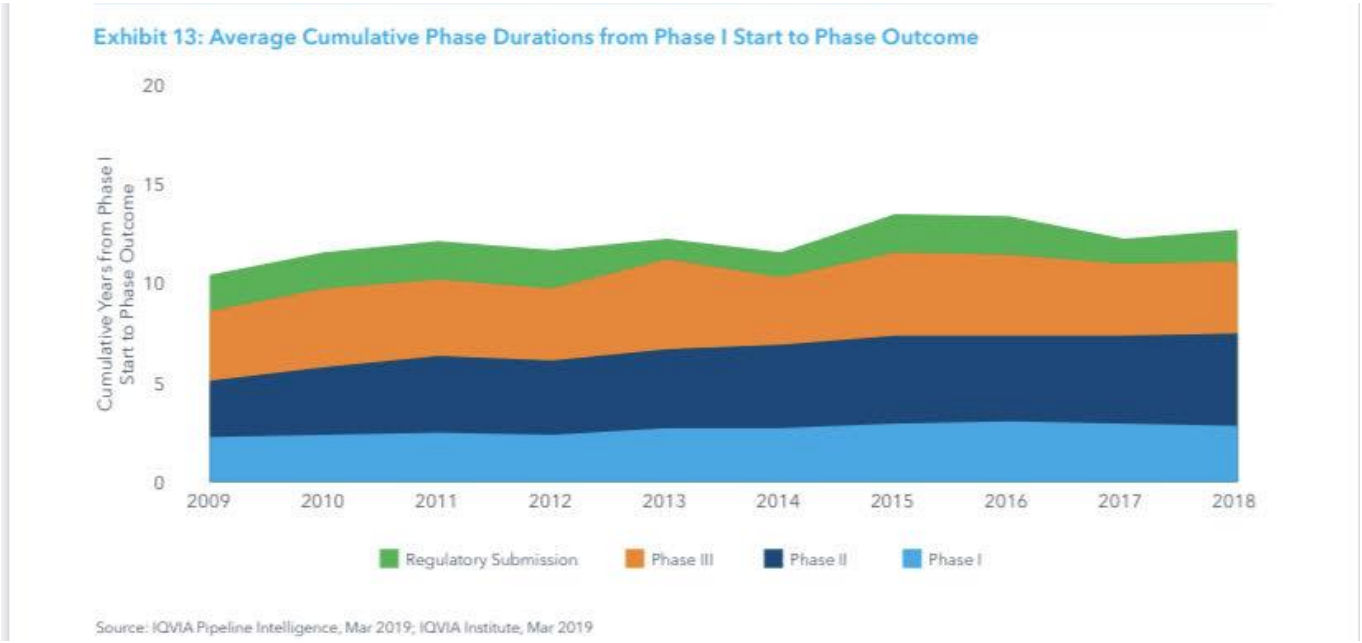
The six studies of multiple drugs or devices each ascribe reasons for the time lags observed and some offer policy measures. These are now presented by study.

IQVIA (2019)

IQVIA (2019) provides an annual comprehensive overview of the time lags for new drugs. Figure 6.2 shows the changes recorded over time for drugs approved in the years 2009 to 2018. The longest lags were in 2015, and subsequently the cumulative period required has reduced slightly, mainly because of faster FDA regulatory decisions. The phase II period is the longest and has the lowest average success

rate at 39% for the period 2008 to 2018, compared with 57% for phase I, 68% for phase III trials and 90% with regulatory submissions. In 2018, 59 new active substances took a median of 13.6 years from the time of first patent filing to the launch of the medicine in the USA. This was two years faster than those in the prior two years and almost 6 months faster than the median of the past five years. Among these 59 new drugs launched in 2018, 4 were launched in less than 8 years from first patent filing, while 12 were launched more than 20 years after their first patent filing. Now over 70% of new drugs came through the FDA regulatory process under one of several tracks (priority review, accelerated approval, fast track or breakthrough status) intended to accelerate development and review. These processes have shortened average time lags; for example over the past 3 years, the drugs with accelerated approval designation and breakthrough status have had shorter times by 15% to 19% from patent filing to launch compared with those not on such pathways. Over the same period, the total time a drug has been tested in a patient population at time of approval has declined, together with a reduction in the mean number of patients included in trials. The latter reflects that new drugs are increasingly in niche indications or are orphan drugs.

Figure 6.2 Average cumulative phase durations from phase 1 start to phase outcomes



(Source IQVIA, 2019)

IVQIA (2019) looks at eight trends which it anticipates will reduce time lags:

- Biomarker test availability – this is judged to have the largest potential impact on duration of trials and success rate.
- Digital health and mobile technologies including use of wearables to collect quality data on efficacy, safety and patent experiences.
- Real-world data sources.
- Predictive analytics and AI.
- Shifts in types of drugs being tested, with more biologics, orphan and niched indications.

- Shifts in the regulatory landscape to encourage adaptive, iterative and pragmatic trial designs (e.g. expanding directly from phase 1 to efficacy trials), using risk-based monitoring and offering accelerated pathways.
- Increased focus on patient-reported outcomes.
- Registries with pre-screened patients/direct-to-patient recruitment to speed up enrolment by identifying eligible patients quicker.

Also relevant is an increased focus on patient-reported outcomes which can lead to accelerated trial times. For example, in cardiovascular trials, if the goals of care are patient-centred (such as exercise and quality of life), trial duration may shorten because such endpoints do not require lengthy study durations compared with survival related based endpoints.

IQVIA estimate there is an 85% likelihood that the impact of these developments will be positive in terms of reducing the duration of trials and increasing their success rate, with the benefits realised within the next 2 to 4 years.

6.7.1 The Institute of Cancer Research (2018)

The Institute of Cancer Research (2018) analysed each of 97 cancer drugs in 177 indications licensed by the European Medicines Agency (EMA) from 2000 to 2016, across 2 periods, 2000 to 2008 and 2009 to 2016. The analysis found drugs appraised by NICE (n = 107) took 14.1 years from patent to NICE decision in the later period, 1.4 years longer than the 12.7 years achieved in the earlier years. A second analysis of all 177 indications measured the time lags from phase 1 trial launch to EMA authorisation and found the period has increased from 7.8 years to 9.1 years.

A more detailed comparison showed:

- The time required to progress drugs from the filing of patents through preclinical development to the start of phase I trials was steady at about 3.5 years in each period.
- The average time from the start of a phase I trial to EMA authorisation increased from 7.8 years (2000 to 2008) to 9.1 years (2009 to 2016).
- Since 2009, NICE has reduced the lag time between EMA authorisation and beginning its appraisal from a mean of 21 months to 6.5 months, with the median time now being 0 months as NICE is often starting its appraisal before EMA has issued a licence.
- The NICE average time from starting an appraisal to final approval is still 16 months.

Hence delays in taking drugs through clinical trials and licensing is the cause of the longer approval period. Reasons include that researchers now face excessive bureaucracy in setting up and gaining approval for clinical trials under the EU Clinical Trials Directive. This may have inhibited pharmaceutical companies adopting innovative trial designs and the authors suggest companies are becoming more risk averse which means decisions take longer. These hurdles are causing delays which mask any benefit

from various licensing and regulatory initiatives (such as the Cancer Drugs Fund) aimed at speeding up access to new cancer drugs.

The authors see a greater role for academic organisations in bearing the risks associated with developing drugs for hard-to-treat cancers where unmet need is greatest. They are also seen as innovators in terms of clinical trial design and using biomarker tests to select patients for treatment. Other changes recommended include:

- Adopting outcomes such as patients' health-related quality of life and progression-free survival rather than overall survival.
- Introducing price negotiations earlier in the evaluation.
- NICE reviews its approach to decision-making for highly innovative cancer drugs to address why only 40% of such drugs received a positive recommendation.
- Monitoring the recently introduced EU Clinical Trials Regulation.

6.7.2 Horgan (2018)

Horgan (2018) separates the drug development process into three phases being:

- Phase 1: Lab to industrial application includes all development activities and undertaking clinical trials.
- Phase 2: Industrial application to market includes developing marketing strategies, market approval dossiers and managing intellectual property rights.
- Phase 3: Market to healthcare system implementation includes developing the drug's place in the clinical pathway and reimbursement decisions.

Phases 1 and 2 are judged to take 5 to 10 years, with a further 5 to 10 years required for phase 3.

The authors make two suggestions to reduce these timelines being:

- Involving all major stakeholders throughout the decision-making process to reduce time and investment uncertainty. The EMA's pilot adaptive licensing approach is an example of this. This is a prospectively planned process, starting with the early authorisation of a medicine in a restricted patient population, followed by iterative phases of evidence gathering and adaptations of the marketing authorisation to expand access to the medicine to broader patient populations. The aim is to improve timely access for patients to new medicines. The authors proposed that HTA agencies also be involved in this process thereby enabling parallel assessments of safety, clinical efficacy and cost effectiveness of the technology.
- Ensuring a public health perspective is considered at each phase, identifying 10 public health issues which need to be addressed before genome-based technologies can be introduced widely.

The paper goes on to develop a model which parallels health technology assessment alongside the stages of clinical development and requires intensive involvement of a wide range of stakeholders at every step (e.g. when moving from phase II trials to phase III and again at phase IV trial design).

6.7.3 Uygur (2017)

Uygur (2017) measured the time lag between patent application and approval of 97 new cancer drugs indicated for breast, prostate or lung cancer. The authors then reported the reasons identified for these lags as identified by interviewing key opinion leaders.

The average time from patenting the drug to FDA approval was calculated to be 11 years, 10 years and 10.4 years, respectively for drugs to treat breast, lung and prostate cancer.

Reasons identified for the time lags included:

- Problems in reproducing similar results across several research studies. These can arise from weak/over complex study design, inappropriate statistical analysis, small sample size, and stability or contamination issues with the chemical and biological ingredients.
- Competition between pharmaceutical companies to commercialise compounds prevents collaboration which could speed up processes.
- Intellectual property restrictions prevent effective dissemination of new scientific discoveries thereby limiting the knowledge base to inform future R&D.
- Difficulties in aligning objectives, cultures, controls and decision-making within public/private partnerships leading to weak or ineffective partnerships.

The authors also observed that a 'general disconnect' existed between academia and pharmaceutical companies concluding that 'stronger connections between academia and pharmaceutical companies, thus increasing clinical research knowledge of academic scientists would go far to bring better pace and synergy in biomedical research.'

6.7.4 Putera 2015

Putera 2015 compared the time from publication of the pivotal clinical trial (PCT) to informing a clinical guideline recommendation to achieving 90% practice uptake for 15 drugs to manage acute coronary syndrome. The median time lags were 2 years (interquartile range IQR, 1-4 years) from PCT to practice guideline recommendation, 14 years (IQR, 11-15 years) from guideline recommendation to 90% practice uptake, and overall, a 16-year median (IQR, 13-19 years) from PCT to 90% practice uptake.

Reasons given for the slow adoption of clinical guideline recommendations were: poor knowledge diffusion, a tendency to await feedback from early adopters, the lack of experience with new agents and their indications, and clinical inertia. Steps to improve the adoption rate include new learning

methodologies and platforms for disseminating information, more effective quality improvement initiatives (pay for performance incentives), and developing decision support tools to embed the guidance into electronic health systems.

A key limitation with the study was it did not consider external factors that were occurring during the study period. Examples include the impact of:

- Newer competing therapies particularly percutaneous coronary intervention which changed completely key clinical pathways.
- Outcomes from post-surveillance studies which were not as good as the efficacy results from the clinical trials.
- The indications for ACS evolved across the study period.

Such new knowledge impacted on the uptake of several of the drugs included in the study.

6.7.5 Ward 2015

Ward 2015 measured the time period from first studies in humans to receipt of Marketing Authorisation (MA), subdivided into clinical trial and regulatory approval periods for 48 antiviral drugs licensed in the UK between 1981 and 2014. The overall mean duration of clinical development was 6.4 years, of which 5.4 years was spent in clinical trials before regulatory submission. The clinical development phase increased steadily from 3.5 years for drugs licensed between1981–1992, to 5.3 years for the period 1993 to 2003 to 7.6 years for drugs licensed 2004–2014. This increase was accounted for by an increase in the clinical trials period and not the regulatory approval period. The latter reduced slightly from 1.3 years to 1.1 years.

The authors noted initiatives are underway within the regulatory environment to address the problem including implementing a revised EU Clinical Trials Directive [35] and the EMA's adaptive licensing pilot[36] and the MHRA's Early Access to Medicines Scheme, which allows patients with serious conditions to access medicines that have not yet been approved but where there is a clear unmet medical need.[37] These schemes all have a greater role for the collection and use of real-world data to support regulators in delivering earlier adoption of innovative new drugs. These also example earlier dialogue between regulators and pharmaceutical companies. Health technology assessment (HTA) agencies in Europe,

[35] The Clinical Trials Regulation came into force in 2019 to 'to address the disharmonised interpretation of the Directive across EU countries, and the administrative and regulatory burdens it imposed on the conduct of clinical trials.' https://ec.europa.eu/health/human-use/clinical-trials/regulation_en

[36] The aim is to improve timely access for patients to new medicines. The pilot is a prospectively planned process, starting with the early authorisation of a medicine in a restricted patient population, followed by iterative phases of evidence gathering and adaptations of the marketing authorisation to expand access to the medicine to broader patient populations. https://www.ema.europa.eu/en/news/european-medicines-agency-launches-adaptive-licensing-pilot-project

[37] Under the scheme, the MHRA will give a scientific opinion on the benefit/risk balance of the medicine, based on the data available when the early access submission was made. https://www.gov.uk/guidance/apply-for-the-early-access-to-medicines-scheme-eams

either alone or in parallel with safety regulators, are also encouraged to start discussions with pharmaceutical companies earlier to influence data collection, particularly in respect of patient outcomes.

6.7.6 Farkas 2016

Farkas 2016 undertook the first and so far, only study of the time lag between date of the first patent application and CE mark approval for medical devices. Analyses were conducted by risk category for 61 devices. In risk category I (low risk) the median time period was 5.8 years, rising to 6.1 for category II devices and 10.3 years for those in category III.

One reason for the increase in time for category II devices is the increased regulatory requirements on evidence. A major limitation with the study is only a few manufacturers patent their discoveries and hence the sample is completely biased to a sample of such manufacturers. This start date was selected to facilitate comparisons with the development pathway for new drugs. However, as a consequence, the results may not generalise to all devices.

6.8 Discussion

The Institute of Cancer Research (2018) provides the most robust evidence about time lags and their trajectory over time from a European perspective. Whilst the analyses are limited to cancer drugs these do form up to 30% of the new drugs being launched (IQVIA, 2019).

Under both measures (time from phase 1 trial launch to EMA authorisation and time from patent date to NICE decision) the researchers reported times had increased by about 1.3 years from 2009 to 2018 compared with 2000 to 2008. The increases all occurred between the start of phase 1 and the regulatory submission. This is despite the EMA offering accelerated pathways for drugs addressing areas of unmet need. The authors identify increasing bureaucracy under the 2004 EU Clinical Trials Directive as a key driver of the increase in time lags, together with the pharmaceutical industry becoming increasingly risk adverse. The latter effect may be associated with a trend to a lower success rate. For example, IQVIA (2019) reported the success rate from phase 1 to regulatory approval was 12.0% over the 3 years from 2016 to 2018, down from a long-term annual average 13.8% from 2008 to 2018

These findings align with those reported by IQVIA. The data for the couple of years from 2016 to 2018 suggest that in the USA time lags from patent to launch have started to fall gradually, with several reasons to anticipate that this trend will continue.

The Institute of Cancer Research (2018) anticipated the new (now introduced) EU Clinical Trials Regulation, hoping it would encourage innovation in trial design such as the use of more adoptive trials. They suggest academic organisations may need to lead the way in such innovation, as these

organisations may be better placed to bear the risks associated with such trials. However, as Uygur (2017) notes academic institutions and pharmaceutical companies have to overcome difficulties arising from the differing backgrounds cultures and finance structures to make effective public/private partnerships.

IQVIA and The Institute of Cancer Research agree that using biomarker tests and patient reported outcomes can also improve trial productivity, with the latter also encouraging NICE to start price negotiations earlier in the evaluation. Indeed, earlier engagement by clinical efficacy, safety and economic regulators is endorsed by others including Horgan (2018) and Ward (2015). The authors suggest earlier dialogue could help shape late stage trials and ensure endpoints are available to inform important patient outcomes and populate economic models.

Only one of the studies (Ward, 2015) referred to the model and milestones developed by Hanney (2015), noting that the time line adopted in their study was limited to just two of Hanney's four tracks (first in human trial to regulatory approval). Similar timelines were reported for the single drug studies. The problem with adopting Hanney is uncertainty about the start date for primary research and how to define clinical practice. For example, Putera (2015) sought to measure the time to widespread clinical adoption but the analyses are partial and ignored confounders, particularly new developments occurring at the same time as a case study drug which impacted materially on the potential take-up of a drug. Ward (2015) relied on data from national sources to ensure the dates were accurate and comprehensive.

The data from the single drug studies are difficult to assimilate because the studies are into new indications and not new chemical entities. This approach ignores the research and development and existing studies undertaken before the first phase II study. Often no phase I is needed for a new indication as the optimal dose and safety profile is already established.

These lags are somewhat shorter than the lags observed by the studies calculating the IRRs for the four diseases (see Section3). The disease specific lags were 12 years for new mental health interventions, 15 years for cancer drugs, 16 years for MSK and 17 years for coronary vascular disease interventions. The differences can be attributed to different start and stop periods, with the disease specific interventions extending beyond regulatory approval to include a measure of the time associated with adoption activities.

6.9 Conclusion

Large studies have shown the time lag between patent registrations or date of first human trial and conclusion of the regulatory process has increased over the last ten years in Europe and the USA. These increases occur during the clinical trial phase and reflect the increasing complexity of trials and the associated regulation. Both regulators, the EMA and FDA have taken steps to accelerate the approval of

drugs where the drug is 'of major interest for public health and therapeutic innovation' (EMA) or manages 'serious conditions that fill an unmet medical need' (FDA).

Recently in the USA this trend has been reversed, with time lags reducing year on year for the last three years. The EMA has introduced a new Clinical Trial Regulation with the aim of improve trial efficiency and transparency,[38] whilst the FDA has issued guidance on using adaptive trials to: 'make drug development more efficient, less costly, while also increasing the amount of information we can learn about a new product's safety and benefits and increase the amount of competition in the market'.[39]

Improving the regulatory environment is only one of several initiatives which are anticipated to reduce the time lag during the clinical trials and regulatory phases of translational research. Monitoring whether the benefits from this and other anticipated changes are delivered should be possible through the annual IQVIA reports. Research is needed into speeding up the pure research and adoption phases, neither of which have been explored. Data from the single trials suggest the research stage is possibly the longest of any of Hanney's four tracks.

Reducing time lags improves the IRR from investment in new drugs and are an important driver to encourage new innovation. For example, a drug with an anticipated IRR of 16%, assuming a 15 year lag, could improve the IRR to:

- 16.9% with a reduction of 1 year in the lag to 14 years
- 18.9% with a reduction of 3 years in the lag to 12 years
- 21.5% with a reduction of 5 years in the lag to 10 years.

[38] https://www.ema.europa.eu/en/human-regulatory/research-development/clinical-trials/clinical-trial-regulation

[39] https://www.fda.gov/news-events/fda-brief/fda-brief-fda-modernizes-clinical-trial-designs-and-approaches-drug-development-proposing-new

7 Cost of Capital

7.1 Summary

A high-level literature search was conducted on the cost of capital in the private and public sectors and specifically that applying to pharmaceutical companies.

Findings include that the hurdle rate applied to new investment by private sector companies is around 12%, substantially higher than the cost of private sector capital of around 6.5% post-tax and 8% pre-tax (both nominal). The cost of capital for the pharmaceutical sector seems to be similar or higher than the market overall (excluding financials), possibly reflecting the risky nature of the spend on R&D.

The private sector rates are about 1% higher than the nominal rates of 5.5% implied by HM Treasury's annual discount rate of 3.5% in real terms. This difference can be 'explained/justified' because all external government borrowing is debt funded. This has a lower cost of capital than equity. However, the Treasury's rate is not calculated with reference to the cost of raising funds.

The differences between the public and private rates could in theory result in misallocation of investment funds in favour of the public sector, but this does not factor in capital rationing. The public sector does not have access to unlimited funds so this potential detriment may not arise; rather capital rationing limits investment.

7.2 Background

The cost of capital is closely related to the discount rate and sometimes the terms are used interchangeably. Indeed the term has been used to mean:

- The cost to a private sector company to service its current debt and equity funding.
- The minimum required (ex-ante) rate of return on a project or investment which must be achieved before the project will be commissioned.
- The discount rate used to calculate the present value of future cash flows from a project or investment for balance sheet valuations or other similar purposes (e.g. in the national accounts.

Where we are summarising a paper we have used the terms in the original papers but also clarified their meaning in respect of these three functions.

In this section we report the findings of a high-level literature search on the cost of capital. The cost to the public sector is reported initially followed by an analysis of findings on the cost to private sector entities before focusing on pharmaceutical companies.

7.3 Methodology

A literature search of the following databases: JSTOR and RePEC (Research Papers in Economics) using the terms 'discount rates' and 'cost of capital' was undertaken. Studies were limited to from 2000 and in English. The following websites were also searched using the same terms: HM Treasury, ONS, Bank of England, Office of Budgetary Responsibility and the National Institute of Economic and Social Research.

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- The cost to a private sector company to service its current debt and equity funding.
- The minimum required (ex-ante) rate of return on a project or investment which must be achieved before the project will be commissioned.
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Where we are summarising a paper we have used the terms in the original papers but also clarified their meaning in respect of these three functions.

7.4 Values Used in the Public Sector

HM Treasury's Green Book provides public sector bodies with guidance on the long term discount rates to be applied when discounting future cash flows in policies, programmes and projects (HM Treasury, 2018). The current annual discount rate of 3.5% in real terms has been applied since 2003. It has two components:

- Time preference rate of 1.5% capturing the preference for cash now rather than later.
- A wealth effect of 2% that captures the expected growth in per capita consumption over time.

More details on the calculations and application are provided by HM Treasury (2018).

One exception is that the discount rate to apply to health and life values is 1.5% i.e. the social time preference rate only.

HM Treasury used to prescribe much higher test discount rates (hurdle rates) for the public sector (8% in real terms in 1967, raised to 9% in 1969). The rationale was that a necessary condition for welfare maximisation requires that the marginal rate of return on new investment in the public sector should be equal to that in the private sector (Heald, 1980). Applying a lower rate in the public sector was judged to lead to an inefficient allocation of resources. In 1978 the Government moved away for a test discount rate to requiring that public sector bodies achieved a rate of return on investment of 5% in real terms. Higher hurdle rates were to be set by each public sector body to reflect aspects such as the

proportion of new investment that was non-revenue producing and observed project optimism (obtained by comparing ex-post and ex-ante returns across their portfolio of investments.

Note a 3.5% real annual discount rate in the public sector is not directly comparable to the rates reported in the next section for the private sector. The latter are nominal rates. A recent Office of Budgetary Responsibility (2020) forecast is for inflation of 2% over the medium term, consistent with a nominal rate of 5.5%. A second difference is that the private sector uses a cost of capital based on the cost to raise funds; the Treasury's rate is not linked to the cost to the Government of raising funds.

7.5 Department of Health and Social Care Group

The DHSC Group Accounting Manual (GAM) 2019 - 20 provides guidance on the Treasury discount rates to be applied by DHSC Group companies in respect of valuing financial assets and liabilities such as pension liabilities and financial instruments. The rates are revised each year in a Public Expenditure System paper, with the most recent one issued in December 2019 (HM Treasury. 2019). Other than for valuing these highly specific assets all DHSC Group companies should comply with the provisions in the Green Book (HM Treasury, 2018).

7.6 ONS

It almost all its work, the ONS applies a real 3.5% annual discount rate to discount future cash flows to their net present value. The justification for this rate is taken from HM Treasury guidance in the Green Book. A recent review of discount rates, commissioned by ONS, recommended that it continues to use this rate (Freeman, 2017). Reasons for retaining this rate included consistency of treatment across the accounts and comparability with the assessment of social costs and benefits in other areas of discounting, including the appraisal of public project proposals.

An exception identified by Freeman (2017) was when ONS is valuing non-financial investment capital held by the private sector. In such circumstances the authors recommended using a risk-adjusted discount rate[40] derived from applying the Capital Asset Pricing Model (CAPM) (see next section on rates in the private sector).

ONS also applies a higher discount rate is in respect of measuring the capital stock within the economy. The approach used is a Perpetual Inventory Method, with the value of capital stock being set equal to the expected value of future capital services, capitalised using an annual cost of capital (discount rate). In 2019 ONS revised its assumptions adopting a cost of capital of 1% real per quarter (approximately 4% per year). This rate was said to be consistent with the 3.5% real annual discount rate set out in the Green Book (ONS, 2019).

[40] The CAPM calculates a risk adjusted cost of capital not discount rates.

7.7 Private Sector

Most companies use a combination of debt and equity to finance their businesses and, for such companies, the overall cost of capital is derived from the weighted average cost of all capital sources, widely known as the weighted average cost of capital (WACC). Most companies use the capital asset pricing model to estimate their WACC.

The cost of equity is a function of the risk-free rate of return,[41] the market rate of return and each company's risk premium (beta). The cost of debt is the after-tax cost of interest charged by lenders.

The private cost of capital is used to inform similar decisions as in the public sector, including investment decisions on projects and programmes and valuing future cash flows as a stock value to carry on the balance sheet. This rate informs, but is lower than, the hurdle rate, which companies impose when making investment decisions. Usually, projects must show expected returns in excess of the hurdle rate before they can commence. The difference is a risk premium associated with the risk that ex-post returns may be lower than ex-antes (e.g. to address project optimism).

Recently, a Bank of England paper identified that the mean hurdle rate used in investment decisions (13.1%) is materially higher than the cost of capital measures (3.9% for WACC[42] and 2% for cost of debt). The hurdle rates were also more stable over time than measures of the cost of capital (Melolinna, 2018).

A related Bank of England paper reported survey evidence that the average hurdle rate across UK businesses was 12%, substantially higher than the cost of capital of around 6.5%. The authors suggested the high hurdle rate may be one reason for underinvestment (Saleheen, 2017).

One difference not explored in the paper is that the WACC is usually calculated after tax whilst hurdle rates are pre-tax. Currently the marginal rate of corporation tax is 19%, suggesting a pre-tax WACC of 8%.

7.8 Sectoral Analyses of the Cost of Capital

The United Kingdom Regulators Network (UKRN) publishes an annual report setting out the cost of capital used by each of the 13 regulators to inform price controls and other regulatory decisions. The median rate used is similar to the 6.5% identified by Saleheen (2017) but there is material variation reflecting sector specific risk. This approach seems consistent with the welfare maximisation argument that at the margin all sectors should face the same marginal cost of capital.

[41] Usually taken to be the yield on long-term gilts.

[42] It is assumed these are post-tax and nominal rates but the article does not discuss wither factor.

7.9 Estimates of the Cost of Capital outside the UK

A review of annual reports in the pharmaceuticals sector[43] identified that AstraZeneca applied a post-tax weighted average cost of capital of 7% for 2019, 2018 and 2017. This was used to value the cash flows from products which are capitalised on its balance sheet and in determining the fair value less costs to sell (AstraZeneca 2019). With a marginal corporation tax rate of 19%, this is equivalent to a pre-tax rate of 8.64%.

An earlier literature search identified that in 2012 there was a consensus that the cost of capital was around 11% real per annum (Mestre-Ferrandiz J, 2012). This rate was was obtained from a survey of 10 pharmaceutical firms and this does not necessarily reflect their weighted average cost of capital. Indeed it may reflect the hurdle rate applied to new investment.

The NYU Stern School of Business provides estimates of the cost of capital by sector showing cost of equity, beta values and cost of debt for quoted companies in Western Europe, the USA and global. Table 7.1 reports the values for drug companies in biotechnology and pharmaceuticals, compared with the market (excluding financial sector) averages for 2019. The WACC reported for pharmaceuticals is 6.5%, a 1% higher rate than the average for all companies. Market returns in Europe are lower than global returns or those in the USA. This may simply be a function of the economies being at different points on the business cycle, with differing expectations of growth future cash flows.

Table 7.1 Components of the cost of capital for Western European companies, USA and global (2019)

	No of firms	Beta	Cost of equity	After tax cost of debt	Cost of capital	Global	USA
Drugs (biotechnology)	202	1.46	10.7%	3.3%	8.5%	9.9%	8.6%
Drugs (pharma)	116	1.15	8.8%	3.4%	6.5%	8.9%	8.5%
Total market excluding financials			8.4%	3.4%	5.5%	7.25%	6.9%

The authors explain that the higher cost of capital for pharmaceutical companies among others, arises from their need to make significant capital investment in research, development, equipment, and factories. This is judged to increase their risk.

KPMG also conduct cost of capital studies but only for 216 companies in Germany, Austria and Switzerland, of which 6 were pharmaceutical companies. This reported an average WACC (after corporate taxes) of 7%, the same rate as in the previous three years. This was also the rate for companies in the chemicals & pharmaceutical sector.

[43] This was conducted to establish the accounting treatment of R&D.

DiMasi (2016) estimated the research and development costs of 106 randomly selected new drugs from a survey of 10 pharmaceutical firms. One input was the cost of capital which was calculated using the CAPM (see Table 7.2). The cost of capital was reported to have declined over time for this sector but no rationale for this is offered.

Table 7.2 Nominal and real post-tax cost of capital for the pharmaceutical industry, 1994–2010

	1994	2000	2005	2010
Nominal cost of capital	14.2%	14.9%	13.3%	11.4%
Inflation rate	3.1%	3.1%	2.5%	2.0%
Real cost of capital	11.1%	11.8%	10.8%	9.4%

A 3% discount rate was used as a proxy for a social discount rate to reflect the cost of publicly funded R&D.

7.10 Conclusions

The hurdle rate applied to new investment by private sector companies is around 12%, substantially higher than the cost of private sector capital of around 6.5% post-tax and 8% pre-tax (both nominal). The cost of capital for the pharmaceutical sector seems to be similar to the market overall (excluding financials), possibly a point higher to reflect the risky nature of the spend on R&D.

The private sector rates are about 1% higher than the nominal rates of 5.5% implied by HM Treasury's real rate of 3.5%. This difference can be 'explained' because all external government borrowing is debt funded. This has a lower cost of capital than equity. However, the Treasury's rate is not calculated with reference to the cost of raising funds.

The differences between the public and private rates could in theory result in misallocation of investment funds in favour of the public sector, but this does not factor in capital rationing. The public sector does not have access to unlimited funds so this potential detriment may not arise.

8 Accounting for Biomedical Research and Development Expenditure

8.1 Summary

Differences in the depreciation/amortisation of research and development expenditures are not between the public and private sectors but rather are a function of geography (USA vs the rest of the world) and between the NHS and universities due to their differing accounting standards. The USA standards and those applying to UK universities apply more stringent rules to capitalising R&D spend than apply to international companies or the UK government sector.

Findings from sectoral studies suggest that the 11% annual depreciation rate applied by ONS in the national accounts to depreciate the stock of R&D related assets is too low, with pharmaceuticals being the one possible exception. Observers have noted several factors that may contribute to the relatively longer asset lives of pharmaceuticals, including the long-term nature of its research, effective patent protection and other entry barriers.

No empirical studies calculated the return to public-funded R&D or a social return. The measure for the public returns as used in the national accounts are informed by surveys and patent information.

8.2 Background

The value of medical research, and consequently the NIHR biomedical investment is affected substantially by the rate at which medical research findings depreciate, and whether this differs between publicly and privately funded research.

We explore this in two ways:

- The accounting standards applying to research and development expenditure in the private, university and NHS sectors.
- The wider literature on the depreciation of medical research within national accounts, or all research where no industry-specific rates are used.

8.3 Methodology

To address the first aspect, a review of the accounting standards applying to research and development expenditure in the UK private, university and NHS sectors and internationally was conducted.

The second aspect was addressed by a literature search of the following databases: JSTOR, MEDLINE, SSRN: Social Science Research Network, EconLit and RePEC (Research Papers in Economics). The terms used were specific being: 'depreciation of medical research', 'depreciation of research', 'depreciation of R&D' and depreciation of pharmaceutical research'. Studies were limited to from 2000 and in English. Two author searches were also conducted: Bronwyn H. Hall *University of California at Berkeley and* Henry Grabowski, Duke University and searches were also conducted of the HM Treasury and Office of National Statistics (ONS) websites.

8.4 UK and International Accounting Standards on Research and Development Expenditure

All UK quoted companies and Government departments must follow the International Financial Reporting Standards (IFRS).[44] Three standards are relevant to the accounting treatment of research and development expenditure.

Firstly, under International Accounting Standard (IAS) 16, research expenditure may create tangible assets (property, plant and equipment) if the assets are:

- Held for use in the production or supply of goods or services, for rental to others, or for administrative purposes.
- Expected to be used during more than one period.

Each asset is depreciated over its useful life, with the cost being a charge to the profit and loss account. The depreciation method used should reflect the pattern of the asset's expected future economic benefits.

IAS 38 sets out the criteria for recognising and measuring intangible assets. An intangible asset is: 'an identifiable non-monetary asset without physical substance. Examples include computer software, licences, trademarks, patents, films, copyrights and import quotas.' Such assets must:

- Give rise to quantifiable future economic benefits.
- Ensure its cost can be reliably measured.[45]

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[44] Small and medium sized companies must comply with a national reporting standard FRS 102.

[45] The full criteria require an intangible asset to demonstrate all of the following:

- The technical feasibility of completing the intangible asset so that it will be available for use or sale.
- An intention to complete the intangible asset and use or sell it.
- An ability to use or sell the intangible asset.
- How the intangible asset will generate probable future economic benefits
- The availability of adequate technical, financial and other resources to complete the development and to use or sell the intangible asset.
- The ability to measure reliably the expenditure attributable to the intangible asset during its development.

Research expenditure is recognised as an expense to charge to the profit and loss account but development expenditure that meets these criteria can be carried on the balance sheet as an intangible asset. If the difference between research and development cannot be distinguished the spend is classed as revenue.

Intangible assets are measured initially at cost but later may adopt a fair value in '*rare case*s' when fair value can be determined by reference to an active market.

An intangible asset with a finite useful life is amortised and is subject to impairment testing. An intangible asset with an indefinite useful life is not amortised, but is tested annually for impairment. When an intangible asset is disposed of, the gain or loss on disposal is included in profit or loss. If entities cannot make a reliable estimate of the useful life of an intangible asset, the life shall not exceed 10 years.

IAS 36 addresses the impairment of assets. The core principle is that an asset must not be valued in the balance sheet at more than the highest amount to be recovered through its use or sale. If the value exceeds the recoverable amount, the asset is 'impaired.' The company must reduce the value of the asset to its recoverable amount, and charge the impairment loss to the profit and loss account.

The recoverable amount is the higher of (a) fair value less costs to sell and (b) value in use. Fair value less costs to sell is the arm's length sale price between knowledgeable willing parties less costs of disposal. The value in use of an asset is its expected future cash flows discounted using an appropriate discount rate.

The recoverable amount must be assessed when impairment is judged likely; for example, if there is a change in market conditions, or useful life or related technological advances that impact on an asset. In such cases, the company must review its previous estimated discounted cash flows and, if current expectations differ, amend the residual value, amortisation method or useful life.

An impairment loss is recognised immediately in the profit and loss account. The depreciation (amortisation) charge is adjusted in future periods to allocate the asset's revised carrying amount over its remaining useful life. An impairment loss can be reversed if subsequently projected cash flows increase.

The disclosure requirements on intangible assets require entities to provide:

- The net book value and remaining amortisation period of any individual asset that is material to the entity's financial statements.
- The total gross book value, accumulated amortisation charges, current amortisation charge and net book value of all intangible assets.
- The methods and significant assumptions applied in estimating the assets' fair values.

- Additions, disposals revaluations and impairment losses, for intangible assets generated internally and separately for those acquired assets.

8.5 Comparison with US Generally Accepted Accounting Principles (GAAP)

Public companies in the United States must follow GAAP when compiling their financial statements. The main differences between IFRS and GAAP in respect of intangibles assets are:

1) GAAP prohibits the revaluations of intangible assets to fair value.
2) GAAP criteria on recognising intangible assets are more restrictive, so recognising internally developed intangible assets is rare and usually only occurs for patents and trademarks.
3) Hence, with limited exceptions, research and development costs are expensed as incurred.[46]

Research suggests that, on average, profit reported under IFRS is higher than that reported under GAAP (Parker, 2020).

8.6 NHS Accounting Treatment of Research and Development Expenditure

DHSC publishes annually a Group Accounting Manual (DHSC, 2020) which sets out the accounting principles to be followed by all DHSC group bodies. The manual states these bodies must adopt IFRS accounting standards and comply with HM Treasury's 'Financial Reporting Manual'. Thus in respect of research and development expenditure, NHS bodies, must adopt the same treatment as large private sector companies, reporting research and development as revenue spend, except where IFRS permits capitalisation of an asset.

8.7 Universities' Accounting Treatment of Research and Development Expenditure

Universities comply with the 'Statement of Recommended Practice' (SORP). These are sector specific accounting standards which contain the provisions in Financial Reporting Standard (FRS) 102 plus supplement these with sector specific guidance.[47] For example, the SORP contains specific provisions related to income received from research grants and contracts awarded by UK research councils and other bodies. It also has provisions related to arrangements between universities and teaching hospitals which cover BRCs.

SORP provisions in respect of intangible assets differ marginally from IFRS provisions. For example, the SORP adopts a slightly narrower definition of intangible assets requiring that the asset must be capable

[46] Source: Parker S. National Professional Standards Group, RSM US LLP. U.S. GAAP vs. IFRS: Intangible assets other than goodwill. 2020. Available at https://rsmus.com/pdf/us_gaap_ifrs_intagible_assets_other_than_goodwill.pdf

[47] FRS 102 applies to the financial statements of all UK entities that are not applying EU-adopted IFRS, including those that are not constituted as companies and those that are not profit-oriented.

of being separated from the entity and sold or licensed. Asset lives are limited to the period of any contractual or legal rights. However, the approach to amortisation, recognising impairment and disclosure are very similar. Overall, SORP is likely to result in possibly more costs being charged to the profit and loss account than is the case for the larger entities applying IFRS.

8.8 Conclusion on the Depreciation of Medical Research and Development

Large UK companies and NHS bodies must comply with IFRS standards on research and development expenditure. These differ slightly from the equivalent standards that apply to large US companies, with the effect being to enable more expenditure to be capitalised by companies adopting the international standards. UK universities must comply with a sector-specific SORP that aligns with FRS 102. These standards also are likely to have the effect of charging more research and development expenditure to the profit and loss account. Hence the difference in treating depreciation/amortisation of research and development expenditures is not between the public and private sectors but rather is a function of geography (USA vs the 166 countries that require quoted companies to comply with IFRS) and between the NHS and universities due to their differing accounting standards.

Under all accounting standards, BRC funded investment should be expended in the year it is incurred.

8.9 Example of the Application of the Accounting Standards

This section has extracted the accounting policies from AstraZeneca's (AZ) annual report and accounts to demonstrate use of the standards. It provides a good example of the recording of impairment value under IAS 38. AZ accounting polices include that intangible assets are linked to individual products and that product cash flows and value are determined as the higher of an asset's fair value less costs to sell or value in use, in both cases using discounted cash flow calculations where the products' expected post-tax cash flows are risk-adjusted over their estimated remaining useful economic life. The risk-adjusted cash flows are discounted using AstraZeneca's post-tax weighted average cost of capital (7% for 2019, 2018 and 2017).

AZ notes that the estimates used in calculating the recoverable amount are a key audit matter being: 'significant, highly sensitive and depend on assumptions e.g. on the outcome of outcome of R&D activities, probability of technical and regulatory success, market volume, share and pricing and sales erosion following patent expiry'.

In 2019, the Group recorded impairment charges of $425m in respect of four launched products as a result of revised market volume, share and price assumptions. AZ also recorded impairment charges of over $600m against products in development as a consequence of failed or poor performing trials. Sensitivity analysis assuming a 10% change in revenue projections and a one-year change in useful economic lives were presented.

In contrast, Abbott and Bristol-Myers Squibb, both domiciled in the USA, have a policy of expensing all internal research and development costs and third-party costs related to clinical trials as incurred.

GSK, a UK company, capitalises development expenditure when the criteria for recognising an asset are met, 'usually when a regulatory filing has been made in a major market and approval is considered highly probable'. This seems more conservative than AZ.

We examined the report and accounts of several NHS Trusts and all noted they adopt the IAS criteria before capitalising internal development expenditure.

Several reports and accounts for major universities were read. None reported capitalising development expenditure, which is in accordance with SORP 2019.

8.10 Accounting for R&D in National Accounts

The System of National Accounts (SNA) is the internationally agreed recommendations on compiling national accounts of economic activity[48] (Rassier, 2014). The latest version in 2008 recommended treating R&D[49] as an intangible asset rather than as a charge in the year it was incurred. One driver for the change was to enable countries to measure R&D's contribution to growth in real GDP (Fixler, 2009). This change required national bodies to address how to measure the capital value of R&D, its economic life and matching the annual amortisation charge to the economic benefit accruing to the nation. The SNA defines direct costs be the basis for measurement, thereby excluding any value from externalities, or third-party benefits.

R&D was first introduced into the UK national accounts in 2014. Then the ONS adopted a 7-year average life for all R&D, using methods set out in Ker (2014).[50] In 2019, the life was increased to 9 years (ONS, 2019). The increase was recommended by Rincon-Aznar (2017) in a study for ONS. This study reported the following comparisons for R&D asset lives: 7 years in Spain, 10 years in France and New Zealand, 9 to 11 years for South Korea, 9 to 15 years in the Netherlands and 5 to 30 years in Germany (5 years is used for intangible assets).

The UK uses data from business and government surveys and patent renewal data to calculate asset lives for R&D. International guidelines advise if no such information is available, an average service life

[48] The SNA 2008 is a collaboration of five international organisations: the United Nations, the European Commission, the Organisation for Economic Co-operation and Development, the International Monetary Fund, and the World Bank Group. Countries are encouraged to follow the recommendations provided in the international guidelines in order to facilitate the comparability of national income and product statistics.

[49] R&D was defined as: "Research and experimental development consists of the value of expenditures on creative work undertaken on a systematic basis in order to increase the stock of knowledge, including knowledge of man, culture and society, and use of this stock of knowledge to devise new applications." (SNA 2008, paragraph 10.103, 206).

[50] Ker's paper sets out the strengths and weaknesses of using surveys and patent information to calculate asset lives for R&D.

of 10 years should be used (Rincon-Aznar, 2017). The UK depreciates R&D expenditure using a Weibull distribution to match the declining productive efficiency of an asset over its life (ONS, 2019).

Australia and Israel also undertook surveys to estimate the average life of R&D and both adopted 11 years. Other countries used annual patent renewals as indicative of the duration of the innovation.

8.11 Pharmaceutical Specific Asset Lives

No UK industry-specific analysis of R&D depreciation rates was identified beyond the limited detail reported by Rincon-Aznar (2017). However, Mead (2007) described a literature survey which informed the assumptions used by the Bureau of Economic Analysis (BEA) in creating the USA's R&D accounts in 2008. The annual depreciation rates were industry specific: transportation 18%, computers and electronics 16.5%, chemicals 11% and for all other industries 15%. In 2006 the BEA applied 15% to all industries. The current rates are 9% for health R&D funded by the US Federal Government and 16% for any state or local government R&D (Rincon-Aznar, 2017).

Sectoral depreciation rates in the USA were most recently modelled by Li and Hall (2018). Their analyses built on earlier work by Hall (2005) that identified obsolescence rates and the extent of competition as the key drivers for differences in depreciation rates across industries. Their model used BEA industry-level data over 21 years from 1987 to 2007 for ten R&D-intensive industries. It assumed a two-year lag between the expenditure and profit generation, except for pharmaceuticals where a four-year lag was found.

The resultant rates showed a wide variation in depreciation rates from 49% for computer systems design, 36% for computers and peripheral equipment, 34% for aerospace, 31% for software, 30% for scientific R&D, 19% for communications equipment falling to the lowest rate of 11% for the pharmaceutical industry. This low rate was said to reflect 'the long-term nature of pharmaceutical research and the fact that R&D resources in pharmaceuticals are more appropriable by the firms that fund the R&D than those in other industries due to effective patent protection and other entry barriers.' The high entry barriers and associated low level of market competition enabled a low R&D depreciation rate compared to all other industries.

The authors also produced a time series of depreciation rates from 1990 to 2004, with the rate for pharmaceuticals halving over the period. This was attributed mainly to a slowing rate of technological change, possibly arising from stricter FDA approval guidelines impacting negatively on the industry's productivity growth in R&D.

The authors also calculated depreciation rates of 16% for the Japanese pharmaceutical industry, concluding that U.S. pharmaceutical firms have can better appropriate the returns from their investments in R&D assets.

Only one other recent study, Warusawitharana (2010), has reported depreciation rates for the US pharmaceutical industry for virtually the same period (1987 to 2006). This adopted a market valuation method and reported rates of 37% for the medical equipment industry and pharmaceuticals at 41%. An earlier study by Knott (2003) using a production function method reported rates of 88% to 100%.

Mead (2007) noted four different types of models (production functions, amortisation models, patent renewal models, and market valuation models) have been used to estimate R&D depreciation rates. The authors note there is no consensus on the best model, with all based on strong assumptions e.g. that firms operate in a perfectly competitive market place. Such assumptions are inconsistent with findings that low rates are consistent with monopolistic structures.

De Rassenfosse (2017) used survey responses and data from patents issued between 1986 to 2005 to model the R&D depreciation rate for Australian patented inventions. They found that in the first 2 years the depreciation rate averaged 8% to 9%, falling thereafter to between 1% and 5% per year. Patent protection was reported to reduce the annual depreciation rate by 1% to 2%. The pharmaceuticals and medicinal chemicals industry had the lowest depreciation rate and the smallest early decline in value but no values were reported.

No empirical study measured the depreciation rate of public-funded R&D, nor attempted to measure a social depreciation rate of R&D.

8.12 Conclusions on Accounting for R&D

The findings from the sectoral studies suggest that the 11% rate applied by ONS and the 15% rate applied by the BEA for many industries are too low, with pharmaceuticals being the exception. Given this evidence an 11% depreciation rate, equivalent to assuming a life of 9 years, seems appropriate to apply to biomedical related R&D.

- However, the methodology to calculate depreciation rates for private sector R&D is poorly developed, with four competing models all requiring strong assumptions. Recent studies of individual industries have consistently reported that the pharmaceutical industry has depreciation rates well below the average across private sector industries. Observers have noted several factors that may contribute to the relatively longer asset lives of pharmaceuticals, including the long-term nature of its research, effective patent protection and other entry barriers.

No empirical studies calculated the return to public-funded R&D or a social return. The best measures for the public returns are hence those used in national accounts. These are informed by surveys and patent information not econometric models. These sources have led authorities to adopt longer lives than those reported from detailed models.

Further research is warranted on the format of models and their underlying assumptions to enable them to model the monopolistic market structures that are often displayed by research and development/capital intensive industries.

9 Foreign versus UK Ownership of Biomedical Companies

9.1 Summary

The Office for Life Sciences estimated that in 2018 companies with owners outside the UK accounted for about 65% of the turnover in this sector, with UK owned companies accounting for 32% and unknown ownership the remaining 3%. Foreign owned companies also employed 52% of all staff, with UK companies employing 42% and 'unknowns' 6%. The 2017 statistics reported that 59% of all companies with ownership information were UK owned but that statistic is not reported for 2018.

9.2 Background

The ownership of companies is an important input into the DHSC model to calculate the return on capital to the UK public sector. This section reports findings on the ownership of pharmaceutical and biomedical companies operating in the UK.

9.3 Methodology

No literature search was undertaken. Rather the following websites were searched using terms including 'import', 'foreign', 'overseas', 'USA' and 'EU': Office of National Statistics (ONS), Office for Life Sciences (OLS), Association of British Healthcare Industries (ABHI), Association of British Pharmaceutical Industries (ABPI), Association of Medical Research Charities (AMRC), National Audit Office and Medical Research Council (MRC).

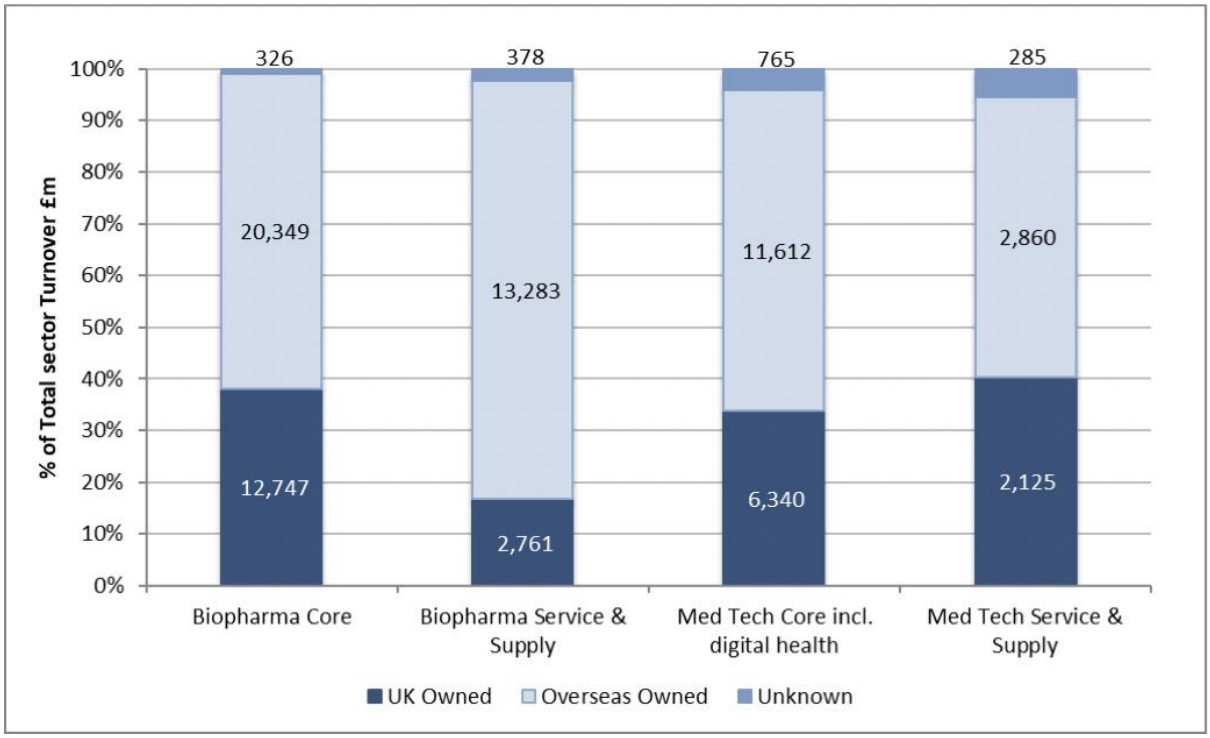
The importance of exports and imports to the R&D sector, using data from national input output tables, is also reported to provide a measure of import intensity in the production function and the importance of exports as a market for its output.

9.4 Findings

9.4.1 Office for Life Sciences

The Office for Life Sciences (2018) reported that there were 5,870 life sciences businesses with a presence in the UK, generating turnover almost £74bn and employing nearly 248,400 people. For 4,556 businesses (69%) ownership information was available. An analysis by ownership and turnover is set out in Figure 9.1. Companies with owners outside the UK accounted for 65% of the turnover in this sector, with UK owned companies accounting for 32% and unknown ownership the remaining 3%.

Figure 9.1 Distribution of sector turnover between UK and Overseas life sciences businesses 2018



Source Figure 12: OLS 2018

Foreign owned companies employed 52% of all staff, with UK companies employing 42% and 'unknowns' 6%. The 2017 statistics reported that 59% of all companies with ownership information were UK owned but that statistic is not reported for 2018.

Ownership varied by sector: under both measures, UK biopharma businesses had a higher foreign ownership component than MedTech businesses. For example, foreign owned companies generated 71% of biopharma's turnover and employed 62% of all staff in that sub-sector.

The earliest value reported by The Office of Life Science is for 2011, where 43% of companies in that sector were UK owned, similar to the value in 2017 of 41%. The impact of BRCs/BRUs on this value is unknown.

9.4.2 ONS

The ONS publishes details on spend by businesses on research and development, by sector and by ownership (ONS, 2018). Pharmaceuticals were the largest product group undertaking R&D, accounting for £4,463m (18%) of all such spend in the UK in 2018. This is down from a 29% share of R&D spend in 2010. Table 9.1 shows slightly more of this spend (52%) was made by overseas owned companies compared with 48% invested by UK owned companies.

Table 9.1 Expenditure on Pharmaceutical R&D Performed in UK Businesses by UK or Overseas Ownership

	UK owned	Overseas owned	Total
Pharmaceuticals	£2,135m (48%)	£2,327m (52%)	£4,463m

US owned companies conducted about 21% of all R&D performed by UK businesses, with EU owned businesses accounting for 15% and the rest of the world 17% (the balance is UK owned at 47%).

Table 9.2 shows how this spend was funded, with the majority of companies using internally generated funds, but 23% was associated with capital inflows from overseas sources.

Table 9.2 Sources of funds for pharmaceutical R&D spend 2018 (£M, %)

	UK Government	Overseas	Own Funds	Other	Total
Pharmaceuticals	£5m (0%)	£1,041m (23%)	£3,259m (73%)	£158m (4%)	£4,463m

The ONS notes the proportion of total R&D funding from overseas sources has declined from 24% in 2010 to 13% in 2018. No similar analysis for the pharmaceutical industry is available but given its dominant position in the sector, one can surmise that the importance of overseas funding to that sector has also declined.

9.4.3 UK Clinical Research Collaboration

The UK Clinical Research Collaboration publishes information on research conducted in the UK (UK Clinical Research Collaboration, 2020). This estimated that the UK has received £254m of funds for research from international organisations, overseas public bodies (mostly the European Union) and global charities. The estimated total R&D funds were £8.6bn, suggesting about 3% of these funds were from non-UK sources. However, it is not possible to separate out the proportion of the 97% funded by non-UK headquartered companies.

9.4.4 AMRC

AMRC's most recent impact report noted that 34% of their awards generated additional funding of £2.7bn. Of this sum:

- 73% of awards were funded by organisations in the UK.
- 19% were funded by any European source.
- 4% from the USA.
- 4% other counties or funds from more than 1 country.

The top 3 countries in Europe providing further funding (in terms of value) were Belgium, France and Germany (AMRC, 2019).

In 2013, the National Audit Office published a report on R&D funding for science and technology. Its findings are not reported as the data used have been superseded by later data from the ONS.

9.4.5 MRC

The MRC reports on the funding of 38 spin-outs emerging from research funded through its directed translational research portfolio. All but 2 of these spin-outs are UK headquartered companies. These raised £1.1 billion funding from 205 investors, of whom a third were headquartered overseas (largely in North America).

9.4.6 Foreign Content of Scientific Research & Development

The import and export content of the UK's non-profit R&D sector is now compared with that for all industries. The aim is to show the importance of imports to the industry's output and exports to its final demand. The most recent information is from the detailed 2015 input-output table. These report that imports are 5% of the total output of the non-profit R&D sector, rising to 8% for the R&D company sector, compared with 10% for all industries. R&D thus has a below average import content. In contrast, employees' compensation accounts for 33% of output in the R&D non-profit sector, double the

all industries average of 16%. Value added (57% of output) and gross operating surplus (23%) are also materially higher in this sector compared with all industry averages (33% and 13% respectively).

Turning to the demand for products produced by the non-profit R&D sector, 91% of the output is consumed by non-profit institutions serving households, essentially universities and charities, with 6% going to scientific R&D (companies) and the balance to health-related activities. No output is reported as being exported and none giving rise to gross fixed capital formation.

9.5 Conclusions

The Office for Life Sciences estimated that in 2018 companies with owners outside the UK accounted for about 65% of the turnover in this sector, with UK owned companies accounting for 32% and unknown ownership the remaining 3%. Foreign owned companies also employed 52% of all staff, with UK companies employing 42% and 'unknowns' 6%. The 2017 statistics reported that 59% of all companies with ownership information were UK owned but that statistic is not reported for 2018.

ONS data report that foreign owned companies were responsible for 53% of spend by pharmaceuticals companies on research and development.

Imports are not a major contributor to the output of the non-profit R&D sector and it exports hardly any of its output.

10 Regional Impact of BRC Funding

10.1 Summary

Since 2007, the Oxford, Cambridge and London BRCs have been awarded over 75% of NIHR funding and been the most successful at leveraging funds from other sources. Hence these BRCs have received 85% of total funds.

All other regions have received a share of funds which is materially below their population share. This is particularly notable for the North West, Yorkshire and Humber and the West Midlands.

Welfare economics suggests that increasing funding to these areas could improve equity.

Government policy to double R&D spend over the next five years offers the opportunity to 'level-up' these disadvantaged regions, consistent with other stated government priorities.

10.2 Background

The overall economic return on investment in biomedical research is not distributed evenly throughout the country. Biomedical research centres exist across England (see Figure 10.1), but funding is highly skewed towards the 'golden triangle': Oxford, Cambridge and London. Returns on this investment – particularly in terms of employment benefits to the local economy, but also in terms of health gains if innovation is more likely to be adopted in the area it is developed - are likely to be highly unevenly spread.

10.3 Methodology

No literature search was undertaken. Rather websites known to have information on regional economic indicators and populations were searched, with ONS being the key such database. Information was also found on the EU's statistical office website, 'eurostat'.

We also undertook a Google search to identify recent Government policy statements and policy documents.

The funds received by BRCs/BRUs in total and from NIHR were extracted from the annual data provided by the NIHR Programme Manager.

10.4 Findings

A regional analysis of BRC and BRU investment from DHSC/NIHR and in total is set out in Table 10.1 for the periods 2017/18 and 2018/19 and since 2007. The regional populations are also provided for comparison purposes.

Figure 10.1 Location of BRCs across England

Table 10.1 Regional analysis of investment from DHSC/NIHR received by BRCs and BRUs (£m)

Region	2017/8 to 2018/19	As % total	2007/08 to 2018/19	As % total	% of population
North East	£14.42m	4.3%	£64.81m	5.7%	4.7%
North West	£17.88m	5.4%	£45.10m	4.0%	13.0%
Yorkshire & The Humber	£2.94m	0.9%	£18.85m	1.7%	9.8%
East Midlands	£32.23m	9.7%	£78.45m	6.9%	8.6%
West Midlands	£7.02m	2.1%	£8.27m	0.7%	10.5%
East of England (Cambridge)	£24.59m	7.4%	£120.97m	10.6%	11.5%
London	£161.60m	48.6%	£551.77m	48.4%	15.9%
South East	£48.14m	14.5%	£217.75m	19.1%	16.3%
(Of which Oxford)	£38.95m	11.7%	£193.66m	17.0%	
South West	£23.50m	7.1%	£35.09m	3.1%	10.0%
England	£332.32m	100.0%	£1141.06m	100.0%	100.0%

The London centres have consistently received just under 50% of NIHR funding, with the Oxford/Cambridge/London groups receiving over 75% of all funds since 2007. In the last two years the proportion has dropped to 68%, with both Oxford and Cambridge receiving a smaller percentage of funds (down from 10.6% to 7.4% at Cambridge and 17.0% to 11.7% at Oxford. Further analyses of changes in funds, employees and staff costs across London, Cambridge, Oxford and others is provided in Section 4.

Comparing the relative share of NIHR funds received by BRCs and BRUs with their relative populations reveals that:

- The North West has 13.0% of the population but has received 4.0% of funds.
- The West Midlands has 10.5% of the population but has received 0.7% of funds.
- Yorkshire and the Humber has 9.8% of the population but has received 1.7% of the funds.
- London has 16% of the population but has received 48% of the funds.

Table 10.2 provides a regional analysis of total funds received by BRCs and BRUs, together with their regional populations.

Table 10.2 Regional analysis of total funds received by BRCs and BRUs (£m)

Region	2017/8 to 2018/19	As % total	2007/08 to 2018/19	As % total	% of population
North East	£46.31m	1.9%	£252.31m	2.8%	4.7%
North West	£123.02m	5.1%	£389.63m	4.3%	13.0%
Yorkshire & The Humber	£18.67m	0.8%	£171.55m	1.9%	9.8%
East Midlands	£125.92m	5.3%	£321.22m	3.6%	8.6%
West Midlands	£39.46m	1.6%	£72.93m	0.8%	10.5%
East of England (Cambridge)	£320.25m	13.4%	£1,292.15m	14.4%	11.5%
London	£1,185.68m	49.5%	£4,779.28m	53.1%	15.9%
South East	£468.88m	19.6%	£1,615.00m	17.9%	16.3%
(Of which Oxford)	£431.4m	18.0%	£1,475.52m	16.4%	
South West	£64.84m	2.7%	£108.01m	1.2%	10.0%
England	£2,393.01m	100.0%	£9,002.00m	100.0%	100.0%

Total BRCs and BRUs funding is even more geographically concentrated on Oxford, Cambridge and London, with these centres receiving over 85% of all funds since 2007. This has slightly reduced to 82.5% for the last two years. Under this measure, London's 16% population share has received 53% of total BRC/BRU funding.

10.5 Ratio of Total Funds to NIHR Funds

As shown in Table 10.3, centres have had different experiences in leveraging other funds in addition to core NIHR funds.

Table 10.3 Ratio of total funds to NIHR funds for 201718 and 2018/19 and since 2007

Region	BRCs and BRUs	Ratio total funds/ NIHR funds for 2017/18 to 2018/2019	Ratio total funds/ NIHR funds 2007 to 2019
North East	Newcastle	3.21	3.89
North West	Manchester & Liverpool	6.88	8.64
Yorkshire & The Humber	Leeds & Sheffield	6.35	9.10
East Midlands	Nottingham & Leicester	3.91	4.09
West Midlands	Birmingham	5.62	8.82
East of England	Cambridge	13.02	10.68
London	Many	7.34	8.66
South East	Oxford & Southampton	9.74	7.42
(Of which Oxford)		11.08	7.62
South West	Bristol	2.76	3.08
England		7.20	7.89

The centres in the North East, East Midlands and South West have been least successful in leveraging NIHR funds, all well below the average of 7 to 8 times. Cambridge BRC has been, and remains, the most successful in attracting additional funds, with the Oxford BRC in second place. These two are well ahead of the other BRCs. A recent publication by Hernandez-Villafuerte (2017) found mixed evidence on the economies of scale and scope at the level of individual universities or research institutes, with the studies more often pointing to positive economies of scale and scope than to diseconomies of scale or scope. Hence the ability to leverage additional funds is very likely to be affected by the scale of NIHR investment – both because of the critical mass of scientists and equipment that result, and because of the perception of higher quality from the larger scale. Without a change in approach, these are likely to perpetuate non-NIHR funds being attracted to the 'golden triangle' centres at the expense of other research groups.

10.6 Regional Analysis of 'Income' Per Head

The geographical distribution of funds is important from a social welfare and equity perspective. ONS provides two measures of regional income per head: regional gross domestic product (GDP) per head and regional gross disposable household income (GDHI). The GDP measure shows how much economic production (output) value can be attributed to each individual citizen, whilst GDHI is the amount of money that all of the citizens in the household sector have available for spending or saving after income distribution measures (for example, taxes, social contributions and benefits) have taken effect. Both measures are important, GDP measures productivity per head and is indicative of long-term income

potential (Nguyen, 2019), whilst GDHI is a more comprehensive view capturing the impact of all transfer payments. As ONS notes: 'GDHI is a concept that is seen to reflect the "material welfare" of the household sector'.

Table 10.4 provides both measures for each region. Under the GDP per head measure, London's value of 1.66 is much higher than elsewhere. Indeed only London and the South East region have above average productivity (the distribution is highly skewed because the London value is so much higher than all others). The South East and East of England regions have the second and third highest GDP per head; these contain Oxford and Cambridge respectively.

Under the GDHI measure, London was still the highest region but the differential was reduced to about 40% above the average. The range was also narrower (60 points versus 94 with GDP per head) and rankings changed somewhat with the South East dropping from 2nd to 8th. The North East was bottom under both measures.

Table 10.4 Analyses of regional GDP per head and GDHI per head

	GDP per head (£)	England = 100	Rank	GDHI per head (£)	England = 100	Rank
North East	23,569	72	9	15,809	79	9
North West	28,449	87	4	16,861	107	3
Yorkshire & The Humber	25,859	79	7=	16,119	96	6
East Midlands	25,946	79	7=	16,932	105	4
West Midlands	27,087	82	6	16,885	100	5
East of England	30,069	92	3	20,081	119	2
London	54,686	166	1	27,825	139	1
South East	34,083	104	2	22,568	81	8
South West	28,231	86	5	18,984	84	7
England	32,857	100		19,988	100	

Sources:
https://www.ons.gov.uk/economy/grossdomesticproductgdp/bulletins/regionaleconomicactivitybygrossdomesticproductuk/1998to2018 and
https://www.ons.gov.uk/economy/regionalaccounts/grossdisposablehouseholdincome/bulletins/regionalgrossdisposablehouseholdincomegdhi/latest

10.7 Marginal Utility of Income and Maximising Social Welfare

According to the law of diminishing marginal utility, the more of a good that is consumed, the less additional satisfaction can be derived from consuming another unit; the law of diminishing marginal utility of income suggests that as income increases, individuals gain a correspondingly smaller increase in satisfaction. Hence it is important to consider the geographical distribution of funds as its 'value' will differ depending on existing patterns of income.

The marginal utility of income is defined as the incremental change in utility (or satisfaction) that is due to a unit change in income. Evidence from revealed preferences indicate that the marginal utility of income declines with an increase in income. Increasing income equality can lead to an overall net gain in social welfare because the poor see a bigger increase in utility than the loss faced by high earners. Thus, in some circumstances, a Pareto efficient allocation can be reached by redistributing initial endowments.[51] However, the ideal state of affairs can only come about if four criteria are met, only one of which relates to the condition when no consumer can be made better off without making others worse off.

Factors giving rise to regional inequalities are many and varied including differences in skill mixes and levels, infrastructure, access to markets, propensity to migrate, health inequalities, population age structures, access to funds, proximity to universities, access to clusters of similar businesses and organisational mix (e.g. use of private/public partnerships, degrees of self-employment, large and small firm mix). The funds allocated to BRCs and BRUs could be targeted at reducing these wide regional inequalities by funding aspects such as increasing skills and enhancing infrastructure in poor performing regions.

Moreover, given that poor health is associated with low socio-economic status, increasing spend on biomedical R&D in low income regions may also enhance the access of the sickest citizens in society to leading edge R&D. Currently the citizens benefiting through access to clinical trials are in the Oxford, Cambridge and London regions- where healthy life expectancy is highest (ONS, 2019a). Empirical data show there is low recruitment to health research studies in areas with higher prevalence of total long-term and mental health conditions (Bower, 2020).

10.8 Other Geographical Analyses of Biomedical R&D Spend

Two other publications by the MRC (2019) and the UK Clinical Research Collaboration (2020) confirm the biases in biomedical research funding in favour of Oxford, Cambridge and London. These also give some insights into the reasons for these location decisions.

10.8.1 MRC (2019)

- 65% of MRC's directed translational funding is spent outside of London and the South East, in contrast to 48% of total MRC funding.
- Professionals from Technology Transfer Offices (TTOs) agreed that it was difficult to recruit staff with commercial expertise outside London, Oxford and Cambridge. Fundraising for spin-out companies was overwhelmingly concentrated amongst spin-outs established in these regions. This will partly reflect differences in the characteristics of the underlying science being completed in these regions, where much of the research into advanced therapies was being

[51] Many economists use Pareto efficiency as their efficiency goal. According to this measure of social welfare, a situation is optimal only if no individuals can be made better off without making someone else worse off.

completed. There are questions, however, as to whether the depth of the capital resources and investor networks outside of these hubs is enough to maximise the potential commercialisation impacts of translational research.

- This means that for university spin-out companies to grow, there is an advantage to locating in these regions, and at least one example of a company re-locating from the Midlands to the South East to enhance opportunities for investment was identified.

10.8.2 UK Clinical Research Collaboration (2020)

- The geographical distribution of health research funding has been stable between 2004 and 2018, with less than 1.9% variances across the 12 regions of the UK.
- Cambridge, Oxford and London receive 65% of funds provided to English regions (16%, 13% and 37% respectively).
- The regional distribution of health research funding - particularly the clustering around London, Oxford and Cambridge - is not surprising. All three have a long history of research as well as a considerable capacity and infrastructure to support a high proportion of the UK's research funding.

10.9 Conclusions

Since 2007, the Oxford, Cambridge and London BRCs have been awarded over 75% of NIHR funding and been the most successful at leveraging funds from other sources. Hence these BRCs have received 85% of total funds. All other regions have received a share of funds which is materially below their population share. This is particularly notable for the North West, Yorkshire and Humber and the West Midlands.

This evidence suggests there is a self-perpetuating cycle in operation - centres with an existing critical mass of high quality researchers are successful in attracting NIHR funds, enabling them to recruit more such researchers.

Welfare economics suggests that increasing funding to areas disadvantaged by this cycle could improve equity. Currently Government policy has the stated aim of doubling R&D spend over the next five years. This offer the opportunity to start 'levelling-up' these disadvantaged regions by providing NIHR funding, thereby enabling them to attract top-class researchers to undertake translational medical research.

11 Cost of Publications

11.1 Summary

The cost per publication is a crude measure of knowledge productivity, ignoring impact and quality, but without more detailed information enabling a targeted citation search to be conducted at BRC level, it is one of the few measures available. The results show a strong relationship between the level of funding and cost per publication, with BRCs receiving above average funding having a higher than average cost per publication. The low costs at some centres are indicative of data quality issues.

The potential for double-counting and the attribution problem means there is material uncertainty about the absolute cost per publication derived using the NIHR figures.

11.2 Background

A recent evaluation of the Oxford BRC (Hampson, 2017) undertook a bibliometric study comparing the publication record of the Oxford BRC with two non-BRC centres. It suggested extending this approach to calculate a field-weighted citation impact[52] for each BRC and calculate the cost per citation. We have limited the analyses to a simple value for money test. Hence this section reports the cost per publication for each BRC and BRU.

Publication output in peer reviewed journals has been used as measure of the productivity of researchers for many years (Aragon, 2013). This basic measure incentivises publications but does not quantify the impact of research. Ideally an evaluation would adopt a wider measure to encompass quality and impact measures. However, this has not proved possible as information on publications, and hence citations, and citation-impact, is available for the parent institutions only and not for those specifically generated by the BRC projects.

11.3 Methodology

The data used were all provided by NIHR and were available by BRC/BRU by year. Three variables were extracted for each BRC or BRU:

a) NIHR funding to date.
b) Total funds to date.
c) Total publications to date.

[52] https://www.elsevier.com/solutions/scopus/how-scopus-works/metrics

An NIHR and total cost per publication were calculated but only the former is reported. We assume the publications reported by each centre relate only to those attributable to NIHR funding but this has not been substantiated. If the assumption is wrong the total cost per publication can be substituted.
We also do not know how publications with joint authors are recorded. For example would a publication including at least one author who spends any fraction of their working life doing NIHR-related BRC work be included in the dataset reported to NIHR?

The crude data also do not provide sufficient details to enable us to weight the quality of the journal.

11.4 Findings

Table 11.1 reports the NIHR cost per publication for each BRC and BRU.

Table 11.1 NIHR cost per publication for each BRC and BRU

BRU	Cost per publication	BRC	Cost per publication
NIHR Birmingham BRU	£2,669	NIHR Sheffield BRC	£3,110
NIHR Cambridge BRU	£3,577	NIHR Royal Marsden London BRC	£6,189
NIHR Barts &London BRU	£3,921	NIHR Leeds BRC	£6,514
NIHR Royal Brompton London BRU	£4,452	NIHR Great Ormond Street London BRC	£6,761
NIHR Manchester BRU	£4,581	NIHR Southampton BRC	£6,932
NIHR Sheffield BRU	£6,089	NIHR Moorfields London BRC	£10,315
NIHR Maudsley London BRU	£9,501	NIHR Birmingham BRC	£11,931
NIHR Southampton BRU	£12,805	NIHR Manchester BRC	£12,983
NIHR Leeds BRU	£14,670	NIHR Nottingham BRC	£13,928
Mean value	£15,137	NIHR Guy's & St Thomas' London BRC	£14,253
NIHR Queen Square London BRU	£16,399	NIHR Barts London BRC	£17,084
NIHR Nottingham BRUs	£16,771	NIHR Imperial London BRC	£19,078
NIHR Oxford BRU	£23,590	Mean value	£21,256
NIHR Bristol BRU	£24,998	NIHR Cambridge BRC	£26,385
NIHR Leicester BRU	£26,942	NIHR Leicester BRC	£27,335
NIHR Newcastle BRU	£36,225	NIHR Maudsley BRC	£28,333
NIHR Liverpool BRU	£44,300	NIHR Oxford BRC	£28,388
		NIHR UCL London BRC	£37,090
		NIHR Newcastle BRC	£41,715
		NIHR Liverpool BRC	£45,597
		NIHR Bristol BRC	£77,801

For both BRCs and BRUs there is a strong correlation between level of funding and cost per publication. Those receiving less than the mean funding (£9.1m for a BRU and £49.75m for a BRC) were highly likely to have lower than average NIHR cost per publication. Only Newcastle BRU received below average funding (£8.1m) but had higher than average cost per publication. For the BRCs, both Liverpool (£8.9m) and Bristol (23.5m) received below average funding but had higher than average costs per publication; whilst Imperial received above average funding (£126m) but had slightly below the average cost per publication.

Seven BRUs and five BRCs reported publication costs of under £10,000 each article. This seems relatively low and may indicate problems in validity of the data. It may be one publication is counted in more than one year, for example, it was in draft over a year end. Alternatively the centre may be reporting all publications including those unrelated to projects using NIHR funding, or claiming any publication that includes at least one author who spends any fraction of their working life doing BRC work. Clarity of the attribution to an NIHR publication is thus essential

11.5 Limitations and Conclusions

The cost per publication is a crude measure of productivity, ignoring impact and quality, but without more detailed information enabling a targeted citation search to be conducted it is one of the few measures available. The results show a strong relationship between the level of funding and cost per publication, with BRCs receiving above average funding having a higher than average cost per publication. The low costs at some centres is likely to indicate data quality issues. The potential for double-counting and the attribution problem means there is material uncertainty about the absolute cost per publication derived from the NIHR figures.

12 Net Benefit of Marginal Spending on BRCs

12.1 Summary

Using the values identified in earlier sections to populate the model described in Figure 1.1, the marginal return for an additional £1 spend on BRCs by NIHR is estimated at about 29%. This includes economic and health gains. It is judged conservative as some potential supply chain benefits are not captured.

12.2 Background

The high-level aim of this project is to help answer question: "What is the net marginal value to society of the NIHR BRCs compared to stopping / not having launched the schemes?". This section uses the findings on individual parameters to try to answer this question using the DHSC model.

12.3 Inputs to model

12.3.1 NIHR R&D investment and link to private R&D

Based on the most recent year's data (2017), Government R&D funding of biomedical research was £2.98bn, with private sector funding of £4.32bn and £1.49bn from charities. Results from re-running the VECM using the updated data, reported the combined public sector elasticity was 0.75% which is of a similar order of magnitude to that proposed by Sussex (2016). The updated analysis reported a statistically significant relationship between government and private funding of 0.68%.

Applying the elasticity of 0.68% for government research spending implies that a £1.00 increase in government spending on biomedical research would result in a £0.98 increase in private pharmaceutical R&D (0.68 * 4.32/2.98).[53]

12.3.2 Foreign and UK funded investment

Of the £0.98 additional private sector R&D, typically 52% (£0.51) would be made by foreign-owned private sector companies and 48% (£0.47) by UK-owned companies (ONS, 2018).

[53] In 2017, £4.32bn private sector R&D; UK Government R&D £2.98bn

12.3.3 UK private sector cost of capital, return and depreciation

The best estimate of the opportunity cost of capital for private sector pharmaceutical companies is 7% post-tax (8.6% pre-tax). This is the value reported by AstraZeneca (AZ, Annual report and accounts 2019) and also consistent with other evidence identified in this report (See Section 7).

For the annual rate of return achieved by the private sector we have used 10%. Pharmaceutical and other private sector companies in the UK report adopting a hurdle rate of 12 to 13% for project appraisal purposes (Melolinna, 2018 and Saleheen, 2017) but this rate is expected to be higher than is achieved in practice because of project optimism. The difference between the 10% achieved return and the cost of capital is the profit margin for entrepreneurship.

The evidence from Li and Hall (2018) suggested that there is a 4 year lag from initial spend on an asset to it being a completed asset and thence depreciated, with a rate of 11% a year applied (i.e. assuming a 9 year life); this is also the life used by ONS for public sector R&D nationally.

12.3.4 Spillover and social rate of return

HERG (2008) identified three types of spillovers generated by private R&D:

(1) improving the productivity of other firms' R&D
(2) encouraging entry of potential competitors
(3) reduction of production costs.

Their analyses, informed by a literature review, concluded R&D spend by the private pharmaceutical industry in the UK yielded a 50% social rate of return to the national economy. This value was adopted by Sussex (2016) and is also adopted here. The latest literature review found no specific measure relating to biomedical research. It found evidence from other sectors, and mainly from the USA, that the social rate of return was at least 50%. Hence this analysis continues to use the 50% social rate of return.

12.3.5 Combined private and public sector

The DHSC model (figure 1.1) can now be populated. Table 12.1 summarises the discounted cash flow associated with an initial investment of £100 NIHR investment in BRCs (See Appendix A12 for the full cash flows). The initial investment is associated with a multiplier of 0.68% which suggests £98.59 This is calculated by applying the 0.68% reported by the VECM to the ratio of private sector R&D (£4,320m) and public sector R&D (£2,979.7m). Of this total, 48% (£47.32) is estimated to be funded by UK companies.

The annual net income required assuming:

- a 9 year life of the investment
- a 4 year lag from the initial investment in developing an asset to it earning a return,
- a 10% post tax return on the initial private sector investment of £47.32 is £12.07 a year (real terms).

There is no evidence related to the time period over which the social return of 50% is achieved. However, the work by Link and Scott (2019) adopted the same life for the private sector return as the social return so this assumption is adopted here. Hence applying the same lag and life, the annual return consistent with a social rate of return of 50% on the initial private sector investment of £47.32 is £116. The IRR from the total spend of £147.32 (being the initial NIHR investment of £100 plus the additional UK private sector investment of £47.32) is 28%.

Table 12.1 Discounted cash flow from £100 public sector investment in BRCs

Year	NIHR funds	Private sector	Of which UK companies	Net income (a)	Income including spillover (b)	Net cash flow
0	-£100	-£98.59	-£47.32	0	0	-£147.32
Years 1 to 4				0	0	0
Years 5 to 14				£12.07	£123.0	£123.0
IRR						27.8%

(a) Net income is set at the level to yield a 10% IRR over 9 years with 4 year lag from initial investment

(b) Income including spillover is set at the level to yield a 50% IRR over 9 years with 4 year lag from initial investment

12.3.6 Health gain

Updated estimates of the rates of return from health gains associated with UK investment in medical research range ranged from 17.5% for cancer drugs to 13% for musculoskeletal therapies, with a weighted average of 16% (See Section 3).

12.3.7 Combined private and public sector return plus health gain

Adding the two cash flow suggests an annual IRR of 29.2%. The Treasury (HM Treasury 2018) advises that Government bodies should discount costs and benefits by applying the Social Time Preference Rate currently set at 3.5% per annum in real terms. This is a risk-free rate. The 29% return is appreciably in excess of this rate.

12.4 Limitations

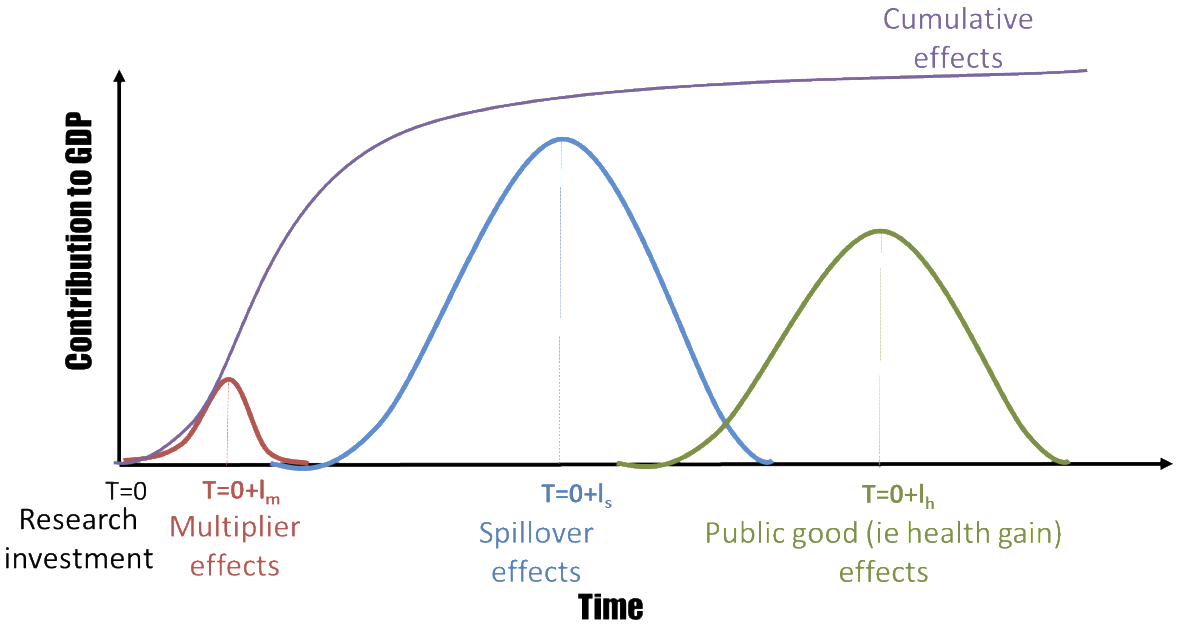
The model assumes no opportunity cost to England from foreign companies investing in UK R&D and that there are no benefits associated with the spend. This is more questionable given the staff employed

to conduct the research are employed in the UK, plus the import/export leakages are small (8% in the company sector and exports are virtually nil). Hence output and employment benefits, as measured by type 1 multipliers, would seem to accrue to the English economy from such expenditure. The most recently published type 1 output multiplier for this sector is 1.575 and the employment multiplier is 1.96.

These multipliers measure the direct and indirect supply chain effects and assume a responsive supply chain and a fixed production function. They measure interdependencies across industries but assume these are fixed. In contrast spillover measures dynamic effects which change production functions. So whilst there may be some overlap in the benefits measured by spillover and the type 1 multipliers the overlap may be quite limited. If this is the case the rate of return of about 29% is conservative as it does not capture the impact of the R&D on the direct and indirect supply chain.

Sousa (2020) in an unpublished paper discuss three types of economic benefits from public investment in health research being: (i) short-term multiplier benefits, (ii) mid-term spillover benefits to the private sector and (iii) long-term economic benefits to the wider society derived from health gains (see Figure 12.1).

Figure 12.1 Conceptual approach to the contribution to GDP of public investment in health



(Source: Sousa, 2020)

Using their model produced an economic return to UK GDP of £2.08 at year 25 for each £1 invested by the NIHR. This approach captured all three benefits as shown in Figure 12.1, with the values used for each benefit reported in Table 12.2.

Table 12.2 Parameters estimates

Parameters	Multiplier benefits	Spillover benefits	Health gains
Annual GDP per £1 spend on health research	£0.2 (£0 - £0.25)	£0.26 (£0.2-£0.35)	£0.1 (£0.1- £0.2)
Time lag to 'peak' benefit	1 year (1 year-1.5 years)	11 years (8 years-15 years)	15 years (10 years-20 years)
Rate of obsolescence	0%	20% per year (12%-26%)	10% per year (5%-20%)
Decay function	Not available in the literature. Three hypothesis are tested: Baseline scenario: normal-shaped. Sensitivity analysis: right-tailed and left tailed		

Values within brackets are 'lower bound'-'upper bound'.

This return is materially higher than the £1.35 return calculated here. Part of the 'gap' is the addition of a spillover effect and a multiplier effect within the one methodology. The draft manuscript is not in sufficient detail to enable us to understand how the authors adjusted for the magnitude of benefits captured by the multiplier effect and those by spillover. The diagram suggests these were tiny.

The final limitation is the uncertainties with the data inputs to and hence results from the VECM.

12.5 Conclusion

The marginal return for an additional £1 spend on BRCs by NIHR is estimated at around 29%. This includes economic and health gains. It is judged conservative as some potential supply chain benefits are not captured.

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Appendix A2

	Deterministic trend	Number of lags	Short term dynamics intercepts	Interruptions	Disease areas excluded	Lags with serial correlation	Coefficient log(public)	Significant
Model 1-9	3	1	None	None	One at a time	up to lag 2	-1.46 to -192.8	9 out of 9
Model 10-18	4	1	None	None	One at a time	up to lag 2	-1.43 to 5.22	9 out of 9
Model 19-30	1 to 4	1 to 3	None	None	Others	variable	-1.86 to 3.14	0 out of 12
Model 31-42	1 to 4	1 to 3	None	None	Vision and others	variable	-1.02 to 8.26	1 out of 12
Model 43-48	3 and 4	1 to 3	None	None	CVD and vision	variable	-2.74 to -1.07	6 out of 6
Model 49-54	3 and 4	1 to 3	None	None	CNS and vision	variable	-3.16 to -0.81	6 out of 6
Model 55-61	3 and 4	1 to 3	None	None	CNS and CVD	up to lag 2	-121.6 to 12.19	6 out of 6
Model 62-63	3 and 4	1	None	None	Vision and respiratory	up to lag 3	-1.47 and -1.56	2 out of 2
Model 64-65	3 and 4	1	None	None	CNS and skin	up to lag 3	4.84 and 5.94	2 out of 2
Model 66	3	1	All disease areas	None	None	lag 2	-0.23	ns
Model 67-75	3	1	All disease areas	All up to none in 2010	None	lag 1, 2 and 7	-0.26 to -0.48	1 out of 9
Model 76	3	1	All disease areas	Gastrointestinal and Vision in 2010	None	lag 2 and 7	-0.25	ns
Model 77	3	1	All disease areas	Vision and Others in 2010	None	lag 2 and 7	-0.19	ns
Model 78	3	1	All disease areas	Blood and others in 2010	None	lag 2 and 7	-0.34	ns
Model 79	3	1	All disease areas	Blood, CNS, and others in 2010	None	lag 2 and 7	-0.36	ns
Model 80	3	1	All disease areas	Blood and CNS in 2010	None	lag 2 and 7	-0.37	ns
Model 81	3	1	All disease areas	CNS, CVD and infectious in 2010	None	lag 2 and 7	-0.35	s
Model 82	3	1	All disease areas	CNS, CVD, others and infectious in 2010	None	lag 2 and 7	-0.32	ns
Model 83	3	1	All disease areas except CNS	None	None	lag 2 and 7	-0.38	s
Model 84	3	1	All disease areas	All disease areas in 2010	Others	lag 1, 2 and 7	-0.25	ns
Model 85	3	1	All disease areas	All disease areas in 2010	Infectious	lag 1, 2 and 7	-0.39	ns
Model 86	3	1	All disease areas	Gastrointestinal and Vision in 2013, in 2010 for the rest	None	lag 1, 2 and 7	-0.24	ns

	Deterministic trend	Number of lags	Short term dynamics intercepts	Interruptions	Disease areas excluded	Lags with serial correlation	Coefficient log(public)	Significant
Model 87	3	1	All disease areas	None	Blood	lag 2 and 7	-0.39	ns
Model 88	3	1	All disease areas	None	Infectious	lag 2 and 7	-0.28	ns
Model 89	3	3	All disease areas	None	None	lag 4 and 7	-0.0008	ns
Model 90	3	3	All disease areas except Vision	None	None	lag 7	-1.64	s
Model 91	3	3	All disease areas except Vision	Others in 2010	None	lag 7	-1.48	s
Model 92	3	3	All disease areas except Vision	Blood and others in 2010	None	lag 7	-1.54	s
Model 93	3	3	All disease areas	Others in 2010	Infectious	lag 7	-0.21	ns
Model 94	3	3	All disease areas except Infectious	Gastrointestinal and Vision in 2013	Blood	lag 7	-1.6	s
Model 95	3	3	All disease areas except CNS and others	Gastrointestinal and Vision in 2013	Blood	lag 7	-0.64	s
Model 96	3	3	All disease areas except blood, CNS, respiratory and others	Vision in 2013	Blood	lag 7	-0.73	s
Model 97	3	3	All disease areas except blood, CNS, respiratory and others	Vision in 2013	Blood	lag 5	-0.65#€	s
Model 98	3	3	Cancer, CVD, infectious and vision	Vision in 2013	Blood	lag 7	-0.96	s
Model 99	3	3	Cancer, CVD, infectious and vision	Vision in 2013	Blood	lag 4, 5	-0.94#¥	s
Model 100	3	3	All disease areas except blood, CNS, respiratory and others	Gastrointestinal and Vision in 2013	Blood	lag 7	-0.75	s
Model 101	3	3	All disease areas except blood, CNS, respiratory and others	Gastrointestinal and Vision in 2013	Blood	lag 7	-0.68#¶	s

Coefficients are reliable when they are between 0 and -1, significant and there is no serial autocorrelation up to lag 6

Deterministic trend 1: No intercept or trend in the cointegration equation (CE) and the vector autoregression (VAR); Deterministic trend 2: No trend in the CE or the VAR, but there is an intercept in the CE; Deterministic trend 3: intercept in the CE and both an intercept and a trend in the VAR; Deterministic trend 4: Trend and intercept in the CE, and an intercept but no trend in the VAR. s:significant at 0.05 level; ns: non-significant.

Government and charity spending were introduced as separate terms

€ Coefficient for log(charity) was -0.10 (non-significant)

¥ Coefficient for log(charity) was -0.004 (non-significant)

¶ Coefficient for log(charity) was -0. 09 (non-significant)

Appendix A4

Worked example of internal rate of returns

This example assumes an investment of £133m, with the net health benefits having an internal rate of return (IRR) of 16.0%. This is expressed as a lump sum in year 19 of £1,920m, assuming a 17 year gap. The national income gain of 1.57 is equivalent to £208.81m assumed to accrue in year 2, giving an IRR of 57.0%. Combining the health benefit and the multiplier benefit results in an IRR of 57.6% (rounded to 58% in the report). The cashflows are set out in Table A4.

Table A4: Illustrative cash flows

Years	Health gain	National output	Net cash flow
1	-133	-133	-133
2	£0	208.81	208.81
3	£0	£0	£0
4	£0	£0	£0
5	£0	£0	£0
6	£0	£0	£0
7	£0	£0	£0
8	£0	£0	£0
9	£0	£0	£0
10	£0	£0	£0
11	£0	£0	£0
12	£0	£0	£0
13	£0	£0	£0
14	£0	£0	£0
15	£0	£0	£0
16	£0	£0	£0
17	£0	£0	£0
18	£0	£0	£0
19	1920	£0	1920
IRR	16.0%	57.0%.	57.6%

Appendix A5

Search strategies
A.1: Source: PubMed
Interface / URL: https://www.ncbi.nlm.nih.gov/pubmed
Database coverage dates: Information not found
Search date: 31/03/20
Retrieved records: 696
Search strategy:

medical AND ("R&D" OR research) AND (spillover OR spillovers OR spill-over OR spill-overs OR externalities OR synergies OR "rate of return" OR "rates of return") Filters: Publication date from 2015/01/01 to 2020/12/31; English

A.2: Source: EconPapers
Interface / URL: https://econpapers.repec.org/
Database coverage dates: Information not found
Search date: 31/03/20
Retrieved records: 123
Search strategy:

The advanced search at the following URL was used: https://econpapers.repec.org/scripts/search.pf

The following search terms were entered in the 'free text search' box:

medical AND ("R&D" OR "R & D" OR research) AND (spillover OR spillovers OR "spill-over" OR "spill-overs" OR externalities OR synergies OR "rate of return" OR "rates of return")

The 'Sort by' option 'Date modified' was used to sort results in date order. The 'Date is Creation/revision of item' was selected.

331 documents were retrieved.

Records for studies with a 'created / revised date' before 2015 were excluded. 'Register author' returned results (i.e. a result called 'Registered author:name') were excluded (these results contain author details). Results with non-English abstracts were excluded.
The remaining results (123) were copied into a Word document. Abstracts were located via the EconPapers record and copied into the Word document.

A.3: Source: Econlit
Interface / URL: OvidSP

Database coverage dates: Econlit 1886 to March 26, 2020
Search date: 01/04/20
Retrieved records: 13
Search strategy:

1 (medical and (R&D or "R & D" or research) and (spillover or spillovers or spill-over or spill-overs or externalities or synergies or rate of return or rates of return)).mp. mp=heading words, abstract, title, country as subject (43)
2 limit 1 to (yr="2015 -Current" and english) (13)

Note: The search terms were entered into the search interface with no field restrictions specified, as follows:

(medical and (R&D or "R & D" or research) and (spillover or spillovers or spill-over or spill-overs or externalities or synergies or rate of return or rates of return))

Searching for a term without specifying a field in Advanced search defaults to a 'multi-purpose' (.mp.) search

A.4: Source: British Library main catalogue
Interface / URL: http://explore.bl.uk/
Database coverage dates: Information not found
Search date: 01/04/20
Retrieved records: 281
Search strategy:

The 'main catalogue' can be searched via 'Explore the British Library'. This is found at: http://explore.bl.uk/

Searches were conducted using the simple search interface at: http://explore.bl.uk/primo_library/libweb/action/search.do?vid=BLVU1. 'Main catalogue' was selected.

After consulting the British Library 'Guide to Explore the British Library' (https://www.bl.uk/help/guide-to-explore-the-british-library#explorefurther) and conducting test searches, the Information Specialist was not confident the search interface was working as the Information Specialist would expect for searches using terms nested in brackets combined with Boolean operators. The Information Specialist was also not confident how the interface was interpreting searches including the term 'externalities'. The British Library was contacted for information on search interface functionality at Customer-Services@bl.uk (01/04/20). Customer Services replied and suggested humanities-enquiries@bl.uk should be contacted. The query was sent to this address, but in the absence of a reply within the

required timelines for conducting the search, it was decided to conduct the search via a number of individual searches using relatively simple search syntax.

The following searches were conducted separately. Results were displayed in date order (newest first). All results with a date of 2015 to date were added to the 'My Workspace' area.

medical AND research AND spillover = 71 added (from 84)
medical AND research AND spillovers = 23 added (from 30)
medical AND research AND spill-over = 10 added (from 12)
medical AND research AND spill-overs = 5 added (from 5)
medical AND externalities = 103 added (from 299)
medical AND research AND synergies = 69 added (from 104)
medical AND research AND "rate of return" = 10 added (from 15)
medical AND research AND "rates of return" = 6 added (from 9)

After the above were added, 275 records in total were listed in the 'My workspace' area. The full set was too large to download as one PDF, so the results were downloaded as 2 PDF files. All available results were selected for download.

medical AND R&D AND spillover = 2 added (from 2)
medical AND R&D AND spillovers = 2 added (from 2)
medical AND R&D AND spill-over = 0 results returned
medical AND R&D AND spill-overs = 0 results
medical AND R&D AND synergies = 2 added (from 2)
medical AND R&D AND "rate of return" = 1 added (from 1)
medical AND R&D AND "rates of return" = 1 added (from 1)
medical AND "R & D" AND spillover = 1 added (from 1)
medical AND "R & D" AND spillovers = 0 results returned
medical AND "R & D" AND spill-over = 0 results returned
medical AND "R & D" AND spill-overs = 0 results returned
medical AND "R & D" AND synergies = 1 added (from 1)
medical AND "R & D" AND "rate of return" = 0 results returned
medical AND "R & D" AND "rates of return" = 0 results returned
After the above were added, 6 records in total were listed in the 'My workspace' area. The results were downloaded a one PDF file. All available results were selected for download.

Appendix A6

Search strategies

A.1: Source: PubMed
Interface / URL: https://www.ncbi.nlm.nih.gov/pubmed
Database coverage dates: Information not found
Search date: 27/03/20
Retrieved records: 608
Search strategy:

("bench to bedside" OR "time lag" OR "time lags") AND (research OR development) AND ("medical device" OR "medical devices" OR "health intervention" OR "health interventions" OR pharmaceutical OR pharmaceuticals OR drug OR drugs OR "medical technology" OR "medical technologies") Filters: Publication date from 2014/01/01 to 2020/12/31; English

A.2: Source: Embase
Interface / URL: OvidSP
Database coverage dates: Embase 1974 to 2020 March 26
Search date: 27/03/20
Retrieved records: 685
Search strategy:

1 ((bench to bedside or time lag or time lags) and (research or development) and (medical device or medical devices or health intervention or health interventions or pharmaceutical or pharmaceuticals or drug or drugs or medical technology or medical technologies)).mp. mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word (1623).
2 limit 1 to (english language and yr="2014 -Current") (685).

Note: The search terms were entered into the search interface with no field restrictions specified, as follows:

((bench to bedside OR time lag OR time lags) AND (research OR development) AND (medical device OR medical devices OR health intervention OR health interventions OR pharmaceutical OR pharmaceuticals OR drug OR drugs OR medical technology OR medical technologies))

Searching for a term without specifying a field in Advanced search defaults to a ‘multi-purpose’ (.mp.) search.

Appendix A12

The full cash flows to calculate the internal rate of return obtained by populating the DHSC model are provided in Table A12.

Table A12: Cash flows from populating DHSC model

NIHR	Private	Funded from overseas	Funded from UK	UK annual rate of return of 10%	With spillover to give 50% social return	Total economic IRR
-100.00	-98.59	-51.27	-47.32	-47.32	-47.32	-147.32
				0.00	0.00	0.00
				0.00	0.00	0.00
				0.00	0.00	0.00
				0.00	0.00	0.00
				12.07	123.00	123.00
				12.07	123.00	123.00
				12.07	123.00	123.00
				12.07	123.00	123.00
				12.07	123.00	123.00
				12.07	123.00	123.00
				12.07	123.00	123.00
				12.07	123.00	123.00
				12.07	123.00	123.00
IRR				**10.0%**	**50.0%**	**27.8%**


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