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MRC Medical Research Council

Outputs, outcomes and impact of MRC research: 2013/14 report

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Front Cover Image Credits:

Top Row: *Football Fans in Training*

Middle Row: *Stem cell. Image credit: iStock; A mammogram. Image credit: Shutterstock.; My Meal Mate iPhone app*

Bottom Row: *MRSA; The Cardiff University team. Image credit: BMJ; a mouse*

List of case studies by output type

Publications

Collaborations

Further funding

Engagement activities

Influence on policy

Research materials

Intellectual property

Products and interventions

Impacts on the private sector

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MRC Medical Research Council

Outputs, outcomes and impact of MRC research: 2013/14 report

SECTION 01: Introduction

Introduction

Overview

The MRC celebrated 100 years of supporting ground-breaking research and innovation in 2013. Although the research landscape may have changed in the decades since it was established in June 1913 to study tuberculosis, the primary aim — to improve the health and wellbeing of society — has remained the same.

From the discoveries of penicillin and the structure of DNA to demonstrating the links between smoking and lung cancer and high blood pressure and heart disease, MRC-funded research teams have been at the forefront of medical advances. A timeline of the MRC's key discoveries and achievements over the past 100 years can be found on the MRC Centenary website[1].

The MRC will continue to support excellent discovery science and strengthen partnerships where there is the greatest potential to deliver improved health and economic impact. This vision is set out in the MRC's strategic plan for 2014-19, *Research Changes Lives*.

For the MRC to achieve its strategic aims and objectives it has to be able to track the progress, productivity and quality of the research it funds. The 2013/14 *Outputs, outcomes and impact* report showcases some of the latest developments and the societal, academic and economic gains arising from MRC-funded research, as reported to us by our researchers via Researchfish[2] (see the section on Researchfish for more information on our data collection system and uses of the data).

The results demonstrate that MRC-supported research teams are making international impact to deliver health gain, economic growth and changes to absorptive capacity across all sectors.

Half of all reported outputs concerned a research publication, with 25 per cent of MRC awards reporting at least one publication within a year and 82 per cent reporting at least one publication within five years. Bibliometric analysis continues to show that MRC-funded journal articles and reviews have twice the citation impact of the world average.

More than half of our respondents (52 per cent) reported that their work had been supported by collaborations between 2006 and 2013. The nature of these collaborations varies greatly, from industry interactions to facilitate the translation of research, such as the production of the successful weight loss smartphone app My Meal Mate by researchers at the **University of Leeds** with the help of Blueberry Consultants (see page 72), to the coming together of researchers from different fields to stimulate interdisciplinary research, like the Critical Care Alliance — a partnership of clinicians, mathematicians and physicists established to facilitate translational research in the area of sepsis and the critically ill patient (see page 75).

Recipients of just less than half of our awards (46 per cent) reported that their research had attracted further funding, taking the total awarded to £3.2bn between 2006 and 2013, from more than 1,000 different funders. £197m (six per cent) of this was from the private sector; including £131k from Janssen-Cilag to **Dr Stephen Newhouse** at the **MRC Social, Genetic and Developmental Psychiatry Centre** to identify biomarkers for progression in Alzheimer's disease (see page 75).

There were reports of almost 8,000 staff moving from MRC support between 2006 and 2013; the majority were researchers, post-doctoral researchers and research fellows, leaving to pursue roles in a natural career progression. Over time, we expect to discover more about the flow of skilled people from MRC support to other sectors.

Researchers reported taking part in more than 23,000 engagement activities between 2006 and 2013. These included academic papers that received substantial media coverage, such as research from the **MRC Clinical Sciences Centre's** Metabolic Signalling Group showing for the first time how variations in the *FTO* gene – the strongest obesity risk gene – are linked to obesity (see page 32). Other activities included talks and open days which specifically invited the public to learn more about research and its outputs, including one held by the **MRC Centre for Neurodegeneration Research** at **King's College London** to showcase its cutting edge research into Alzheimer's disease, in conjunction with Alzheimer's Research UK (see page 41).

MRC researchers reported that their work had had an influence on local, national or international policy in one fifth of awards, totalling almost 3,500 influences. These included citations in clinical guidelines, such as **Dr Emma Thomson's (MRC-University of Glasgow Centre for Virus Research)** work on the WHO guidelines for the 'Screening, care and treatment of persons with hepatitis C infection' (see page 37). Researchers also reported influences on policy-setting processes, such as **Professor Sheila McCormack (MRC Clinical Trials Unit)'s** membership of the Chief Medical Officer's seminar on the future public health policy for HIV research which resulted in the updating of the UK's HIV policies in order to help people get diagnosed earlier (see page 38).

Recipients of almost a third of awards (31 per cent) reported that their work had resulted in the generation of research materials for others to use, from cell lines and transgenic animal models to databases and new techniques. These include advances in regenerative medicine, such as the growth of 3D structures resembling brain and intestinal structures and Müller glial stem cells (see page 45 and page 46), and a new method of studying a specific mutation implicated in early-onset dementia (see page 48).

There are 849 reports of intellectual property in the Researchfish database, including a new diagnostic marker for heart attacks (see page 60), the use of a protein to treat osteoarthritis (see page 60) and the use of nitric oxide to treat ventilator-associated pneumonia (see page 57).

Researchers reported that their work had led to the development of a product or intervention in 12 per cent of awards. These ranged from drugs such as the use of monoclonal antibody Alemtuzumab (Campath or Lemtrada) for the treatment of Multiple Sclerosis (see page 50) and clinical trials including the successful Phase II trial of peanut allergy treatment (see page 54), to public health interventions such as Football Fans in Training (see page 61).

The MRC has evidence of MRC-supported research leading to the creation or growth of 109 companies. Recent additions include DefiniGEN, established to supply human induced pluripotent stem cells (hIPSC)-derived liver cells to the drug discovery and regenerative medicine sectors (see page 81) and Floceleris from the University of Cambridge, which won the 2013 Carpe Diem Life Science Award in the university's Entrepreneurs Business Creation Competition (see page 74).

Recipients of 50 per cent of awards reported that their work had resulted in an award or personal recognition for either themselves or a member of their research group. These included being invited to speak at a conference, being appointed to the editorial board of a journal and being awarded a research prize, such as **Dr Conor Farrington** at the **Open University**, who was awarded the **Royal Statistical Society's Bradford Hill medal** (see page 89). and **Professor Peter Somogyi, (MRC Anatomical Neuropharmacology Unit), Professor Gero Miesenböck (University of Oxford)** and **Professor Trevor Robbins (University of Cambridge),** who all received the **Grete Lundbeck European Brain Research Prize**, in 2011, 2013 and 2014, respectively (see page 90).

Further examples of these outputs can be found throughout the pages of the report, as well as the associated impact where reported. The outputs and impact in this report are divided into 11 different types, as indicated by the headings and accompanying icons in the key below.

Key

 **Publications**

 **Collaborations and partnerships**

 **Further funding**

 **Next destination and recruitment**

 **Engagement activities**

 **Influence on policy, practice, patients and the public**

 **Research materials (tools, methods and databases)**

 **Intellectual Property and licensing**

 **Development of products, interventions and clinical trials**

 **Impacts on the private sector**

 **Awards and recognition**

Researchfish

Researchfish is the system used to collect information on the outputs, outcomes and impact of MRC-funded research. MRC-funded researchers are asked to record these data all year-round and, once a year, to formally submit this information to the MRC (usually between October and November).

Formerly MRC e-Val, the approach was licensed to Researchfish Ltd in 2012, which created a federated version of the system to allow it to be used by multiple funders to collect comparable research outputs. There are currently more than 80 research organisations and funders using Researchfish[3]. In June 2014, it was announced that the five remaining research councils would be joining the MRC and the Science and Technology Facilities Council in using Researchfish as the means of collecting data on the outputs and impact of their research from September 2014. A harmonised approach to collecting output information suitable for all research disciplines will enable funders to obtain a common qualitative and quantitative view of the progress, productivity, quality and impact of the research they individually and collectively support.

The data collected — both qualitative and quantitative — is invaluable to the MRC and is used in a multitude of ways, from contributing to the evidence submitted to the Government to make the continued case for sustained investment in medical research, assessing progress against the MRC's Strategic Plan, *Research changes lives 2014-2019*[4], and importantly, making the data available to universities for use in their REF submissions[5] or any other internal processes or communications.

The data collected through Researchfish are published on the Research Councils UK (RCUK) Gateway to Research[6]. The Gateway to Research aims to make available information about what all seven research councils are funding and the outputs that have arisen from this work. The MRC expects that the public availability of Researchfish data will help continue to encourage accurate and complete reporting within Researchfish. Further information on the research featured in this report can be found in the Gateway to Research by using the search function to enter the project reference number listed underneath each case study.

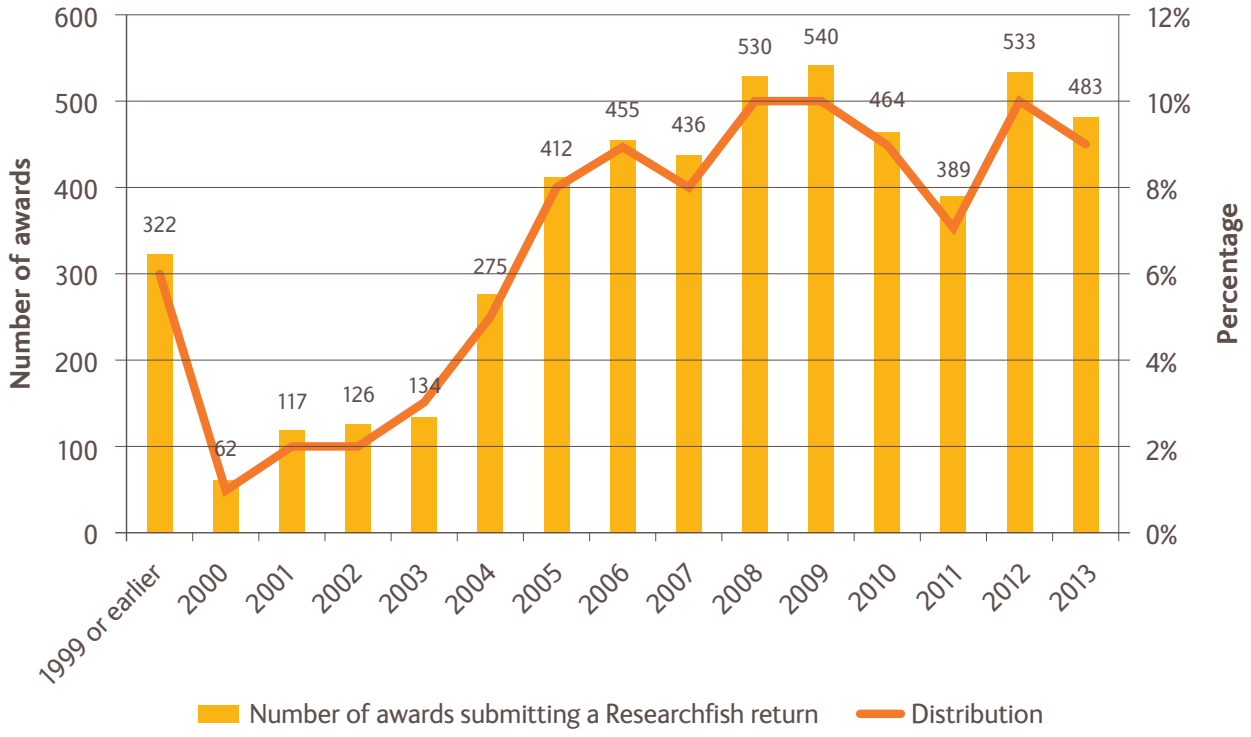
For more information on the history of Researchfish and its principles of use, please see:
http://www.mrc.ac.uk/funding/guidance-for-applicants/researchfish/

2013 data collection

The October-December 2013 Data Gathering Period (DGP6) for Researchfish had a compliance rate of 94 per cent with 4,901 responses out of an expected 5,226.

The majority of awards (72 per cent) submitting data to Researchfish started between 2006 and 2013. The distribution of the start dates of awards as a percentage of all awards submitting Researchfish returns is shown in figure 1.

Figure 1: Distribution of the start dates of awards submitting information to Researchfish



Notes on the quantitative data

Percentages in this report are rounded up or down to the nearest whole number and so some may appear as zero if this represents less than half of one per cent and not all tables may sum to 100 per cent because of rounding.

Where instance of further funding are reported in currencies other than Pounds Sterling the values are converted using an average exchange rate for each calendar year as reported on **http://www.oanda.com/currency/historical-rates/**.

One particular output, for example a publication or a collaboration, might have arisen from more than one award. In this report a particular output is always reported against each individual award where the analysis focus on activity at the award level (for example the number of instances or distribution of activity). These outputs are de-duplicated, to the extent possible, in analyses on the type of outputs generated (for example publications per year, top five locations for collaborations). Usually de-duplication is done using system generated codes to indicate when a researcher has attributed an output to more than one award. This does under report duplication if researchers enter

similar information independently of one another. Supplemental information is used to de-duplicate where available, for example PubMed Ids or Digital Object Identifiers (DOIs) for publications. In the case of further funding details of duration and amount of money are also used.

In addition to de-duplication, outputs were also removed from analysis if the researcher indicated that they occurred before the start of the funding for their award. We have used the term valid and invalid in relation to these outputs. A valid output is one that was realised during or after the award to which it has been attributed. An invalid output is one realised before the start of the award to which it has been attributed. In most cases researchers are asked to indicate the year only for their outputs and not specify a month. This means that a one year difference in year could be almost two years in actuality (for example, January 2012 – December 2013). For removal from analysis a particular output would have to be in at least the year before the funding started.

All of the data is correct as at July 2014, however, as data is further cleaned, mapped or made available, it may be subject to alteration.

For any queries related to the content of this report, please contact the MRC Evaluation Team at MRCEvaluationTeam@headoffice.mrc.ac.uk

Report by Ellen Charman with quantitative data and analysis provided by Gavin Reddick, MRC Evaluation Team.

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SECTION 02: Case studies

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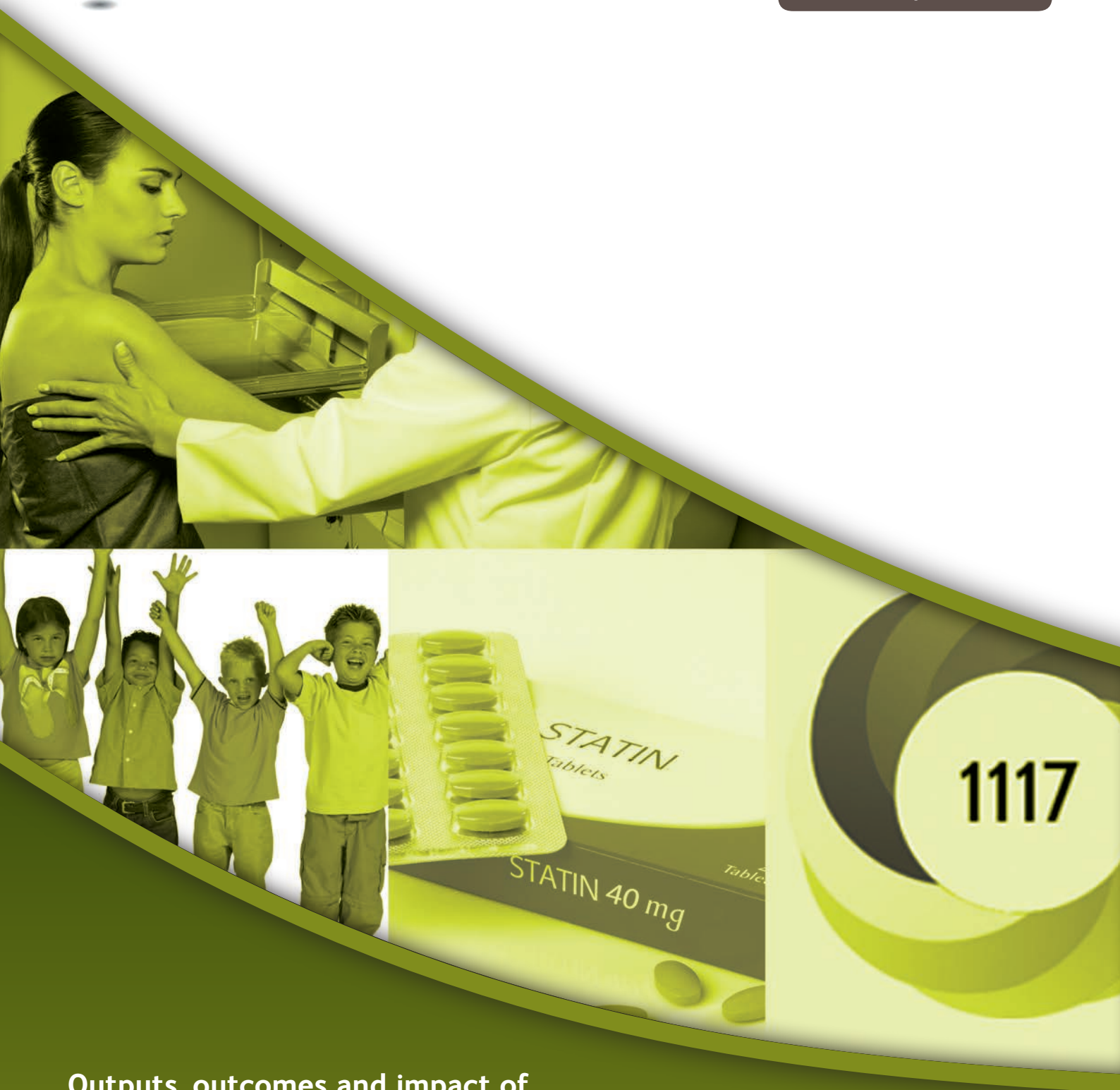
MRC Medical Research Council



Outputs, outcomes and impact of MRC research: 2013/14 report

SECTION 2.1: Published research

Published research

Peer-reviewed journal articles are an important primary output from research, and an integral part of the scientific method. Scholarly journals have been in existence for almost 350 years[7]. And their main functions – communicating information, building a collective knowledge base, validating the quality of research, influencing the distribution of rewards and building scientific communities – have largely remained unchanged in this time despite innovations in publishing and new models for accessing this information[8]. While we also capture, via Researchfish, information about "secondary" publications such as systematic reviews, editorials and other types of literature such as conference proceedings and books, this and the quantitative analysis chapter focus mainly on publications categorised by Thomson Reuters as 'journal articles' and 'journal reviews'.

Bibliometrics

After the Researchfish data-gathering period, bibliographic details of unique papers were provided to Thomson Reuters[9], who returned citation information for every publication they could match to the Thomson ISI Web of Science database[10]. The ISI database does not include all journals in which MRC researchers publish and so papers in those journals could not be included in our analysis. In addition, some papers, for example, published in conference proceedings, do not have standard citations and they are also excluded. Citation data were however returned for around 89 per cent of the papers sent for analysis (55,601/62,751).

THOMSON REUTERS

Logo reproduced with the permission of Thomson Reuters.

Citation impact of MRC papers

The citation of publications in other peer-reviewed research articles is often used as a proxy measure of academic and wider user impact. Citation counts can be normalised by scientific field and year of publication which gives a normalised citation impact (NCI). An NCI score of 1 means that the paper is behaving as would be expected for that subject area in that year, and this is referred to as the world average. An NCI of above 1 means that the paper is cited more often than would be expected and is above the world average. A further measure of the impact of publications is the number or percentage of articles that are either uncited or conversely, those deemed as highly cited (identified as those with an NCI score that is greater than or equal to 4)[11]. Having assessed several measures of citation impact and metrics, including the 'h index' and its variants, we consider the NCI score to be the most consistent and robust bibliometric measure available, although the limitations of purely citation-based measures should be noted. For example the Thompson Reuters NCI is not designed to capture references to a publication outside of scholarly literature. There is evidence that scholars are increasingly adopting the Internet to manage their everyday work[12] (online reference managers Zotero[13] and Mendeley[14] each claim to store over 40 million articles), which highlights the need for tools to capture the extent to which papers are downloaded from a wide range of repositories, alongside a growing interest in monitoring discussion of papers via social media and other networks (see the section below on Altmetrics for more information on the occurrence of impact through the use of social media).

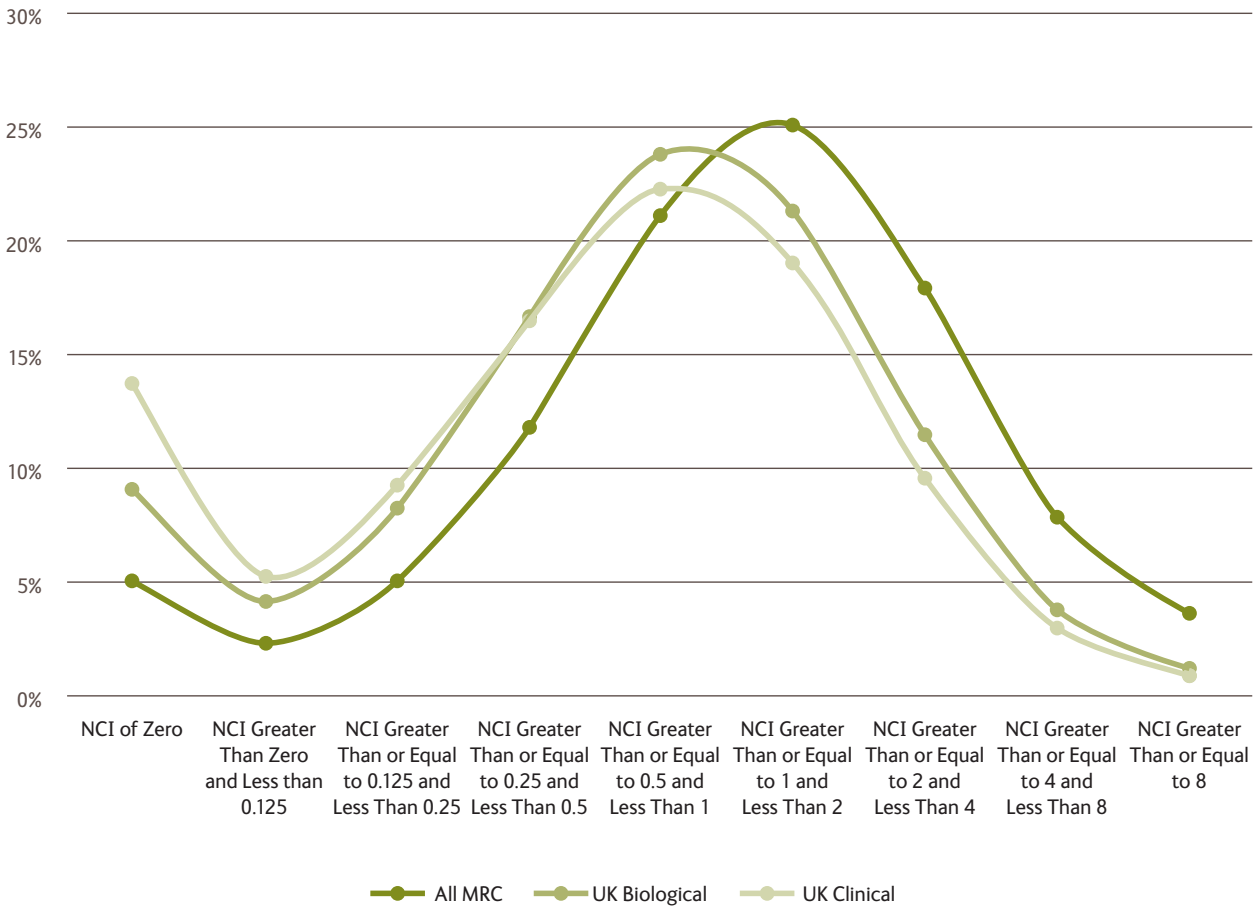
The average NCI across all MRC papers published between 2006 and 2012 is 2.1[15].

Figure 1 shows an Impact Profile ® of MRC publications between 2006 and 2012[16]. This enables an examination and analysis of the balance of MRC publications relative to world average, and in comparison to publications generated by other UK medically-related and biological sciences research. It shows the proportion of uncited papers and the proportion in each of the eight categories of relative citation rates, normalised to world average.

Figure 2 is a box and whiskers plot showing the distribution of the average NCI by year. The inclusion of the second and third quartiles of data and the interquartile mean for each year allows us to determine whether or not the average NCI is skewed by anomalies in any year. In this case, it shows that the data is consistent across the years. This representation of the data is particularly useful for comparing distributions and showing differences which are not always easily apparent in an Impact Profile ® plot.

Table 1 shows the distribution of NCI for the top 20 subject areas (by number of publications)[17].

Figure 1: *Impact Profile ® of MRC publications between 2006 and 2012*



Data & analysis: Thomson Reuters (Evidence)

MRC-funded research generates a greater percentage of highly-cited[18] papers than other UK clinical and UK biological sciences research (11.5 per cent compared to 4 per cent and 4.9 per cent respectively). It also generates a greater percentage of very highly-cited papers[19] than UK clinical and UK biological sciences research (3.6 per cent compared to 1 per cent and 1.1 per cent respectively).

Figure 2: *Box and whiskers plot showing the distribution of average NCI by year*

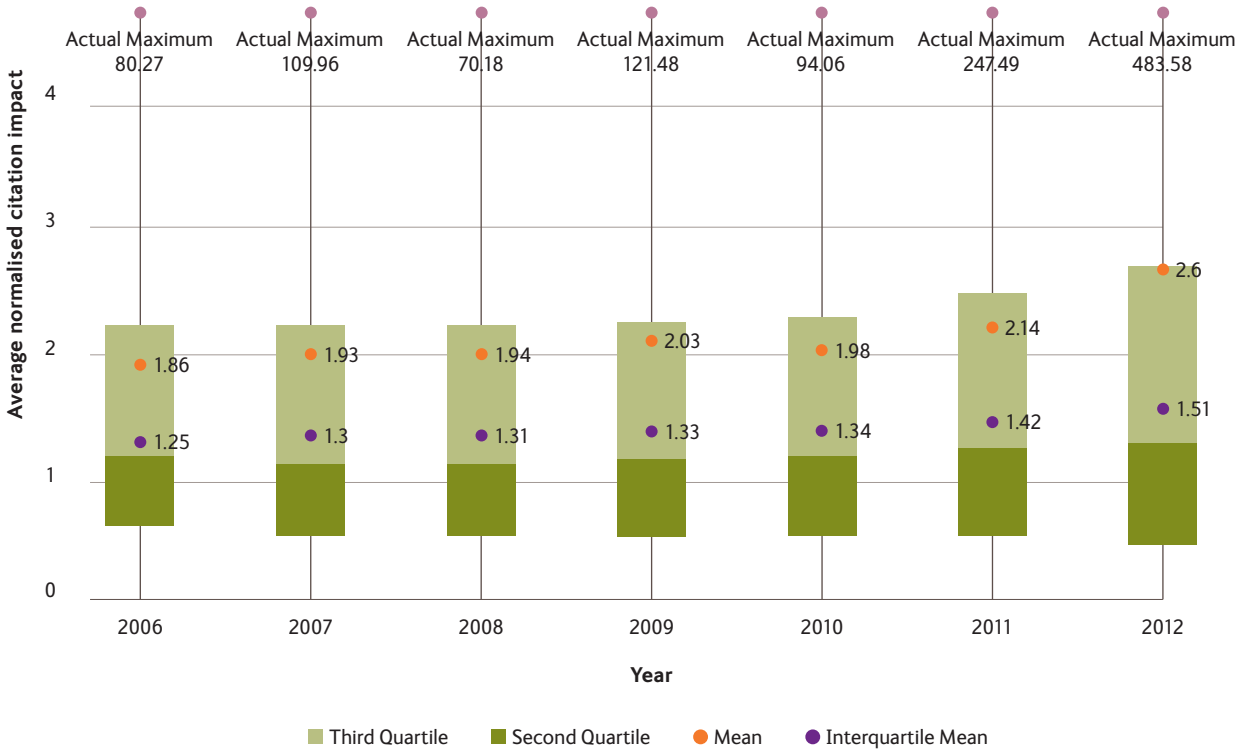


Table 1: *Distribution of NCI for the top 20 subject areas*

Subject	Average of category specific NCI	Number of papers	NCI 1 or more	NCI 1 or more %	NCI 4 or more	NCI 4 or more %	NCI 8 or more	NCI 8 or more %
Biochemistry and Molecular Biology	1.834389	6,401	3,254	51%	580	9%	187	3%
Neurosciences	1.79602	6,258	3,389	54%	601	10%	152	2%
Cell Biology	1.530351	4,144	1,912	46%	314	8%	75	2%
Immunology	1.861843	3,328	1,669	50%	357	11%	102	3%
Genetics and Heredity	2.497526	3,110	1,648	53%	487	16%	192	6%
Clinical Neurology	2.274877	2,794	1,597	57%	372	13%	123	4%
Psychiatry	2.084158	2,579	1,549	60%	331	13%	89	3%
Public, Environmental & Occupational Health	2.067787	2,339	1,301	56%	289	12%	82	4%
Oncology	1.866596	2,082	1,011	49%	175	8%	62	3%
Endocrinology and Metabolism	1.571735	2,046	1,004	49%	150	7%	25	1%
Pharmacology and Pharmacy	1.853421	1,409	807	57%	142	10%	28	2%
Infectious Diseases	1.607657	1,406	689	49%	96	7%	37	3%

Subject	Average of category specific NCI	Number of papers	NCI 1 or more	NCI 1 or more %	NCI 4 or more	NCI 4 or more %	NCI 8 or more	NCI 8 or more %
Virology	1.642989	1,366	721	53%	93	7%	19	1%
Research and Experimental Medicine	2.435576	1,253	666	53%	219	17%	79	6%
Microbiology	1.958167	1,177	725	62%	128	11%	33	3%
Haematology	1.630296	1,162	631	54%	86	7%	13	1%
Developmental Biology	1.39089	1,159	536	46%	71	6%	9	1%
Biotechnology and Applied Microbiology	1.908144	1,122	592	53%	103	9%	26	2%
Radiology, Nuclear Medicine and Medical Imaging	2.16155	1,103	693	63%	146	13%	31	3%
Respiratory System	2.032199	896	500	56%	115	13%	27	3%

Five of the top MRC publications by NCI between 2006 and 2012[20]

Further information on the research referred to in these publications can be found on the Research Councils UK (RCUK)'s information portal — *the Gateway to Research*[21] — by entering the project reference number listed under each case study in the search field.

Establishing a standard definition for child overweight and obesity worldwide: international survey[22]. NCI: 142

In this paper, **Professor Tim Cole** at **University College London's Institute of Child Health** outlines the development of a new definition of overweight and obesity in childhood, based on pooled international data for body mass index (BMI) and linked to the widely accepted adult overweight and obesity cut off points of 25kg/m^2 and 30kg/m^2 respectively.

Due to the association between childhood obesity and later heart disease and other chronic conditions — that may be independent of the link between childhood and adult obesity — it is important that childhood obesity trends are monitored.

The traditional use of BMI, the standard adult obesity measurement, was previously not considered wholly reliable as in childhood it changes substantially with age. In 1979 Professor Cole produced an amended BMI calculation for children by adjusting the height and weight for age[23].

However, trends in childhood obesity are still difficult to quantify or compare internationally due to the wide variety of definitions of child obesity.

The analysis conducted by Professor Cole in 2000 provides a centile curve for BMI in childhood that is based on international frequency estimates at age 18 of 5-18 per cent for overweight and 0.1-4 per cent for obesity. These cut off points were recommended for use in international comparisons of prevalence of overweight and obesity.

The study benefited from funding from the Childhood Obesity Working Group of the International Obesity Task Force.

The MRC has funded Professor Cole's research in medical statistics for almost 50 years and his work on child growth has yielded many key findings and influenced national and international policy. Childhood growth is a powerful indicator of childhood health. Illnesses involving a growth hormone deficit have a direct impact on growth, whereas others such as asthma may affect growth indirectly. Analysis of growth can often signify health issues before other symptoms develop[24].

Professor Cole overhauled the traditional growth charts for the measurement of a child's height, weight and head circumference. The earlier charts plotted centile curves against age with each curve defining a constant proportion of children below the cut-off, based on a reference population. However, the curves were plotted as smooth and ignored any skewness in the distribution. Professor Cole developed a technique called LMS (least mean squares) as a way to address this[25]. He extended this method by developing the Super-Imposition by Translation And Rotation (SITAR) method that plots a series of measurements for an individual as a growth curve rather than the individual measurements. This corresponds to the individual's relative size and underlying development age, so for example, can detect if puberty is early or late[26].

Project reference number: G9827821

Screening and prostate-cancer mortality in a randomized European study[27]. NCI: 121

This paper presents the follow-up results from the European Randomized Study of Screening for Prostate Cancer (ERSPC) trial started in the early 1990s to determine whether a reduction of 25 per cent in prostate-cancer mortality could be achieved by prostate-specific-antigen (PSA)-based screening.

The study identified 182,000 men between the ages of 50 and 74 years through registries in seven European countries (there were 162,243 men in the core age group of 55-69). The men were randomly assigned to a group that was offered PSA screening at an average of once every four years or to a control group that did not receive screening. Mortality follow-up was completed in December 2006 with average and median follow-up times of 8.8 and 9.0 years in the screening and control groups. There were 214 prostate-cancer deaths in the screening group and 326 in the control group in the core age group. The study demonstrated a relative reduction of 20 per cent in the rate of death from prostate cancer among men between the ages of 55 and 69 years at study entry.

Dr Sue Moss at the **Institute of Cancer Research**, who worked on the National Cancer Research Institute South of England Prostate Cancer Collaborative (part-funded by the MRC), was a co-author on the paper.

The study was also supported by grants from Europe Against Cancer and the Fifth and Sixth Framework Programme of the European Union, by other grants from agencies and health authorities in the participating countries and by unconditional grants from Beckman Coulter.

Project reference number: G0501019

MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial[28]. NCI: 92

This paper presents the results of a trial examining the link between use of the cholesterol-lowering drug simvastatin and a reduction in incidence of heart attacks, stroke and other vascular conditions. The study recruited 20,536 UK adults (aged 40-80 years) with coronary disease, other occlusive arterial disease, or diabetes who were randomly allocated to receive 40 mg simvastatin daily (average compliance: 85%) or matching placebo. The study concluded that taking 40 mg of simvastatin daily reduced the rates of heart attack and stroke by about one-quarter (after making allowance for non-compliance, the authors concluded that use would reduce these rates by about one-third).

This trial was conducted by researchers at the **MRC Clinical Trial Service Unit** and was funded predominantly by the MRC and British Heart Foundation. The study was the largest of its kind worldwide. In addition to examining the effects of simvastatin on particularly high-risk patient groups, it also provided evidence that the drug was effective for use in other groups, such as women and the over 70s, for whom there was uncertainty as to how worthwhile and safe the treatment was.

It is likely that the NCI of this paper has increased due to the recent media and public attention given to the use of statins following the publication of two BMJ articles referencing adverse effects of statins and the subsequent withdrawal of those statements[29].

Statins. Image credit: Shutterstock.

For similar reasons, this paper has a high altmetric[30] score, particularly for a paper of this age[31]. Altmetric for ScienceDirect puts the article in the top five per cent of all articles ranked by attention, rates it as good compared to other articles of the same age and journal (78th percentile) and very good when compared to articles of the same age (97th percentile).

Project reference number: MC_U137686853

Intratumor heterogeneity and branched evolution revealed by multi-region sequencing[32]. NCI: 83

With rare exceptions, spontaneous tumours originate from a single cell. Yet, at the time of clinical diagnosis, the majority of human tumours display startling genetic differences in many morphological and physiological features, such as expression of cell surface receptors.

This paper summarises the result of a study that used multi-region genetic analysis to provide evidence of intratumour heterogeneity — a single tumour containing genetically different cells — in four consecutive tumours.

Genetic intratumour heterogeneity can contribute to treatment failure and drug resistance. Intratumour heterogeneity may have important consequences for personalised-medicine approaches that commonly rely on single tumour-biopsy samples to portray tumour mutational landscapes. This is an example of the MRC funding research that is key in shaping the field of personalised medicine.

The work was reported by **Professor Charles Swanton** (University College London Hospital) and was additionally funded by Cancer Research UK, the Royal Marsden Hospital Renal Research Fund, Novartis, the European Commission, and the Wellcome Trust.

Project reference numbers: G0701935, G0902275

Abiraterone and increased survival in metastatic prostate cancer[33]. NCI: 67

This paper presents the results of a Phase III multinational, randomised, double-blind, placebo-controlled trial of abiraterone acetate and prednisone in patients with advanced prostate cancer. Inhibiting the action of androgens — steroid hormones — is the standard treatment for men with advanced prostate cancer. For most patients, this reduces levels of prostate-specific antigen (PSA), elevated in the presence of cancer, as well as shrinking tumours and relieving symptoms. However, in patients with advanced cancer, the response to treatment is not sustainable and levels of PSA steadily increase.

In these patients, it has been shown that the enzymes responsible for androgen production are up-regulated, leading to an increase in androgen concentration within the tumour[34,35,36].

Abiraterone acetate blocks androgen production by the adrenal glands, testes and within the prostate tumour by blocking the action of an enzyme critical for the production of testosterone.

At 147 sites in 13 countries, 1,195 patients were randomly assigned to receive abiraterone acetate plus prednisone — a replacement steroid hormone (797 patients) or a placebo plus prednisone (398 patients).

At the time of the pre-planned interim analysis[37], treatment with abiraterone acetate plus prednisone resulted in a 35.4 per cent reduction in the risk of death compared to the placebo group. The median overall survival was 14.8 months in the abiraterone acetate group and 10.9 months in the placebo group. On the basis of the PSA concentration, abiraterone acetate was associated with a 42 per cent reduction in the risk of disease progression. In addition, patients in the abiraterone acetate group had consistently improved pain management as compared with those in the placebo group.

The paper was reported by first author **Professor Johann de Bono** at the **Institute of Cancer Research**, who was supported by the MRC. The study was additionally funded by Ortho Biotech Oncology Research and Development (a unit of Cougar Biotechnology), the Experimental Cancer Medical Centre, the National Institute for Health Research Biomedical Research Centre, and the Prostate Cancer Foundation.

Project reference number: G0601308

MRC papers published in 2013 already exhibiting high citation impact

Further information on the research referred to in these publications can be found on the Research Councils UK (RCUK)'s information portal — *the Gateway to Research* — by entering the project reference number listed under each case study in the search field.

Innate lymphoid cells — a proposal for uniform nomenclature[38]. NCI: 100

Innate lymphoid cells (ILCs) are a family of cells involved in immunity and tissue development. Several distinct members of the group have recently been identified; however, different names have been used to label them.

Dr Andrew McKenzie at the **MRC Laboratory of Molecular Biology**, together with international colleagues, proposes in this paper a classification system to define ILCs, based on the type and mechanism of cytokine production. They define group 1 ILCs by their ability to produce interferon-γ (IFNγ), an important activator of macrophages; group 2 by their ability to produce T helper 2 cell-associated cytokines such as interleukin-5 and interleukin-13; and group 3 by their ability to produce T helper 17 cell-associate cytokines interleukin 17 and 22.

The paper also credits funding from the NIH, Wellcome Trust and the Howard Hughes Medical Institute.

Project reference number: MC_U105178805

TREM2 variants in Alzheimer's disease[39]. NCI: 79

This paper was reported by **Professor Julie Williams** at the **MRC Centre for Neuropsychiatric Genetics and Genomics** at **Cardiff University**, who was part of an international collaboration that examined heterozygous mutations of the *TREM2* gene to determine whether they are linked to an increased risk of Alzheimer's disease. The *TREM2* gene codes for the 'triggering receptor' protein found on myeloid cells 2, which are cells produced in the bone marrow. The protein is located on the cell surface where it interacts with the protein encoded by the *TYROBP* gene – these proteins form a complex that transmits chemical signals which activate the cell[40]. The complex was first identified in the immune system where it plays a role in the growth and activation of immune cells to trigger an inflammatory response to injury or disease.

This complex also activates cells in the skeletal system and in the central nervous system. In the skeletal system, the complex is found in osteoclasts — specialised cells involved in the normal process of bone remodelling, specifically, that break down and remove bone tissue that is no longer needed. In the central nervous system, the complex is found in microglia — immune cells that protect the brain and spinal cord from foreign invaders and remove dead nerve cells and other debris.

Homozygous loss-of-function mutations in *TREM2* have previously been linked to a form of early-onset dementia called polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy, or Nasu–Hakola disease[41]. This disease is associated with the presence of bone cysts and subsequent fractures.

This research collaboration has also identified homozygous TREM2 mutations in three Turkish patients showing symptoms associated with frontotemporal dementia and leukodystrophy — a group of disorders associated with the degeneration of white matter in the brain — but without the bone-associated symptoms[42]. Additionally, a genome-wide analysis has identified eight linkage regions, including one on chromosome 6 — the site of *TREM2* — with significant associations to late-onset Alzheimer's[43].

The researchers used different types of sequencing to analyse the genetic variability of TREM2 in 1,092 patients with Alzheimer's disease and 1,107 controls. They found significantly more variants in a part of the gene in patients with Alzheimer's compared to those without the disease — 22 compared to five. The most commonly-associated variant

rs75932628 — encoding R47H —showed significant association with Alzheimer's disease. The authors therefore conclude that the reduced function of TREM2 is key to the pathogenic effect of these risk variants associated with Alzheimer's disease.

Professor Williams and **Professor Michael Owen's** research into the genetic risk factors for complex psychological and neurodegenerative disorders such as Alzheimer's and schizophrenia has been funded by the MRC for more than 20 years.

Both have played a fundamental role in leading international collaborations, substantially increasing the number of genes identified to play a part in the development of Alzheimer's. In 2013, Professor Williams led one of the four international teams making up the consortium that discovered a further 11 genes connected to a person's increased risk of developing Alzheimer's, taking the total to 21, and widening the potential for new treatments.

Project reference numbers: G0902227, G1100695, MC_U123192748, MC_G1000735, G0701075, G0802462, G0701441

Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial[44].
NCI: 60

A mammogram. Image credit: Shutterstock.

This paper presents the follow-up analysis of the Adjuvant Tamoxifen: Longer Against Shorter (ATLAS) randomised trial, led by **Professor Christina Davies** at the **MRC Clinical Trial Service Unit**. For women with oestrogen receptor (ER)-positive early breast cancer, treatment with tamoxifen for five years substantially reduces the breast cancer mortality rate throughout the first 15 years after diagnosis. The study demonstrated that continuing tamoxifen to 10 years rather than stopping at five years produces a further reduction in recurrence and mortality, particularly after year 10. These results, taken together with results from previous trials of five years of tamoxifen treatment versus none, suggest that 10 years of tamoxifen treatment can approximately halve breast cancer mortality during the second decade after diagnosis.

The five-year survival rate for breast cancer has increased by 18 per cent between 1986-1990 and 2005-2009[45], predominantly due to the introduction of breast cancer screening[46] and improved treatment regimens such as this.

This trial also benefited from funding from Cancer Research UK, AstraZeneca UK, the US Army and EU-Biomed.

Project reference number: G0901530

Open Access

Free and open access to publicly-funded research offers significant social, academic and economic benefits. The Government, in line with its overarching transparency pledge, is committed to ensuring that open access is customary.

In July 2012, the Government announced that it had accepted the recommendations of the report from the National Working Group on Expanding Access to Published Research Findings (the 'Finch Group') – "Accessibility, sustainability, excellence: how to expand access to research publications"[47]. Research Councils UK (RCUK) has used the findings of this report to strengthen its open access policy, which came into force on 1 April 2013[48]. The key elements of the MRC policy in support of open access (OA), first issued in 2006, have been integrated in the new joint RCUK Open Access policy. The key aspect of the MRC mandate is that whether a researcher publishes in an open access or subscription- based journal, they must ensure that their article is deposited into Europe PubMed Central (Europe PMC) and made freely available as soon as possible, and in any event, within six months of the journal publisher's official date of final publication.

The MRC, in line with RCUK's policy, is expected to see compliance with the policy grow over five years to reach 100 per cent compliance in 2018. This should include 75 per cent of papers published and available in OA immediately on publication, with full use and re-use rights (also referred in the policy as the "Gold route"). However, RCUK recognises that this will be a gradual change and so the target has been fixed at 45 per cent in the first year, growing to 53 per cent in 2014/15. The data we collect through Researchfish and Europe PMC will assist in the monitoring of the MRC's compliance rates.

Image credit: PLOS

A graph showing the proportion of unique MRC publications produced each year that are available in Europe PMC (as at July 2014) is in the quantitative analysis section 3.1.

Altmetrics

Altmetrics is a relatively new term, coined in 2010 by Jason Priem, a doctoral student in information science at the University of North Carolina. It can be defined as 'social media-based metrics'[49], which take into account digital use and sharing of data — such as through 'likes' on Facebook, being tweeted or cited on Wikipedia — when gauging impact[50].

To reflect the growing use of social media by academics — Procter R et al reported in 2010 that 13 per cent of UK academics frequently use Web 2.0[51] in novel forms of scholarly communications[52] — the research and academic community is making increasing use of altmetrics. Many journals now display some altmetrics on their sites automatically, either generated in-house or provided by an external service. PLOS includes an online metrics tab for each article it publishes, showing views, downloads and social-media mentions. In addition, the Higher Education Funding Council for England (HEFCE) allows scientists to use them when demonstrating social impact in reports for the Research Excellence Framework (REF).

Many consider that almetrics should be applied with caution[50]. They do not always discriminate between positive and negative attention. Most altmetric analysis services rely on picking up URLs for the study, which are not always included in news items, so at best the metrics are partial. And, as with journal citations, social media 'citations' differ between

years and disciplines (but currently there is no 'normalisation' for this) — computational biology researchers, for example, tend to be more active on social media than others[50].

Many studies have shown that there is a positive, albeit weak correlation with traditional methods such as citations[53,54]. It is proposed therefore that altmetrics and citations measure different types of impact and that altmetrics should be used to complement, rather than replace, traditional methods[56].

Altmetric[56], a London-based company set up to track and analyse the online activities around scholarly literature, published a list of the top 100 articles that had received the most online attention in 2013[57]. At number 18 was "Cerebral organoids model human brain development and microcephaly", a paper on the growth of a 3D structure resembling human brain tissue, co-authored by researchers at the **MRC Human Genetics Unit**[58]. (For more information on this paper, please see the case study 'Research materials: Growth of 3D structure resembling human brain tissue' on page 45.)

The 'Altmetric' score for Cerebral organoids model human brain development and microcephaly as at June 2014. www.altmetric.com

researchfish

MRC Medical Research Council

Outputs, outcomes and impact of MRC research: 2013/14 report

SECTION 2.2: Policy and engagement

Policy and engagement

The MRC recognises the immense value of researchers engaging with audiences outside of academia, and this is why the MRC strives to embed public engagement and dialogue with policymakers at the heart of everything we do.

From the centenary open days we held in 2013 to the annual Max Perutz award[59], the MRC runs a varied public engagement programme involving many of our researchers. But public engagement is not limited to these MRC-run events. The MRC encourages our scientists to engage, educate and inspire the public through a variety of mediums, should that be participating in exhibitions or workshops, giving lectures or being interviewed by the media. MRC researchers are often also involved in the many public engagement activities run through their own university or research organisation.

The MRC has a long history of engaging and consulting with parliamentarians. The MRC as an organisation frequently submits evidence relating to biomedical research to inquiries and consultations by government departments, Select Committees of the House of Commons and the House of Lords, and to other organisations, drawing on the expertise of particular researchers or research boards and panels as necessary. Our researchers are also often called upon as experts in particular areas of research to give advice or evidence.

The MRC also plays a critical part in shaping and influencing national and international policy, ensuring that public policy decisions and health interventions are based on research of the highest quality. MRC researchers contribute regularly to the development and revision of clinical guidelines — recommendations to clinicians on the diagnosis, management and treatment in specific areas of healthcare based on systematic evidence, such as NICE and WHO clinical guidelines. MRC researchers also have an influence on policy through membership of guideline committees, participation in national consultations, and the training of practitioners. The MRC has played a leading role in critical areas of research and subsequent policy and strategy development, from our public health work on obesity and smoking to the establishment of UK Biobank. Examples of where MRC-supported researchers have influenced policy and been involved in public engagement can be found throughout this chapter, and are categorised by the following research areas:

- Obesity and nutrition
- Infectious diseases
- Neurodegeneration and neurology
- Cancer

Further information on each piece of research can be found on the Research Councils UK (RCUK)'s information portal — *the Gateway to Research*[60] — by entering the project reference number listed under each case study in the search field.

Obesity and nutrition

The UK is a world leader in nutritional science and in research aimed at improving health and reducing the burden of nutrition-related illness. The need for basic, strategic and applied nutrition research has never been greater. We face a double burden of disease caused by the combination of classical nutritional deficiencies and the rapidly increasing problem of ill-health associated with dietary excess and imbalance.

Obesity is one of the greatest threats to health today. Research has shown that obesity severely increases the risk of type 2 diabetes, heart and liver disease, some forms of cancer, and also increases the likelihood of developing other long-standing illnesses. Figures released by Public Health England in January 2014 showed that 64 per cent of adults are now overweight or obese[61], with a body mass index (BMI) of more than 25 and 30, respectively. The number of adults classed as obese has increased by 60 per cent in the last two decades (from 15 per cent in 1993 to 25 per cent in 2014). Health problems associated with being overweight or obese cost the NHS around £5 billion every year, compared to £3 billion each for smoking and alcohol-associated health problems[62].

Influence on policy: Food portion sizes and content

In October 2013 the British Heart Foundation (BHF) published its report 'Portion Distortion' comparing the portion sizes of 245 products sold today with the portion sizes listed in a 1993 Food Standards Agency (FSA) publication showing "typical weights and portion sizes of foods eaten in Britain". The BHF report showed that the majority of portion sizes had increased dramatically in the 20 years since the FSA publication. The report cites research on portion size undertaken by **Professor Susan Jebb** at the **MRC Human Nutrition Research Group (HNR)**[63].

Portion Distortion. Image reproduced with the permission of the British Heart Foundation

Professor Jebb has shown that on the UK market the range of portions was often highly variable, and as a result could lead to consumer confusion and subsequent distrust in on-pack portion size messages, suggesting that there is a need for greater consistency in the portion sizes[64].

As part of the Government's Foresight report, Professor Jebb also recommended decreasing portion sizes as an effective intervention in helping to combat the obesity crisis[65].

Professor Jebb is chair of the Department of Health Food Network, which is part of the Government's Public Health Responsibility Deal[66]. The Public Health Responsibilty Deal aims to encourage businesses to contribute to improving public health through signing up to a series of pledges, such as reducing the calorie, salt and saturated fat contents of foods and improving nutritional labelling. 82 different organisations have signed up to the pledge to reduce salt in their food and 37 have signed up to the calorie reduction pledge[67]. Major food companies are using the Responsibility Deal to shape their business strategies. In particular Subway® have signed up to six of the food pledges, on average have almost halved (48 per cent) the salt content across the entire range of their food and all of their stores have menu boards with calorie content displayed[68].

Project reference number: MC_U105960389

Unexpected impacts of MRC research

Influence on policy: Age of Indonesian fishermen accused of people smuggling

Professor Tim Cole is a Professor of Medical Statistics at **University College London's Institute of Child Health**. He specialises in many areas of child growth assessment, including growth chart construction, growth curve analysis, body size scaling and forensic age assessment.

In 2012 Professor Cole provided evidence to a formal inquiry by the Australian Human Rights Commission, which reported on the validity of using wrist x-rays to assess bone age and decide whether Indonesian fisherman accused of people smuggling were adults or children[69]. The issue is important because those over 18 face a mandatory five-year jail sentence for people smuggling, while those under 18 are repatriated. Professor Cole's evidence led to the Australian government discontinuing this practice of assessment and implementing a more transparent method of deciding age, which also means that accused smugglers claiming to be children are less likely be jailed for months before a decision is taken. Professor Cole also gave expert witness in 11 cases of alleged people smuggling, which led to nine of these cases being dropped, with the accused being repatriated and a longstanding prosecution witness being discredited.

Project reference number: MR/J004839/1

Engagement activities: How obesity-risk gene is linked to obesity

Researchers from the **MRC Clinical Sciences Centre's** Metabolic Signalling Group, in collaboration with scientists at UCL and King's College London, have shown for the first time how variations in the *FTO* gene – the strongest obesity risk gene – are linked to obesity[70]. This study demonstrates that *FTO* gene variations affect circulating levels of 'hunger hormone' ghrelin in the blood. Ghrelin stimulates appetite and so levels are normally high before a meal and then decrease afterwards. However, for one in six people who carry two copies of the high obesity-risk *FTO* variant gene, ghrelin levels do not drop off after eating, and so they soon start to feel hungry again.

The MRC has been investigating obesity for more than three decades and has led the way in examining the links between obesity and genetics. In 2007, a consortium of researchers led by the MRC identified the obesity-risk *FTO* variant gene after undertaking a genome-wide search for type 2 diabetes-susceptibility genes. This gene variant does in fact predispose the carrier to diabetes through its effect on body mass index. The researchers discovered single 'letter' variations in the genetic code of the *FTO* gene and showed that those with the obesity-risk variant were on average 3kg heavier than those with the low-risk version. The link between this gene and obesity was confirmed by MRC researchers at **Imperial College London**.

Image credit: Wellcome Images/LibbyWelch

Until now however, it was unknown exactly how these variations were linked to obesity. In the 2013 study, researchers, led by **Dr Rachel Batterham**, studied two groups of male participants – those with two copies of the high obesity-risk *FTO* variant (AA group) and those with the low obesity-risk version (TT group). Men with the AA variation had much higher circulating ghrelin levels and felt hungrier after eating than the TT group. The researchers also investigated the situation at the molecular level. Boosting the expression of *FTO* in mouse cells effectively increased the production of ghrelin. When they compared this to human cells from the high-risk group, they found levels of *FTO* expression were significantly higher, and correspondingly more ghrelin mRNA was found than in cells from the low-risk group. The *FTO* gene itself encodes a protein enzyme, which changes the methylation status of ghrelin mRNA; increased *FTO* mRNA lowered methylation levels on ghrelin mRNA, which raised production of the protein itself.

The study uncovers a novel mechanism for manipulating ghrelin levels whether by drug or behavioural means. There are some drugs in the pipeline that suppress ghrelin, which might be particularly effective if they are targeted to patients with the obesity-risk variant of the *FTO* gene.

The results of the study were covered widely by the national media, including the BBC, *The Telegraph*, and the *Daily Mail*.

Project reference number: MC_U120097114

Influence on policy: Calcium

All living cells require calcium to remain viable and it is also required for a number of specific functions in the body so it is crucial that people consume sufficient amounts in their diet. Calcium is essential for bone growth as it is needed for the mineralisation of bone; the rate of bone growth is proportional to the rate of calcium deposition in bone. Insufficient calcium intake may lead to a low bone mineral density, which has implications for bone health in later life, such as a risk of osteoporosis. Calcium also plays a role in regulating muscle contraction (including the heart) and blood pressure, digestion and ensuring blood clots normally.

As part of the Government's Red Tape Challenge on 'Hospitality, Food and Drink'[71] to reduce regulatory burdens on business, the Department for Environment, Food and Rural Affairs (DEFRA) was asked in 2013 to review whether mandatory fortification of bread with calcium, iron, niacin and thiamine should continue. **Professor Ann Prentice**, director of the **MRC HNR**, as chair of the Scientific Advisory Committee on Nutrition (SACN), gave advice to the government on this issue. The SACN in particular demonstrated that removal of calcium and iron would adversely affect the intake of certain population groups[72]. **Drs Jonathan Powell, Gail Goldberg** and **Dora Pereira** at the **HNR** also took part in the subsequent national consultation. In line with the views of the SACN, they commented that the current system provided equal health benefits for all consumers and that flour should be preserved as a vehicle for population nutritional intervention. They specifically made reference to the fact that flour was a particularly important source of calcium, especially for those who do not consume dairy products. The Government has since concluded that the mandatory fortification of bread should continue.

It is even more important for pregnant women to obtain sufficient calcium in their diet, both to assist the growth of their baby's developing skeleton, for breast-feeding and also the growth of their infant. Calcium is considered to be key in the regulation of blood pressure throughout life and particularly during pregnancy, to help women avoid developing pre-eclampsia.

The MRC has funded several studies to determine whether calcium supplementation in Gambian women — whose calcium intake is low and whose infants experience poor growth and bone mineral growth is poor compared to those in Western populations — would be beneficial.

In 2006 researchers from the **MRC Unit, The Gambia**, in collaboration with those in the **MRC HNR** showed in fact that calcium supplementation of pregnant Gambian women had no significant benefit for breast-milk calcium concentrations, or infant birth weight, growth or bone mineral status in the first year of life[73]. The study found for women who are accustomed to a very low calcium diet, increased calcium intake does not increase the transfer of calcium to the offspring, during either foetal life or subsequent breastfeeding. This supports research showing that metabolic adaptations occur during human pregnancy and lactation to provide sufficient calcium for foetal growth and breast-milk production[74].

These results were followed up with a clinical trial in 2013, which showed that calcium supplementation had no significant effect on either mother's blood pressure or infant growth[75].

Researchers from the **MRC Unit, The Gambia**, the **MRC HNR** and the **MRC International Nutrition Group** also investigated whether there was an association between maternal calcium supplementation and offspring blood pressure at age five-10 years old[76]. The researchers found no association between maternal calcium supplementation and offspring blood pressure, suggesting that additional calcium was not transferred to the offspring in utero, supporting previous studies[77].

An MRC study undertaken by researchers in these research groups has however conversely demonstrated that calcium supplementation in Gambian children aged 8-12 may increase bone mineralisation and, ultimately, peak bone mass[78].

These findings have implications for nutrition policy in The Gambia and other populations with low calcium intake.

Project reference numbers: MC_U105960371, MC_U105960371

Unexpected impacts of MRC research

Engagement activities: Nutritional advice to the BBC's One Show

Dr Gail Goldberg at the **MRC HNR** was asked to provide nutritional advice on yams to the BBC's One Show on account of the HNR's global work on nutrition. The programme was to host the Olympic gold medallist sprinter Usain Bolt, who had claimed that the secret of his success was Jamaican yams.

Project reference number: MC_U105960371

Influence on policy: Importance of sufficient iodine intake during pregnancy

The MRC-funded **Avon Longitudinal Study of Parents and Children (ALSPAC)** has shown that iodine deficiency in pregnancy has an adverse effect on children's mental development[79].

Iodine is essential for producing the hormones made by the thyroid gland, which have a direct effect on foetal brain development. The potentially harmful effects of severe iodine deficiency are well-established, however, the link between mild or moderate iodine deficiency and cognitive development has until now not been extensively examined. For many years, iodine intake in the UK was thought to be sufficient. A study conducted by researchers at the Universities of Surrey and Bristol has however shown that two thirds of pregnant women are deficient. They measured the iodine concentration in urine samples taken in the first trimester from 1,040 pregnant women and classified those who had an iodine-to-creatinine[80] ratio of less than 150 µg/g as being iodine deficient, and those with a ratio of 150 µg/g or more as iodine sufficient[81]. More than two thirds (67 per cent) of the women were classed as being iodine deficient.

Image credit: iStock

The researchers assessed the mental development of the women's children by measuring their IQ at age eight and reading ability at age nine. The researchers found that children of the women in the iodine-deficient group were significantly more likely to have scores at the low end of verbal IQ, reading accuracy and reading comprehension, even after adjusting for external factors likely to affect the scores, such as parental education and breast-feeding. The lower the mother's level of iodine, the lower the average scores for IQ and reading ability were.

As a result of this study, the British Dietetic Association (BDA) has produced a fact sheet on the importance and sources of dietary iodine, with a focus on the increased requirements of pregnant women[82].

Project reference number: G9815508

Influence on policy: Citation in NICE guidelines "Overweight and obese adults – lifestyle weight management"

In May 2014 the National Institute for Health and Care Excellence (NICE) published guidelines on lifestyle weight management for overweight and obese adults[83]. The guidelines comprise multi-component lifestyle weight management approaches that aim to change someone's behaviour to reduce their energy intake and encourage them to be more physically active in order to reduce the risk of the main diseases associated with obesity. In compiling the guidelines, the Guidelines Development Group drew on research from **Professor Susan Jebb** who, in 2011, showed that participating in commercial weight management programmes, such as WeightWatchers and Slimming World, can lead to a greater weight loss over a 12-18 month period than from following the advice of a doctor[84].

NICE National Institute for Health and Care Excellence

Logo reproduced with the permission of NICE

Project reference number: MC_U105960387

Engagement activities: Association between consumption of sugar-sweetened beverages and cardiometabolic risk factors in adolescents[85]

This paper, published in 2013 by the **MRC HNR**, demonstrated a link between the high consumption of sugary drinks by teenagers and the risk factors, namely lower levels of 'good' cholesterol and higher levels of the 'bad' triglyceride form of fat in their blood, for heart disease in later life. This paper received considerable media interest, including from the BBC, *The Guardian* and *The Telegraph*.

Project reference number: MC_U105960389

Unexpected impacts of MRC research

Engagement activities: Science Museum Painless exhibition

As part of the Science Museum's Painless exhibition in 2013[86], **Professor Geoff Woods** at the **University of Cambridge** sequenced the genome of a man with congenital analgesia, a rare genetic disorder characterised by a total inability to sense pain. Worldwide, the prevalence of congenital analgesia is estimated to be around one in a million. At the exhibition, Professor Woods identified the patient's gene mutations, confirmed his diagnosis and was able to offer him genetic counselling. In 2006 Professor Woods discovered different mutations in the gene *SCN9A* responsible for this condition[87]. *SCN9A* encodes a subunit of a sodium channel expressed in neurons involved in the amplification of the pain signal; the gene mutations cause the protein to lose its function.

Project reference number: MR/J012742/1

Infectious diseases

Infectious diseases — those caused by pathogenic microorganisms, such as bacteria, viruses, parasites or fungi — were the cause of approximately 12.5 per cent of all deaths worldwide in 2011[88]. In the UK, infectious diseases have declined because of improved hygiene, vaccination and antimicrobial drugs, however, costs to the health service, labour market and the individual are still estimated to be around £30 billion per year.

Influence on policy: Addition of rotavirus vaccine into The Gambia's Expanded Programme of Immunization (EPI)

In August 2013 the Ministry of Health and Social Welfare of The Gambian government formerly introduced the rotavirus vaccine into its Expanded Programme of Immunization (EPI), the eleventh vaccine the country has introduced since it joined the global programme in 1979. The EPI was set up by the World Health Organization in 1974 to ensure that children in all countries receive life-saving immunisations.

Research conducted by the **MRC Unit, The Gambia** played a valuable role in ensuring the rotavirus vaccine was added to the programme. **Dr. Jahangir Hossain** at the **MRC Unit, The Gambia** was part of an international study that confirmed that rotavirus was the leading cause of diarrhoeal disease among infants in developing countries[89]. The Global Enteric Multicenter Study (GEMS), the largest study ever conducted on diarrhoeal diseases in developing countries, found that approximately one in five children under the age of two suffer from moderate-to-severe

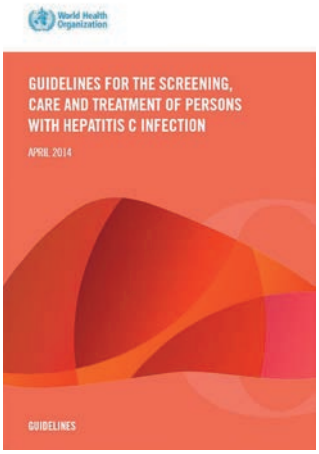
diarrhoea each year, increasing children's risk of death 8.5-fold and leading to stunted growth over a two-month follow-up period.

Rotavirus is responsible for the death of nearly 300 Gambian children under five each year, accounting for approximately one third of all under-five diarrhoeal deaths and diarrhoeal disease hospitalisations in The Gambia. If used in all GAVI-eligible countries[90] rotavirus vaccines could prevent an estimated 180,000 deaths and avert six million clinic and hospital visits each year[91].

Project reference number: MC_UP_A900_1115

Influence on policy: WHO guidelines for the screening, care and treatment of persons with hepatitis C infection

The hepatitis C virus (HCV) infects 170 million people around the world and is a major cause of liver disease, including liver cancer. Unlike Hepatitis A and B, there is currently no vaccine for HCV. Treatment can often have severe side effects such as anaemia, reduced immune system functioning, depression and flu-like symptoms; it is also expensive and only partially effective. Between 15 and 50 per cent of people clear the infection spontaneously and are free of the virus; however, the majority become chronically infected with the virus remaining in the body for many years. It is estimated that around 215,000 people in the UK have chronic HCV. Between 10 and 40 per cent of people with untreated chronic HCV will go on to develop cirrhosis of the liver. Around one in five people with cirrhosis will then develop liver failure, and one in 20 will develop liver cancer.



WHO guidelines for the screening, care and treatment of persons with hepatitis C infection. Image reproduced with the permission of WHO.

Professor Emma Thomson at the **MRC-University of Glasgow Centre for Virus Research** is a leading scientist in HCV research and specialises in the mechanisms behind spontaneous viral clearance and progression to chronicity. She is currently studying HCV diversity during transmission and early viral evolution using next-generation and full-length sequencing of the viral genome. She was the technical writer of the WHO guidelines for the screening, care and treatment of persons with hepatitis C infection[92] published in April 2014 and also provided advice on the use of new direct-acting antiviral drugs for HCV and on the monitoring of patients undergoing therapy.

Project reference number: G0801822

Engagement activities: Science Inspired Tales

In 2012 **Professor Peter Openshaw** at **Imperial College London** gave a Science Inspired Tales public stage performance at the Albert Hall Theatre in Brussels. During the lecture entitled "Our germs, our guns: an uneasy peace", he discussed infection and the immune system, recounting anecdotes and stories of his scientific inspiration[93].

Project reference number: MC_G1001212

Influence on policy: Chief Medical Officer seminar on future public health policy for HIV research

Professor Sheena McCormack at the **MRC Clinical Trials Unit** is a clinical epidemiologist who specialises in the development and implementation of biomedical interventions to prevent, or reduce, the risk of acquiring HIV. In 2013 she took part in a Chief Medical Officer (CMO) seminar on future public health policy for HIV research. As a result of the seminar, the CMO outlined plans to update the UK's HIV policies in order to help people get diagnosed earlier. Following the seminar, Professor Dame Sally Davies wrote to all GPs advising them to test patients presenting with glandular fever symptoms for HIV. The ban on the sale of HIV self-testing kits was also lifted in April 2014 to encourage individuals to get tested as soon as possible.

Project reference numbers: G0100137, MC_U122861322, MC_U122861400

Unexpected impacts of MRC research

Engagement activities: Threat of helium depletion to medical research

Image credit: Flickr/lantzilla

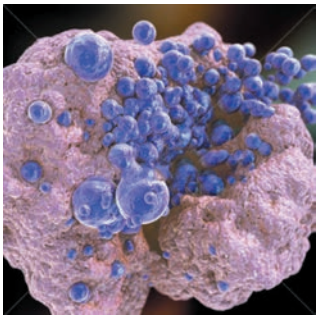
The Federal Helium Reserve in Texas is the world's only strategic helium reserve and provides approximately 35 per cent of the world's helium[94]. As the US had accrued a US$1.3 billion debt after a large buy-up of helium in the 1960s, the government passed the Helium Privatization Act in 1996, its goal being to sell off the reserve, with a scheduled closure date of October 2013. This triggered a supply problem, affecting many users, including **Professor Mark Stokes** at **Oxford University's** Centre for Human Brain Activity. Professor Stokes spoke to The Independent in 2013 about how his department's magnetoencephalography (MEG) scanners — used to study the brain — have regularly been forced to shut down due to the helium shortage. Helium is used to cool the scanners to the near-absolute-zero degrees Kelvin temperature they must operate at[95]. Helium is currently the only element on earth that can effectively keep the equipment that cold. Highlighting the importance of helium to several industries, including medical research, persuaded the US government to extend the life of the reserve, which will now auction off more and more of its store each year.

Project reference number: MR/J009024/1

Influence on policy: Contribution to Chief Medical Officer Annual Report Volume II

The CMO published the second volume of her annual report in 2013, focusing on infection and antimicrobial resistance. The discovery of antibiotics is seen as one of the most important medical achievements of the 20th century; the use of antimicrobials benefits both the individual and society as a whole. However, antimicrobial resistance is increasing and is recognised as a significant public health issue, compounded by the fact that there are currently few new antimicrobials

in development. The MRC has developed a strategy for antimicrobial resistance research that aims to tackle the mechanisms of bacterial resistance and strengthen innovation in antimicrobial development through academic-industry partnerships.



Professor Sharon Peacock at the **University of Cambridge** specialises in the role of sequencing technologies in diagnostic microbiology and public health. In 2013 she demonstrated for the first time that whole genome sequencing of methicillin-resistant *Staphylococcus aureus* (MRSA) could help to track the spread of infection on both a local and global scale[96]. In the future challenges chapter of the CMO's report, Professor Peacock wrote a section on the use of whole genome sequencing to track the transmission of infections to improve surveillance and control[97].

Project reference number: G1000803

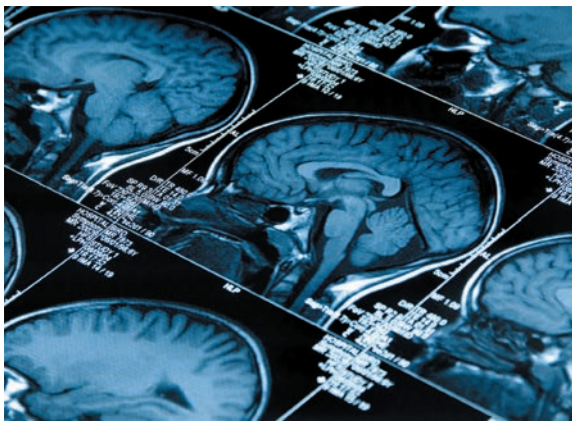
Influence on policy: POSTnote on the surveillance of infectious disease

POST is the Parliamentary Office of Science and Technology, an in-house source of independent, balanced and accessible analysis of public policy issues related to science and technology. Its aim is to help parliamentarians examine science and technology issues effectively in order to support their decision-making.

Dr Nick Loman at the **University of Birmingham** contributed in 2013 to a POSTnote that examined new technologies used in the surveillance of infectious diseases[98].

Project reference number: MR/J014370/1

Neurodegeneration and neurology



A brain scan. Image credit: iStock

The proportion of people in the UK aged over 65 is 17.2 per cent, a figure that is projected to rise to 22.4 per cent in 2032[99]. There is a strong link between age and neurodegenerative diseases, including dementia, Parkinson's disease and multiple sclerosis, and so the number of people with these conditions is constantly increasing. Existing treatments for neurodegenerative diseases are limited and they mostly treat the symptoms, rather than the cause. Therefore, research in this area — particularly to develop our understanding of the biological processes underpinning these diseases — has never been more important.

Influence on policy: Update to National Institute on Ageing-Alzheimer's Association diagnostic guidelines

In 2011 MRC-supported researcher **Professor Nick Fox** at **University College London** was part of a small guidelines committee that updated the US National Institute on Ageing-Alzheimer's Association's clinical diagnostic criteria for Alzheimer's disease for the first time in 27 years[100]. The previous guidelines describe only the latter stages

of the disease, whereas the updated version now covers the full spectrum of the disease as it gradually changes over many years. They describe the earliest preclinical stages of the disease, mild cognitive impairment, and dementia due to Alzheimer's pathology. The guidelines also now address the use of imaging and biomarkers in blood and spinal fluid that may help determine whether changes in the brain and those in body fluids are due to Alzheimer's, a major change in the way the disease will be diagnosed. Professor Fox led on the section covering biomarkers.

Project reference number: G0801306

Engagement activities: Brain implant for Parkinson's disease

Researchers at the **University of Bristol** have developed a brain implant consisting of a system of tubes and catheters that allows them to pump protein therapy deep into the brains of patients with Parkinson's disease, potentially stopping the disease from progressing. Parkinson's, affecting around 127,000 people in the UK, occurs when a lack of a chemical called dopamine causes nerve cells within the brain to die. It is hoped that delivery of the protein — a growth factor called glial cell-derived neurotrophic factor (GDNF) — will encourage these cells to grow again. This new method of delivery will allow the protein to bypass the blood/brain barrier. A clinical trial[101], led by **Professor Steven Gill**, is on-going and has received publicity from Sky News, the BBC and *Daily Mail*.

Project reference number: MR/J005134/1

Influence on policy: Advice to House of Commons Science and Technology Select Committee inquiry on variant Creutzfeldt-Jakob Disease (vCJD)

The House of Commons Science and Technology Select Committee held an evidence session in 2013 on variant Creutzfeldt-Jakob Disease (vCJD) and the on-going risk it poses to the UK. **Professor John Collinge**, director of the **MRC Prion Unit**, was one expert invited to give evidence, along with **Professor Sheila Bird** of the **MRC Biostatistics Unit**.

Professor John Collinge spoke about the potential prevalence of vCJD in the population, the potentially long incubation period of the disease, modes of on-going transmission, and the current UK surveillance, control and prevention strategies[102].

Project reference numbers: MC_U123160657, MC_U123192748

Influence on policy: Citation in US Federal Drug Administration taskforce advice on designing clinical trials in early Alzheimer's disease

In 2011 an international taskforce of individuals from academia, industry, non-profit foundations, and regulatory agencies was convened to discuss optimal trial design in early (pre-dementia) Alzheimer's disease. The report[103], advising the US Federal Drug Administration, cites research conducted by **Dr Delphine Boche** at the **University of Southampton**, which provided evidence that even successful treatment to eliminate amyloid plaques may not be sufficient to halt fatal progression in individuals already showing clinical signs of dementia[104]. This helped the taskforce

reach the conclusion that it is necessary to start therapies before the onset of clinical dementia in order for it to have any positive effect.

Project reference number: G0501033

Engagement activities: Falling dementia rates

Researchers at the **Cambridge Institute of Public Health** at **Cambridge University** reported in 2013 on results from the MRC Cognition Function and Ageing Study (CFAS) showing that the number of people with dementia in the UK in 2011 was much lower than had been predicted based on trends two decades earlier[105]. Using age- and gender-specific dementia rates collected from interviews in 1991, researchers estimated that around 884,000 people over 65 (8.3 per cent) would have dementia in 2011. However, fresh interviews in 2011 indicated around 670,000 (6.5 per cent) had dementia. The story was widely reported in the UK media, including in *The Telegraph*, BBC news, *The Independent* and the *Daily Express*. Much of the discussion focused on whether rates of dementia would continue to decrease in the future, considering the rising levels of obesity — shown to be a significant risk factor for dementia[106, 107].

Project reference number: G0601022

Engagement activities: Alzheimer's disease open day

Since 2006, **King's College London's Institute of Psychiatry** has held an annual open day hosted by Alzheimer's Research UK and the **MRC Centre for Neurodegeneration Research** to showcase its cutting edge research into Alzheimer's disease. In 2011 the event welcomed 150 members of the public, including carers and families of people with dementia, who engaged in workshops, talks and question and answer sessions.

Project reference number: G0700355

Unexpected impacts of MRC research

Engagement activities: Lecture on badger culling

Professor Christl Donnelly at the **MRC Centre for Outbreak Analysis and Modelling** gave a special lecture at the Isaac Newton Institute for Mathematical Sciences in 2013 reviewing the science and current UK policies on badger culling in relationship to bovine tuberculosis. The lecture was attended by around 50 researchers and afterwards made available online to a wider audience. An article about the lecture was also published in *The Sunday Times*[108].

Image credit: Flickr/hehaden

Project reference number: G0600719B

Cancer

More than one in three people will develop cancer at some point during their lifetime, including more than 331,000 diagnosed with cancer in the UK in 2011 alone[109]. Although half of people diagnosed with cancer survive their disease for at least 10 years, cancer still causes more than one in four of all deaths in the UK. The annual cost to the NHS for cancer services, including diagnostics and treatment, is around £5 billion, however, the cost to society as a whole, including for loss of productivity, is £18.3 billion[110].

Influence on policy: The National Comprehensive Cancer Network's guidelines in Oncology

The National Comprehensive Cancer Network® (NCCN®) is a not-for-profit alliance of 23 cancer centres in the US devoted to patient care, research, and education. The NCCN Guidelines® are a comprehensive set of guidelines detailing the sequential management decisions and interventions that currently apply to 97 per cent of cancers affecting patients in the United States. The network updated its guidance on Central Nervous System Cancers in 2013[111] and cites a study undertaken by the **MRC Clinical Trials Unit** showing that patients with high-grade gliomas — fast-growing tumours that arise from glial cells and occur in the spinal cord or the brain — experienced a modest survival benefit when chemotherapy was given in addition to postoperative radiotherapy[112]. The guidelines recommend the use of combined chemotherapy and radiotherapy for a subset of patients with high-grade gliomas. The NCCN also updated its guidance on bladder cancer in 2014[113] and as a result of research undertaken at the **MRC Clinical Trials Unit**[114], recommended neoadjuvant chemotherapy (chemotherapy given in advance of the primary treatment) over adjuvant-based chemotherapy (chemotherapy given after the primary treatment) for muscle invasive cancer.

Project reference number: MC_U122861323

Engagement activities: Gene therapy to treat prostate cancer

In a Phase I clinical trial, researchers at the **University of Birmingham** are using gene therapy to treat prostate cancer that has relapsed after radiotherapy and hormone therapy[115]. The AdUP trial uses a vector made from an adenovirus that has been modified to produce an enzyme called nitroreductase and GM-CSF — a growth factor that enhances the immune system by stimulating the number and function of white blood cells produced by the body. The vector is administered by way of an injection, which is then followed by treatment with CB1954 — a cytotoxic drug made active by the nitroreductase enzyme which kills cancer cells.

The BBC interviewed Bernard Ward, one of the first 20 patients undergoing this therapy, and the surgeons conducting the treatment[116]. Mr Ward has suffered from prostate cancer for six years and standard treatments are no longer working. The clinical trial is designed to establish whether the treatment is safe for clinical use.

Project reference number: G0502050

researchfish

MRC Medical Research Council

Outputs, outcomes and impact of MRC research: 2013/14 report

SECTION 2.3: Development of products, research materials and intellectual property

Development of products, research materials and intellectual property

Clear impacts of the MRC's work include the development of products and interventions, ranging from drugs, diagnostic tests, biomarkers and diagnostic imaging techniques to medical devices, surgical interventions and public health interventions; research materials for other scientists to use and the generation of intellectual property.

There is a long history of MRC-funded research leading to the development of new products and interventions with widespread impact, from the early development of penicillin through to MRI technology and monoclonal antibodies. MRC-funded researchers have remained at the forefront of healthcare intervention with the development of many diagnostics tests. Recent examples include a blood test for Prion disease, an imaging test for dementia and genetic tests for Warburg Micro Syndrome, CFHR5 nephropath, and disorders in DNA repair.

A new example of an intervention that is nearing more wide-scale application is immunotherapy for peanut allergy. A recent clinical trial — the largest single trial of its kind worldwide — successfully treated the majority of the children taking part[117]. This was the result of five years' work in the field. Other successful interventions include the MEND (Mind, Exercise, Nutrition, Do it!) programme for childhood obesity[118] and the Football Fans in Training programme[119].

MRC research groups are involved in the development of many other new treatments and medical interventions, including a respiratory pacemaker, Mirococept proteins for kidney transplants, stem cells for age-related macular degeneration, and gene therapy for diseases such as cystic fibrosis, haemophilia, Duchenne muscular dystrophy and genetic eye disorders.

In addition to the development of products and interventions aimed at directly improving human health, MRC researchers also produce an abundance of research materials, such as new in vivo and in vitro models, databases, techniques and technologies, for other scientists to use to help further their research aims.

Where either these products or research materials cover 'new' functional or technical aspects, researchers take steps to ensure their discoveries are recognised as intellectual property.

This chapter includes case studies on all three types of impact, which are categorised by the following research areas:

- Regenerative medicine
- Neurodegeneration and neurology
- Natural protection
- Cancer
- Liver disease
- Heart disease
- Musculoskeletal
- Public health
- Obesity and nutrition
- Hearing
- The 3Rs
- Drug development
- Text mining

Further information on each piece of research can be found on the Research Councils UK (RCUK)'s information portal — the *Gateway to Research*[120] — by entering the project reference number listed under each case study in the search field.

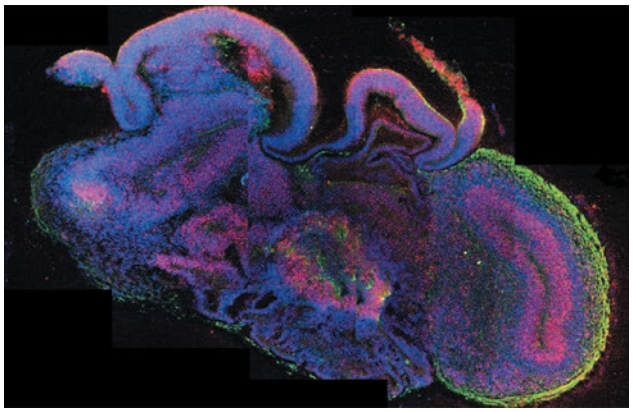
Research materials: Growth of 3D structure resembling human brain tissue

An international team of researchers, led by the Institute of Molecular Biotechnology in Austria, in collaboration with the **MRC Human Genetics Unit**[121] at the **University of Edinburgh** have for the first time used stem cells to grow a three-dimensional structure in the lab that resembles primitive human brain tissue[122].

This provides a unique new laboratory tool for studying human-specific features of brain development and neurological disorders in a way that has not been possible using animal models.

Most of our knowledge of human brain development originates from studies using animals, usually mice. Scientists can also use mice to study a range of human diseases affecting the brain. However, due to the complexity of the human brain, it has been difficult to study some diseases in model organisms, which lack this complexity. Such diseases include microcephaly, in which brain size is significantly reduced.

To create the brain tissue, the researchers developed a finely-tuned culture system that capitalises on stem cells' innate ability to organise themselves into complex organ structures. They began with human embryonic and induced pluripotent stem cells (IPSCs), which they used to produce neuroectoderm – the layer of cells in the embryo from which all components of the brain and nervous system develop. Fragments of this tissue were then embedded in gel droplets that provided a scaffold for complex tissue growth and placed into a spinning bioreactor. The circulation of culture media in the bioreactor improves oxygen and nutrient supply allowing the organoids to grow to a larger size.



A cross-section of a cerebral organoid.
Image credit: IMBA/Madeline A. Lancaster

After a month, the tissue fragments had organised themselves into primitive structures that could be recognised as developing brain regions such as retina, choroid plexus and cerebral cortex. At the microscopic level in the cortex, radial glial stem cells, pivotal in developing the central nervous system, were seen to generate neurons in an identical manner to that known to occur in normal development. At two months, the organoids had reached their maximum size of 4mm.

Using IPSCs from a patient, the researchers were able to model the development of microcephaly. As expected, the organoids created using these cells grew to a smaller size. On further investigation, they found that genetic mutations in the patient cells cause neural stem cells to shift from self-renewal to differentiation into nerve cells at an earlier stage, leading to an overall reduction in cell number and size of the organoid.

Model systems like these are likely to become increasingly important for early testing of new therapies before they progress to human trials.

Project reference number: MC_PC_U127580972

Research materials: 3D in-vitro culture of intestinal organoids

Professor Vivian Li at the **MRC National Institute for Medical Research** has grown "mini-guts" — three-dimensional structures — in Matrigel, a gelatinous protein mixture that resembles the complex extracellular environment found in many tissues. These form intestinal structures encompassing all cell lineages. This system is being used to study the functional role of candidate genes and pathways in the intestine in vitro and may be used for genetic modification, drug screening and tissue engineering.

Project reference number: MC_UP_1202/7

Research materials: Müller glial stem cells

Researchers at **University College London** have produced a line of Müller glial cells derived from the donated eyes of dead people. Müller glia possess stem cell characteristics that can regenerate the injured retina in fish and amphibians. These cells have the ability to transform into the specialised cells at the back of the eye, so may be able to treat a wide range of sight disorders.

In 2014 the team, led by **Professor Astrid Limb**, stimulated these cells to differentiate into rod photoreceptor cells, which detect light in the retina[123]. Injecting these cells into the eyes of blind rats partially restored their sight and brain scans showed that half of the electrical signals between the eye and the brain were recovered following the treatment. It is hoped that the cells might be able to help patients with disorders such as macular degeneration or retinitis pigmentosa. There are currently clinical trials taking place using stem cells from embryos, however, there remains ethical debate around this process. In addition, it takes several months to prepare these cells whereas the Müller glial cells can be prepared within a week.

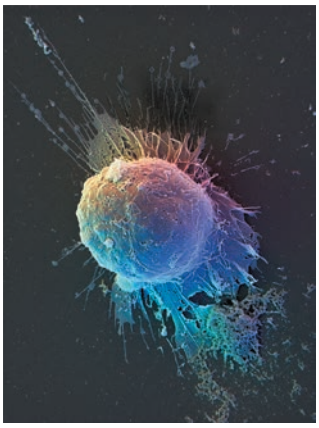
These cells are the only Müller cell lines available for retina research in this field and the group has transferred them to approximately 100 research groups to investigate the role of Müller glia in the mechanism of retinal diseases.

Project reference number: MR/K008722/1

Research materials: Stem cell lines with clinically relevant mutations

Dr Dusko Ilic at **King's College London** has derived 16 stem cell lines that have been approved by the US National Institutes of Health (NIH) and placed on their Stem Cell Registry[124], making them freely available for federally-funded research in the USA. The cell lines carry genes for various hereditary disorders including Duchenne muscular dystrophy, Huntington's disease, cystic fibrosis, and rarer conditions such as Von Hippel-Lindau Syndrome, Wiskott-Aldrich syndrome and spinal muscular atrophy. King's College is now one of the five biggest providers of disease-specific human embryonic stem cells lines on the NIH Registry, and the largest from the UK.

Project reference numbers: G0701172, G0801061



Stem cell. Image credit: iStock

Research materials: Edinburgh Adipose Tissue Bank

Mesenchymal stem cells are adult stem cells that can differentiate into a variety of cells. They were originally identified in bone marrow, but have since been isolated from all adult tissues, including fat – adipose tissue. Adipose tissue is easily accessible and readily abundant, even in individuals of healthy weight. It therefore offers an excellent source of stem cells. Plastic surgeons routinely remove large volumes of adipose tissue through reconstructive and cosmetic procedures; as a result, many surgeons are either directly or indirectly involved in research using adipose-derived stem cells. Adipose tissue is also a good source of fat cells, endothelial cells and vascular smooth muscle cells.

Researchers at the **MRC Centre for Regenerative Medicine** have set up an adipose tissue bank, comprising adipose tissue from different stores — depots — in the body, including subcutaneous, visceral and brown adipose tissue. Since receiving ethical approval in 2010, the bank has collected samples from 58 patients[125]. It also stores genetic information and plasma samples from the subjects. The bank has recently been used to help determine the lineage of different adipose tissue depots and to determine the presence of depot-specific transporters, which may prove important for tissue-specific drug delivery.

Project reference number: MR/K010271/1

Products and interventions: Immunotherapy for Addison's disease

Addison's disease is a rare autoimmune disorder that affects the production of steroid hormones cortisol and aldosterone by the adrenal gland. There are approximately 8,400 people in the UK with the condition[126], which is treated with lifelong steroid hormone replacement. However, despite this treatment, there is still an increased risk of early death. In healthy people, cells in the adrenal gland undergo continuous self-renewal from a population of progenitor cells, under the influence of the adrenocorticotropic (ACTH) hormone.

In 2012 **Professor Simon Pearce** at **Newcastle University** demonstrated in a small clinical trial that synthetic ACTH could revive adrenal steroidogenic function in one patient[127]. This patient has had a sustained remission and is no longer on any form of treatment. Although success was limited to the one patient, this is the first study to demonstrate that established autoimmune Addison's disease is amenable to a regenerative medicine therapy approach.

Project reference number: G0701632

Neurodegeneration and neurology

Products and interventions: Diagnostic tool for inherited dementias

Dr Simon Mead at the **MRC Prion Unit**, in conjunction with researchers at the National Institute of Health Research (NIHR) Queen Square Dementia Biomedical Research Unit (BRU), has developed a new, more efficient and cost-effective way to diagnose early-onset, genetic forms of dementia. There are currently some tests for dementia genes available, however they are expensive and not widely used. The MRC Dementia Gene Panel uses next-generation DNA sequencing to look for abnormalities in all 17 genes known to play a substantial role in causing inherited forms of dementia simultaneously, easily and cheaply.

Using Life Technology's Ion Torrent PGM sequencer, the researchers showed that the technology was highly accurate and comprehensively identified the genetic abnormalities[128].

Dementia is one of the most important healthcare challenges worldwide. In recent years there has been significant progress in understanding the genetic causes of the disease. Genetic mutations in more than 17 genes have been found to cause specific types of dementias, and mutations in several others have been shown to increase a person's risk of developing dementia. Although genetic causes are thought to account for only around two per cent of all dementias, a simple blood test could provide a definitive diagnosis and may also lead to the opportunity for blood relatives to find out if they share an increased risk of developing the disease.

The technique will be used at University College London Hospitals NHS Foundation Trust to offer improved diagnosis to patients in their neurogenetics clinics. The researchers will also use this technology to study further the relevance of these genes as a tool in the diagnosis of patients with dementia, particularly for those developing the condition before the age of 65 where a genetic cause of their illness is more likely.

Project reference number: MC_U123160651

Research materials: *C9orf72* blotting technology

Dr Mead has also developed a new method to enable the study of a specific mutation implicated in early-onset dementia and a motor neuron condition called amyotrophic lateral sclerosis (ALS).

The *C9orf72* gene encodes C9ORF72, a protein that was recently found to regulate essential processes involved in the transport and breakdown of cellular components in nerve cells[129].

In 2011, a mutation in the *C9orf72* gene was found to be the major cause of frontotemporal dementia (FTD) — the second most common form of early-onset dementia after Alzheimer's disease — and ALS, a degradation of motor nerves that eventually causes respiratory failure and death on average three years after onset[130,131]. The mutation of this gene inserts a repeating six letter string of nucelotides GGGGCC into the DNA sequence. In the majority of people without this mutation, there are up to 30 repeats of this hexanucleotide[132], but in people with the mutation, this sequence is repeated many more times. However, further investigation into this mutation has been hampered by the large size of the expansion, which makes it impossible to make the thousands of DNA copies needed to study the gene by conventional PCR-based methods.

Dr Mead has developed a reliable Southern blot method of approximating the *C9orf72* expansion size to resolve some of the outstanding genetic issues, including the numbers of repeats necessary to cause disease, mutation mechanisms, and the feasibility and accuracy of diagnostic testing[133].

Project reference number: MC_U123160651

Research materials: Mouse model for dementia gene

Dr Adrian Isaacs at the **MRC Prion Unit** discovered in 2012 that a mutation in the CHMP2B gene causes frontotemporal dementia. The team has demonstrated that the CHMP2B protein is required for a process of cell degradation called autophagy. They have generated *CHMP2B* knockout mice and transgenic mice expressing mutant and normal forms of human CHMP2B for further study.

Project reference number: MC_U123182015

Products and interventions: Treatments for Duchenne muscular dystrophy

The muscular dystrophies (MD) are a group of inherited genetic conditions that gradually cause the muscles to weaken, leading to an increasing level of disability. Duchenne muscular dystrophy (DMD) is one of the most common and severe forms, affecting around one in 3,500 boys in the UK. It usually affects boys in early childhood and individuals with the condition will usually only live into their 20s or 30s.

DMD is caused by a mutation in the reading frame — the way of dividing the nucleotides in a DNA or RNA molecule into triplets — of the *dystrophin* gene, the largest gene on the X chromosome. The *dystrophin* gene encodes the protein dystrophin, an important part of muscle tissue that provides structural stability.

Genes are composed of both exons, the instruction set for generating a protein, and introns, which are the non-coding portions. When a gene is translated into a protein, the introns are removed (splicing), leaving only the coding exon regions. The DMD mutation means the cell is unable to "read" the genetic code beyond the point where the first error occurs. The result is a severely shortened form of the protein, rendering it non-functional. The loss of the dystrophin protein ultimately leads to the degeneration of muscle fibres, progressive weakness and premature death.

Gene therapy for DMD has proven to be challenging due to the size of the dystrophin protein and the fact that it needs to be delivered to many muscle cells in the body for it to have a therapeutic effect. However, MRC scientists have conducted much research in this area to great success.

One route currently being explored is exon skipping. This takes advantage of the splicing mechanism used by cells to remove the non-coding regions of the gene. A short single strand of RNA binds to the mutation site on the exon, so that when the gene is translated, the mutation is 'skipped' over, restoring the disrupted reading frame. This results in a shorter than normal, but largely functional protein which produces milder symptoms, similar to the much less severe Becker muscular dystropy (BMD).

MRC scientist **Professor Francesco Muntoni** at **University College London** is head of the MDEX consortium, a multidisciplinary enterprise to promote translational research into muscular dystrophies and has led much of the research into exon skipping for DMD. In conjunction with AVI BioPharma, the MRC funded a Phase II clinical trial into the exon skipping drug AVI-4658 (Eteplirsen) in 2011, which induced exon skipping and new dystrophin protein expression in all patients[134]. A Phase IIb trial was taken forward by Serepta Therapeutics, which in January 2014 announced encouraging results[135].

Professor Dame Kay Davies, director of the **MRC Functional Genomics Unit**, is internationally renowned for her research into DMD. In the 1980s, Professor Davies developed the first test for screening pregnant women for DMD. In 1989, Davies discovered the *utrophin* gene, encoding the utrophin protein present in many body tissues, and found that it had similar properties to dystrophin[136]. At 12 weeks during the fetal development of a child, the muscle membranes contain both utrophin and dystrophin. However, utrophin then disappears until, at birth, only dystrophin remains. She has since shown in mouse models that up regulation of the *utrophin* gene in muscle cells can compensate for the absence of dystrophin[137]. At the end of 2007, over 30,000 chemical compounds had been screened for their ability to upregulate the activity of the *utrophin* gene in tissue cultures from dystrophin-deficient mice. Professor Davies has developed one of the lead compounds with University of Oxford spinout Summit plc – SMT C1100. Summit plc has successfully completed a Phase I trial[138] and a Phase Ib trial has started[139].

Project reference numbers: G0502130, MC_U137761449

Products and interventions: Campath as a treatment for multiple sclerosis

Alemtuzumab (Campath or Lemtrada) is a humanised rat monoclonal antibody used for the treatment of patients with resistant chronic lymphocytic leukaemia. MRC researchers **Professor Alastair Compston** and **Professor Alasdair Coles** at the **University of Cambridge** have conducted clinical trials demonstrating its effectiveness in the treatment of multiple sclerosis[140,141], an autoimmune condition in which the immune system mistakes myelin — the layer of protein surrounding nerve fibres in the brain and spinal cord — for a foreign substance and attacks it. The myelin becomes inflamed, disrupting the messages travelling along nerve fibres. Alemtuzumab works by binding to and killing the lymphocytes (immune cells) that attack the myelin. It is believed that the lymphocytes regenerated by the immune system following treatment with alemtuzumab do not include the subset that destroys myelin.

The origins of alemtuzumab date back to MRC-funded experiments on human lymphocyte proteins by Professor Herman Waldmann and colleagues in 1983. It was named 'Campath' after the pathology department of Cambridge University. In September 2013, alemtuzumab was licensed as a treatment of "adult patients with relapsing remitting multiple sclerosis with active disease defined by clinical or imaging feature" in Europe, including the UK. It is now also licensed in Canada, Australia and Mexico. NICE guidance recommending the use of alemtuzumab for the treatment of relapsing–remitting multiple sclerosis was published in May 2014[142].

Project reference number: G1100114

Products and interventions: Clinical trial of drug to reduce autoimmunity after treatment of multiple sclerosis with Campath

Although Campath has proven to be a successful treatment of multiple sclerosis, one in three patients develop a new autoimmune condition after treatment. After the immune system regenerates, it can begin to attack other parts of the body, most commonly, the thyroid gland. Kepivance (Palifermin) has been shown to alter the way in which the immune system grows back in animals by promoting thymic lymphocyte regeneration. **Professor Alasdair Coles** at the **University of Cambridge** is currently conducting a clinical trial[143] to assess the effectiveness of Palifermin. The initial phase of the trial has appeared to be successful; however, the final results are awaited.

Project reference number: G1100114

Products and interventions: Non-invasive neuromodulation device for treatment of migraines

Dr David Wilkinson at the **University of Kent**, in conjunction with Scion NeuroStim, a US-based biotechnology company, has developed a portable, non-invasive neuromodulation system for the treatment of episodic migraine headaches. Although the effectiveness of neuromodulation therapy for migraines is reasonably well-established, conventional methods involve surgical implantation and are typically used as a last resort. It is believed that electrical stimulation to the occipital nerves — that travel from the spine to the back of the head and scalp — stimulates the release of natural pain-relief chemicals, quiets over-excitable nerves, limits pain messages sent to the brain, and may also enhance local blood circulation. The device is currently undergoing clinical trials[144] and approval by the US Food and Drug Administration and Medicines and Healthcare products Regulatory Agency CE.

Project reference number: G1001222

Research materials: Method for tracing the habenula

The habenula are a pair of nuclei — compact clusters of nerve cells — located in the thalamus, the part of the brain that is responsible for transmitting motor and sensory signals. The habenula is thought to be one of the oldest parts of the brain from an evolutionary perspective and is implicated in a range of behaviours including sleep, stress and pain. There has been renewed focus in this area of the brain after research found it to play a crucial role in decision-making.

Standard functional magnetic resonance imaging (fMRI) of the habenula can be challenging; due to its small size, isolating a signal can be difficult. **Dr Jonathan Roiser** at **University College London** has produced a set of guidelines for locating and manually tracing the habenula in humans using high-resolution T1-weighted structural images[145]. They have also made recommendations for appropriate pre-processing and analysis of high-resolution fMRI data so that the signal from the habenula can be accurately differentiated from that in surrounding structures.

Project reference number: G0901275

Products and interventions: Biomarkers for deep brain stimulation in Parkinson's

Electrical deep brain stimulation is increasingly being used in the treatment of neurological disorders such as Parkinson's disease and dystonia. The technique involves inserting a wire into a particular part of the brain. It is then run under the patient's skin to a small machine called an implantable pulse generator, which is placed under the skin on the chest. The generator sends small electrical currents through the wire to the brain, which are thought to block abnormal signals that cause many of the debilitating symptoms of Parkinson's like tremors, slowness, stiffness, and difficulty with speech.

The MRC has played a significant role in the development of deep brain stimulation. It was researchers at the **MRC Cambridge Centre for Brain Repair** who investigated the part of the brain that causes Parkinson's – the subthalamic nucleus – which is stimulated by deep brain stimulation[146]. Although this therapy worked for some patients, it was ineffective for the 40 per cent of patients who don't respond to drugs. The breakthrough came through work by MRC-funded **Professor Tipu Aziz**, a neurosurgeon at **Oxford University's John Radcliffe Hospital**, who identified another target in primate brains, the pedunculopontine nucleus[147]. When this target was stimulated, Parkinson's symptoms were alleviated, even in patients who were not responsive to drugs.

However, due to the cost and side effects of deep brain stimulation, there is still a need to improve the current methods. One main disadvantage is that existing brain stimulators only provide continuous and fixed stimulation, which increases side effects such as other sensory and motor control problems for the patient, and also reduces the battery life, meaning that batteries have to be surgically replaced at periodic intervals.

Professor Peter Brown at the **University of Oxford** has conducted research into the brain signals that can be recorded by electrodes to identify biomarkers – signals that can be used as a way of determining when and how much stimulation is necessary, improving the clinical result and extending battery life. Professor Brown will further determine which biomarkers are linked to symptoms and how deep brain stimulation interacts with each patient's own brain signals to identify the most effective stimulation pattern in individual patients.

Project reference number: G0901503

Research materials: Animal model for early-onset Parkinson's disease

Professor Marysia Placzek at the **University of Sheffield** has developed a zebrafish model — the first vertebrate animal model — of PINK1-related Parkinson's disease, an early onset form of the disease. PINK1 is a protein thought to protect cells from stress-induced mitochondrial dysfunction. PINK1 activity causes the protein parkin — an enzyme that is part of the ubiquitin system that degrades unnecessary or damaged proteins — to bind to depolarized mitochondria to induce degradation of those mitochondria. Mutations in this gene cause one form of early-onset Parkinson's disease and so the development of this model will enable the genetic causes to be studied in greater detail.

Project reference number: G0700091B

Intellectual property: Treatment of disabilities following stroke

Acute stroke is the third largest cause of death in the UK and the leading single cause of severe disability. More than 110,000 people in England will have a stroke each year, costing the NHS £2.8 billion[148]. The number of years with a reduced quality of life due to the disabilities caused by stroke is larger than of any other disease in the elderly population except for dementia. Cognitive impairment is present in more than 30 per cent of long-term survivors of stroke.

Hemispatial neglect is one of the major cognitive disorders following stroke. This is caused by brain injury to the right cerebral hemisphere, resulting in visual neglect of the left-hand side of space. This causes a patient to behave as if the left side of the sensory space is non-existent. When asked to draw a clock, a patient might draw only numbers 12 to six or all 12 numbers on one half of the clock face.

There are currently no reliable drug treatments for neglect, other cognitive impairments or motor deficits following stroke.

Professor Masud Husain at **University College London**, in conjunction with UCB Pharma, has applied for a patent for the use of rotigotine in the treatment of hemispatial neglect and other disabilities following stroke. Rotigotine is a dopamine agonist — a compound that activates dopamine receptors in the absence of dopamine — and an approved treatment for Parkinson's disease. Professor Husain has shown that treatment of stroke patients with rotigotine is associated with a significant improvement in the Mesulam shape cancellation task – a test whereby patients have to search visually for targets and mark these with a pen. The number of targets found on the left-hand side increased by 12.8 per cent after the patient was treated with rotigotine[149].

Project reference number: G0501986

Natural protection

Products and interventions: Mirococept proteins - extending the life of a kidney transplant

Researchers at the **MRC Centre for Transplantation** at **King's College London** have developed a technique that could both significantly extend the duration of a kidney transplant and increase the organ's condition and shelf life, addressing the pressing demand for donor kidneys. Only about half of transplanted kidneys are still functioning after 10 years inside the patient, around one-third of the time a transplanted kidney should last. Five to 10 per cent of transplants fail within one year. This means that the number of people requiring second transplants greatly increases the overall number of patients on the donor waiting list. In the UK, as at September 2013, this number was 5,875,

however, in 2012/13, only 1,750 kidney transplants took place[150]. The reason for this failure is the body's own immune system. When cells of the body meet an 'intruder' organism, such as an infection or the cells of a donor organ, part of the immune system — the 'complement' system — is activated, which then attacks and attempts to destroy the intruder cells. To stop the body from attacking itself, this system is normally controlled by 'regulator' proteins on the surface of its own cells. However, when an organ is removed for transplantation, these regulators are lost from the cell surface due to the lack of blood flow and subsequent lack of oxygen. This means that the complement system will begin to attack the organ's own cells, severely damaging it. This is part of the reason why organs cannot exist outside of the body for more than 24 hours. This effect is often amplified once the transplant is complete, as the complement system supports the recipient's own blood cells in its attack on the organ, resulting in organ rejection. People who have received a transplant will take drugs to suppress their immune system. However, these will often not completely stop the body from reacting.

To address these issues, the MRC team, led by **Professor Steve Sacks**, has developed a method for coating the surface of donor kidneys with a protective layer of Mirococept proteins — an artificial replacement for complement regulators. The application of Mirococept takes just 20 minutes after the kidney is removed from the donor. The team has also engineered a 'tail' to make the protein stick to the kidney cell membrane[151]. As well as preventing rejection, the ability of Mirococept to help maintain the condition of the organ during transfer would also extend their shelf life, greatly increasing the number of donor organs suitable for transplantation. In early tests, one in five organs worked properly after being stored on ice for 16 hours, compared with more than half of those treated with Mirococept[152]. This new technique, which has recently started treating patients in the first clinical trial, may drastically reduce the number of people waiting for a second transplant, cutting the overall number of people on the waiting list and potentially saving many lives.

Project reference number: MR/J006742/1

Products and interventions: Alzheimer's drug to enhance immune response to DNA vaccination

Professor Sir Mark Pepys at **University College London** has repurposed the drug CPHPC — developed as a potential treatment for Alzheimer's disease — to improve DNA vaccination. Successful vaccination induces a protective immune response against particular components of the target pathogen called immunogens. However, for some diseases, the immunogens are unknown, and for others, they are difficult and expensive to produce, transport and administer, for example, the influenza vaccine must be produced in millions of chicken eggs. One solution is DNA vaccination — whereby the DNA gene encoding the immunogen is injected rather than the immunogen itself. The DNA then enters the person's cells, predominantly at the site of injection, and causes them to produce the immunogen locally within the body. DNA vaccination works well and stimulates an excellent protective immunity against a variety of different infections, and even some cancers, in mice, horses, dogs, rabbits and pigs. However, in humans, other primates, cows and sheep, the immune response to DNA vaccination is very poor. Despite enormous academic and pharmaceutical industry efforts, the reasons for this failure have not been understood or overcome.

Sir Mark Pepys and colleagues have previously discovered, in work funded by the MRC, that serum amyloid P (SAP) — a plasma protein — is the only normal plasma protein that binds strongly to DNA[153]. They have now found that in each of the animal species in which DNA vaccination is effective, this protein is either absent, or binds only weakly to DNA. In contrast, non-human primates, cows and sheep share with humans the presence of SAP proteins which bind strongly to DNA. The team believe that the binding of DNA by SAP may be responsible for blocking the immune response by DNA, and therefore, removal of SAP may overcome this inhibition.

The team previously developed the drug CPHPC as a potential treatment for amyloidosis and Alzheimer's as it removes almost all SAP — present in the plaques and tangles of nerve fibres found in the brains of people with Alzheimer's disease — from the blood in humans[154]. Another research team has recently reported that the presence of SAP inhibits DNA vaccination in mice and that this effect is reversed by CPHPC[155].

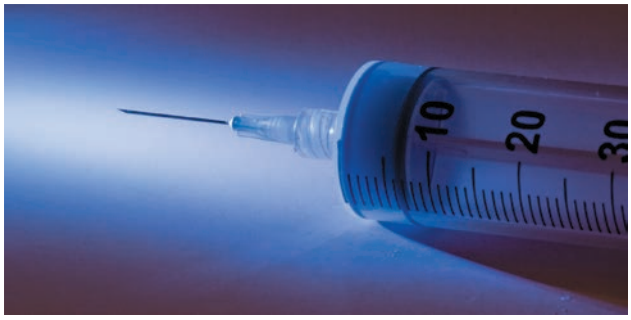


Image credit: Flickr/hitthatswitch

The researchers have now begun the first human clinical trial of DNA vaccination after SAP depletion[156]. The DNA vaccine to be tested is a promising new vaccine against HIV-AIDS, developed and manufactured with previous MRC awards. The group will measure the immune responses to the vaccination in healthy adult men, comparing a group in whom SAP has been completely depleted at the time of DNA vaccination and a control group vaccinated without SAP depletion. Proof of the concept that SAP depletion can enhance immune responses to DNA vaccination in humans will open up this approach for the many other diseases for which effective vaccination does not yet exist and in which it could have therapeutic as well as preventative benefits.

Project reference number: G7900510

Products and interventions: Successful peanut allergy treatment trial

Researchers at the **University of Cambridge** have demonstrated the success of a therapy to treat peanut allergy in a Phase II clinical trial[157] funded by the MRC-NIHR Efficacy and Mechanism Evaluation (EME) Programme[158].

Allergy to peanuts is becoming increasingly common, affecting between 0.5 and 1.4 per cent of children in high-income countries. This equates to around half a million people in the UK and more than 10 million people worldwide. Peanut allergy is the most common cause of severe and fatal allergic reactions related to food, and unlike other childhood food allergies, such as to eggs or cow's milk, it rarely goes away.

This trial involved 99 young people, aged between seven and sixteen. In the first phase, half of the children were given daily doses of peanut protein. Starting with a tiny dose and slowly building up over four to six months, the children were eventually able to tolerate the equivalent of five whole peanuts. The other half avoided peanuts in the first phase, but were then offered this treatment in the second phase. Allergy experts found that 84 and 91 per cent of the two groups of children treated with this new form of immunotherapy could eat at least five peanuts a day at the end of the treatment.

The next step is to make peanut immunotherapy widely available to patients. Further investigation and a licensing review are required to obtain a product licence from the regulatory authorities, which will take several years. In the meantime, Cambridge University Hospitals (CUH) is planning to open a peanut allergy clinic that would make a range of services, including immunotherapy on a named patient basis, available to patients. CUH is working with partners on private and publically funded models.

Project reference number: Not applicable

Products and interventions: Drug for prevention of kidney transplant rejection

In a Phase II clinical trial, **Professor Steven Sacks** at the **MRC Centre for Transplantation** at **King's College London** has shown that the drug eculizumab could be effective at preventing severe antibody-mediated resistance (AMR) in sensitised kidney transplant recipients.

Approximately 30 per cent of kidney transplant candidates on waiting lists are sensitised, or make antibodies, against potential donors. Their antibodies recognise target protein on the donor organ as foreign and subsequently attack it. This can lead to severe kidney damage leading to loss of function and possible loss of the transplanted kidney. Conventional immunosuppressant treatments are ineffective in preventing AMR. Eculizumab is a humanised monoclonal antibody currently licensed for the treatment of paroxysmal nocturnal hemoglobinuria — a disorder characterised by the impaired production of red blood cells and atypical hemolytic uremic syndrome, which can lead to stroke, heart attack, kidney failure and death. It works by inhibiting the activation of the terminal complement, part of the innate immune response that helps antibodies clear the body of pathogens.

The trial involved the treatment of 47 sensitised recipients of kidneys with eculizumab. Initial results indicate that at nine weeks after the transplant, the failure rate due to AMR was 6.4 per cent, compared to an expected rate of 30 per cent.

Project reference number: MR/J006742/1

Products and interventions: Identification of biomarkers of immunological tolerance

Professor Steven Sacks has also identified a series of biomarkers associated with tolerance to kidney transplantation. Kidney transplantation is the main treatment for children and adults with kidney failure. However, the risk of organ rejection is high. Immunosuppressant drugs are given to patients to try and prevent immune system-generated organ rejection, however, often have severe side effects. The most significant side effect is an increased risk of infection; the drugs can also leave the patients more susceptible to cancer.

In some patients, their immune response is eliminated and they establish tolerance to the kidney transplant. If patients who become 'tolerant' of their transplanted organs are identified, it would be possible to use fewer or no drugs for their treatment, thus avoiding the side effects, while not allowing rejection to take place. Professor Sacks' team is currently conducting a clinical trial to see if the group of markers identified can be detected in patients on immunosuppressant drugs. They will also testing how stable the expression of these markers is.

Project reference number: MR/J006742/1

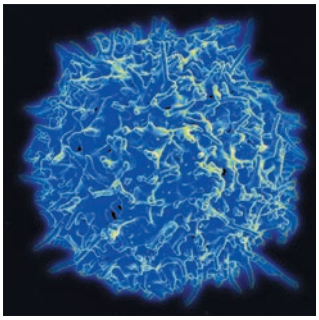
Products and interventions: New class of immunosuppressant drugs

Professor Randolph Noelle at **King's College London** has developed VISTA-Ig fusion proteins – a new class of immunosuppressant drugs – for the potential treatment of autoimmune disorders such as lupus and multiple sclerosis. The drug has been licensed to ImmuNext and the company has been awarded a $2,000,000 STTR Phase 2 grant from the National Institutes of Health for pre-clinical development.

Project reference number: G0802651

Products and interventions: Immunotherapy to improve immunity after donor stem cell transplant

Stem cell transplantation is used to treat many patients with leukaemia and genetic disorders such as sickle cell anaemia. In around 30 per cent of cases, it is possible to obtain replacement stem cells from a family member such as a sibling. However, in the other 70 per cent, stem cells are transplanted from a matched unrelated donor. In these cases, it is necessary to remove the majority of the donor immune T-cells to prevent 'graft-versus-host disease', whereby 'alloreactive' donor T-cells attack the patient. This, however, results in the patient having very little immunity for many months after the transplant, meaning they are highly susceptible to infections affecting the lungs, liver and other organs. These viral complications are a leading cause of death following this kind of transplant.



Scanning electron micrograph of a human T cell

Professor Persis Amrolia at **University College London** has developed a therapy to improve post-transplantation immunity by returning the T-cells from the donor to the recipient, having removed the cells that cause graft-versus-host disease, whilst leaving those that fight viral infections. His team has previously shown in a small clinical study that giving such 'allodepleted' T-cells to patients improves immunity after transplants from half-matched parents[159]. However, T cell responses to viruses that evoke low-frequency responses (for example, adenovirus) were not seen, suggesting that returning larger numbers of T-cells may be needed to protect against such pathogens. The researchers intend to extend this approach to the unrelated donor setting to maximise its applicability. They have now refined this method to more effectively remove the alloreactive cells, leaving more T-cells to be returned to the patient. A Phase I/II clinical trial is due to start in 2014[160].

If successful, this approach could reduce the morbidity and mortality associated with infections after transplant surgery.

Project reference number: MR/K007491/1

Products and interventions: Vaccine for respiratory syncytial virus (RSV)

Dr Geraldine Taylor at the **Pirbright Institute** has developed and undertaken pre-clinical evaluation of a vaccine against respiratory syncytial virus (RSV), a major cause of respiratory infections such as pneumonia and bronchiolitis. RSV affects all ages, but particularly infants, adults with a suppressed immune system, and the elderly. It is the single most common cause of severe respiratory illness in children, affecting approximately 64 million children each year worldwide. In the UK, two to three per cent of infants under the age of one are hospitalised each year due to RSV. Children who experience RSV early in life run a high risk of recurrent wheezing and asthma. The economic impact of RSV in adults and burden of disease in the elderly are comparable to or greater than that of seasonal influenza. There is currently no effective RSV vaccine or anti-viral therapy, apart from antibody prophylaxis for high risk individuals.

In a collaboration between the **University of Oxford** and Okairos, a vaccine development company, the vaccine has now entered Phase I clinical trials[161].

Project reference number: MR/J014648/1

Intellectual property: Use of nitric oxide in prevention of ventilator-associated pneumonia

Ventilator-associated pneumonia (VAP) is the most common healthcare-linked infection contracted by patients in intensive care[162]; it is the basis for about half of all antibiotics given in this hospital department[163]. The biggest risk factor for the development of the condition is the presence of a tracheal tube[164], a tube inserted into the windpipe to maintain a patient's airway. The tubes interfere with the normal protective upper airway reflexes, prevent effective coughing and encourage the entry of infected secretions from the respiratory and upper digestive tracts. It is estimated that over 60,000 patients are mechanically ventilated in UK intensive care units annually and the reported incidence of VAP varies from around 10 per cent to more than 30 per cent.

It has been shown that oxides of nitrogen play a key role in the maintenance of host defence against various microbial pathogens. Ordinarily, oxides of nitrogen (NOx) are present in high concentrations in the stomach where they play an important role in maintaining sterility and preventing gastrointestinal infections.

Professor Charles Hinds at **Queen Mary, University of London**, has shown that during critical illness, the production of NOx is reduced. This predisposes colonisation of the stomach and oral cavity by pathogenic bacteria and therefore the subsequent development of VAP. Professor Hinds has patented a system for the external production and local delivery of nitric oxide (NO) and NOx[165]. The solution is designed to restore normal physiological activity of NOx by nasogastric and oral administration.

Project reference number: MR/J011134/1

Intellectual property: Antimicrobial coating of prostheses

In most developed countries, due to an increase in both life expectancy and obesity, the numbers of joint replacements has steadily increased over the past 20 years. Joint, such as knee and hip, replacements can be undertaken using either cemented or cementless procedures. In cemented procedures, a bone cement, such as poly(methyl 2-methylpropenoate) is used to attach the prosthetic joint to the bone, whereas in a cementless procedure, porous materials are used to create a prosthetic implant to facilitate bone ingrowth and provide a strong method of biologically fixing the prosthetic.

Cemented procedures are typically disadvantageous in that joint manipulation leads to wear over time, resulting in the formation of stress cracks in the cement and ultimately cement erosion and an unstable joint. A cemented procedure however allows the addition of an antibiotic to the cement, preventing post-operative infections, which are a common complication and treatment of which typically involves surgery with continued administration of antibiotics over long periods of time.

Cementless procedures do not allow the execution of this preventative method. Antibacterial sol-gel coatings for cementless prostheses have been developed, however, have a number of disadvantages, such as the integrity of the coatings and the rate and duration of antibiotic release.

Professor Robert Akid at the **University of Manchester** has patented a substrate comprising a sol-gel derived coating for the controlled release of an antimicrobial[166]. In particular, the coating is configured so that the antimicrobial is captured within an organic-inorganic oxide network and is released only at the appropriate time (during and after surgery) allowing the substrate to be stored prior to use, without losing its antimicrobial properties.

Project reference number: MR/J014656/1

Cancer

Products and interventions: Chemotherapy before surgery for oesophageal cancer

Oesophageal cancer is the ninth most common type of cancer in the UK, with more than 8,000 new cases diagnosed each year. Oesophageal cancer does not usually cause any noticeable symptoms until the cancer has spread beyond the oesophagus and into nearby tissue. For this reason it can be more difficult to cure compared with other types of cancer. On average, 30 per cent of people with oesophageal cancer will live for one year after the diagnosis, and eight per cent will live for five years after the diagnosis.

In the early 1990s, people with cancer of the oesophagus were offered an operation to try to cure their cancer. Unfortunately, this was only successful for a small group of people, and only about one in every five people lived for more than two years after the operation.

Some small clinical trials had suggested that it might be helpful to give people chemotherapy before their operation – it seemed that this might help more people to live for longer. To test whether this was the case, in 1992, researchers at the **MRC Clinical Trials Unit** developed the OE02 test, comparing two treatments for cancer of the oesophagus – an operation and chemotherapy followed by an operation.

The trial closed in 1998 having recruited 802 patients from the United Kingdom and European centres. The initial results were published in 2002, with a median follow up after 17 months. The trial showed that both disease-free and overall survival rates were significantly increased after preoperative chemotherapy. The two-year survival rate was 43 per cent in the chemotherapy group compared to 34 per cent in the surgery alone group[167].

Treating oesophageal cancer patients with chemotherapy before surgery is now advised in clinical guidelines as the standard treatment approach and has since changed clinical practice.

Project reference number: MC_U122861327

Intellectual property: Antagonist of gene implicated in cancer

The gene *Lrg1* codes for the glycoprotein LRG1, the expression of which is upregulated in cancer cells. Until recently however, its specific function was unknown. **Professor Stephen Moss** at **University College London** showed in 2013 that in the presence of the growth factor TGF- ß1, LRG1 promotes the division of endothelial cells – the cells lining blood vessels, and therefore angiogenesis, the formation of new blood vessels from pre-existing ones[168]. Angiogenesis is essential for tumour growth to provide the tumour with a supply of nutrients and oxygen and to remove waste and so angiogenesis is one target for cancer treatment.

Professor Moss has patented, via **UCL Business plc**, antagonists of LRG1[169].

Project reference number: G0902206

Products and interventions: Trial of new cancer drug

Professor Tracy Robson at **Queen's University Belfast**, in collaboration with Almac Discovery Ltd, has developed ALM201, a cancer drug candidate derived from a natural protein. The drug is anti-angiogenic, which means it prevents the growth of new blood vessels, thereby inhibiting tumour growth. ALM201 works by an entirely new mechanism to the majority of other anti-angiogenic therapies currently on the market, and therefore has the potential to treat a wider range of patients than currently possible, including those resistant to existing therapies.

ALM201 entered a Phase I clinical trial in patients with ovarian cancer in early 2014.

Project reference number: G1001473

Liver disease

Products and interventions: LiverMultiscan

As many as one in ten adults in the UK have some form of liver disease, which is currently the fifth most common cause of mortality for both men and women. However, symptoms of the disease are often not apparent until the disease reaches an advanced stage. Thus, there is a pressing need for a reliable diagnostic tool for liver disease to identify early disease and target therapies to those patients that may benefit. The current procedure for diagnosing liver disease is a liver biopsy. However, a biopsy allows examination of only 0.002 per cent of the liver[170]. In addition, people with severe liver disease often have blood clotting problems and so there is an increased risk of severe bleeding after the procedure (one in 500 to one in 1,000)[171].

Professor Stefan Neubauer at **Oxford University** developed the LiverMultiscan[172] in 2010, a device that combines three imaging techniques using MRI to accurately stage liver disease. This technique can replace the use of an invasive biopsy which saves money and provides a better patient experience.

This has recently led to the establishment of spin out company Perspectum Diagnostics which has raised seed fund capital of £0.5m and been awarded £1.2m in funding from the Technology Strategy Board.

Project reference number: G0700796

Heart disease

Products and interventions: shMOLLI method

Quantitative T1-mapping is rapidly becoming a clinical tool in cardiovascular magnetic resonance (CMR) to objectively distinguish normal from diseased heart muscle.

In 2010 **Professor Neubauer** developed the Shortened Modified Look-Locker Inversion (shMOLLI) recovery method for T1 mapping of the heart. T1 mapping allows direct in-vivo examination of microscopic changes in the myocardium, the muscular tissue of the heart, providing new diagnostic insights into cardiac disease. Existing methods require long breath holds that are demanding for many cardiac patients. The ShMOLLI method uses sequential inversion recovery measurements within a single short breath-hold. Conditional interpretation of samples for reconstruction of T1-maps is used to yield accurate measurements, and this algorithm is implemented directly on the scanner. This technology has since been licensed to Siemens. A 2012 review comparing this technique with older multibreath-hold FLASH techniques demonstrated that the shMOLLI method was procedurally better tolerated, slightly more reproducible and better correlates with the patient's histology[173].

Project reference number: G0700796

Intellectual property: New diagnostic marker for heart attack

Heart attacks are a common cause of death, however effective treatments are available providing the condition is rapidly diagnosed. Diagnosis relies on the presence of specific biomarkers in the blood, accompanied by symptoms such as chest pain.

The optimum biomarker would be released soon after the heart attack and in proportion to the damage caused, have a high sensitivity and be specific, in that it should only be detected in heart tissue. Many of the biomarkers in current use do not fulfil these criteria.

Professor Michael Marber at **King's College London** has patented a method of diagnosing heart attacks comprising identification of an elevated concentration of cardiac myosin binding protein C (cMyBP-C) or myosin regulatory light chain 2 (MLC2) in a blood sample.

Project reference number: G1000737

Musculoskeletal

Intellectual property: Use of protein to treat osteoporosis

Osteoporosis is a progressive bone disease that is characterised by a decrease in bone mass and density, resulting in an increased likelihood of fractures. The underlying cause is an imbalance in the normal process of bone remodelling — bone resorption, whereby osteoclast cells break down bone and release minerals and bone formation by osteoblast cells. In osteoporosis, there is excessive bone resorption, and inadequate formation of new bone.

Professor Anthony Day at the **University of Manchester** has patented the use of TSG-6, an inflammation-induced protein that has protective roles in arthritis in the treatment of osteoporosis. Professor Day has shown

that TSG-6 inhibits bone resorption by osteoclasts and that the absence of TSG-6 in TSG-6 knockout mice leads to increased bone resorption by osteoclasts[174].

Project reference number: MR/J014621/1

Public health

Products and interventions: Football Fans in Training (FFIT)

Researchers at a consortium of universities led by the **University of Glasgow** and the **MRC/CSO Social and Public Health Sciences Unit** have shown that a gender-specific weight loss and healthy living programme delivered to male fans at the grounds of Scottish professional football clubs can help a large proportion of men lose a clinically important amount of weight[175].

Obesity is one of the greatest threats to health. By 2030, 11 million adults are expected to be obese, amounting to almost 700,000 additional cases of diabetes, 460,000 cases of heart disease and stroke and 130,000 cases of cancer, with the associated increase in medical costs estimated to be around £2 billion per year[176]. In Scotland, more men than women are overweight or obese (69 per cent and 60 per cent respectively), however, men are under-represented in trials of weight loss interventions and weight management programmes.

Football Fans in Training

The researchers undertook a two-group randomised trial of 747 male football fans aged 35-65 years with a body mass index of more than 28kg/m^2, assigning them to either the Football Fans in Training (FFIT) programme or a comparator group. For a period of 12 weeks, the intervention group were given weekly 90-minute sessions combining classroom-based advice on healthy eating and physical activity, delivered by coaches at their club. The comparator group had just the information given to all men at the start of the trial (an advice booklet, their weight and BMI, personalised advice on consulting about high blood pressure, and some information about the programme).

At 12 months after the completion of the programme, the average difference in weight loss between the two groups (adjusted for starting weight and club) was 4.94kg and the percentage weight loss was 4.36 per cent, both in favour of the intervention.

The intervention group also showed significant changes in waist circumference, body fat, BMI, blood pressure, self-reported physical activity, dietary intake, alcohol consumption and measures of psychological and physical wellbeing.

The programme has since attracted £5 million from the European Union to develop and evaluate the programme across Europe. The 'EuroFIT' project team will work with top football clubs from across the continent to encourage fans to take up healthier lifestyles.

Project reference number: MC_UU_12017/3

Products and interventions: Mind, Exercise, Nutrition, Do it (MEND)

Mind, Exercise, Nutrition, Do it (MEND) provides healthy living programmes for children and families in local communities, including ways to make life changes in physical activity, food, self-confidence and personal development. Formally established in 2004 by **UCL Institute of Child Health** and **Great Ormond Street**, it has proven to be a model that is replicable throughout England and Wales and is now the most extensive child obesity treatment programme in the UK.

MEND is currently running more than 200 programmes per school term across the UK and is also being delivered in Denmark, the US, Canada, Australia and New Zealand. The programme is currently looking for partners to deliver the programme in the Middle East[177].

A recent study on the MEND 5-7 programme demonstrated that participation was associated with beneficial changes in physical, behavioural and psychological outcomes[178].

Products and interventions: Medication for smoking cessation

Professor Robert West at **University College London** has conducted a clinical trial into the use of Tabex (cytisine) and demonstrated its efficacy as an aid in smoking cessation[179].

Smoking contributes to five million premature deaths each year worldwide[180] and is extremely addictive; more than 95 per cent of unaided attempts at stopping smoking fail to last six months[181]. However, of the one billion smokers worldwide, many live in countries where the cost of smoking cessation treatment is more expensive than the cost of cigarettes.

Cystisine is a compound that has been extracted from the seeds of the Golden Rain acacia plant. Under the brand name Tabex, it has been available as a smoking cessation aid in former socialist economy countries for more than 40 years. The compound binds to the nicotinic acetylcholine receptor, which has been implicated in the development and maintenance of nicotine dependence. It is substantially cheaper than alternative drugs used in smoking cessation.

The rate of sustained 12-month abstinence was 8.4 per cent (31 participants) in the cytisine group, compared with 2.4% per cent (nine participants) in the placebo group.

Following this trial, Tabex has been put forward for regulatory approval in a number of countries.

Project reference number: G0501300

Research materials: Toolkit to assess robustness of population health research

In 2012 the **MRC/CSO Social and Public Health Sciences Unit** held a series of workshops at which it was agreed that there was a need to develop a user-friendly web-based toolkit to help members of the public and policymakers assess the credibility and applicability of population health studies. The aim of the toolkit is to provide guidance on particularly problematic concepts such as scientific uncertainty, use of statistics and correlation and causation. The toolkit is due to be published in 2014.

Project reference number: MC_U130059821

Intellectual property: DNA methylation predictor of obesity

In 2012 **Professor Cyrus Cooper** at the **MRC Lifecourse Epidemiology Unit** patented his discovery that the DNA methylation status of the coding region of selected genes, preferably in a perinatal tissue sample such as umbilical cord, can be used to predict future development of diverse characteristics. These include obesity or low bone mineral content, impaired cardiovascular structure or function, ability to learn and cognitive function, neurobehavourial problems and allergies such as eczema.

Project reference number: MC_UP_A620_1014

Intellectual property: Human milk fortifier

Professor Jimmy Bell at **Imperial College Londo**n has patented a human milk fortifier with high protein and long chain polyunsaturated fatty acids to increase capability of improving body composition and prognosis in preterm infants.

Project reference number: MC_U120061305

Products and interventions: Map Me

The World Health Organization (WHO) considers childhood obesity to be one of the most serious global public health challenges of the 21st century[182]. Obese children and adolescents are at an increased risk of developing various health problems, and are also more likely to become obese adults. Parents are essential in preventing childhood obesity, however many do not recognise that their child is overweight and therefore do not take action. As part of the National Prevention Research Initiative (NPRI), **Professor Ashley Adamson** at **Newcastle University** has developed gender-specific body image scales of known body mass index for 4-5 and 10-11 year olds and supporting information about the health consequences of childhood obesity. These will be used to improve parental recognition of childhood obesity and its consequences; the effectiveness of which is being tested in a clinical trial[183].

Project reference number: G0501306

Products and interventions: 'FoodSwitch' phone app

Researchers at the **MRC Human Nutrition Research (HNR)** group have contributed to the development of 'FoodSwitch', a free smartphone app that makes it quicker and easier for UK shoppers to compare nutritional information on different products, enabling them to make healthier choices[184]. Shoppers can scan the barcodes of items and the app will instantly provide easy-to-understand, colour-coded nutritional information and suggest similar products that are lower in fat, sugar and salt. The app, launched in February 2014, includes the barcodes and nutritional data of more than 80,000 packaged foods and drinks sold across major UK supermarkets.

FoodSwitch. Image credit: FoodSwitch UK

The project was coordinated by the Consensus Action on Salt and Health (CASH), and fellow contributors included the British Heart Foundation and the Nuffield department of population health at the University of Oxford. The UK organisations worked closely with The George Institute for Global Health in Australia who successfully developed the app originally in Australia and New Zealand leading to the development of a UK version.

The HNR dietary assessment team collected images of supermarket products and checked the data from the nutritional labels. The team also advised on food categorisation, the adaptation of the Australian nutrient profiling score for UK dietary recommendations and the healthy choice messaging.

Project reference number: MC_U105960389

Hearing

Products and interventions: TAIL – Test of Attention in Listening

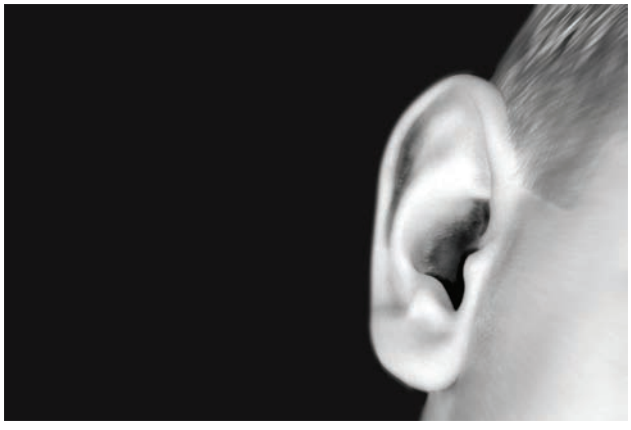


Image credit: iStock

Attention modifies how sounds are perceived, however until now there has been no simple test to specifically measure this. **Professor David Moore** at the **MRC Institute of Hearing Research**[185] developed a test to assess auditory attention using simple sound comparisons and reaction times. The TAIL (Test of Attention In Listening) test looks at separate attentional networks responsible for processing speed (how quickly we respond to sounds), orienting (how quickly we pick out changes in the relevant information in sounds), and conflict resolution (how well we ignore the irrelevant information in sounds)[186]. The test is currently being used in research, training and testing. There are both adult and child versions – the child version being an attractive game-like environment based in space. Work is being undertaken with **MRC Technology (MRCT)** to further develop and register the invention.

Project reference number: MC_U135097130

Unexpected impacts of MRC research

Intellectual property: Genetic tests for canine and bovine neurological disorder

Professor Robert Harvey at **University College London** studies the glycine and GABA-A receptors embedded in nerve cell membranes which receive the signals transmitted from nerve cells across the nerve synapse. Professor Harvey has shown that genetic defects in the glycine transporter GlyT2 are responsible for causing a rare illness called hyperekplexia or startle disease[187,188]. This affects newborn children and is characterised by noise or touch-induced seizures which result in breath-holding episodes. In some instances hyperekplexia can lead to brain damage or sudden infant death. The identification of this gene has enabled the testing of children suspected of having the condition, giving the families concerned a definitive diagnosis. A positive test enables parental training and use of monitoring equipment.

As a result of the publication of these studies, Professor Harvey received various requests to examine unexplained cases of startle disease in other species, such as cattle and dogs, where it causes significant animal welfare issues. The animals often die shortly after birth with extreme muscle stiffness and breathing difficulties.

Since examining the gene by DNA sequencing is relatively inexpensive, Professor Harvey conducted short studies on startle disease in Belgian Blue cattle[189] and Irish Wolfhounds[190]. The Belgian Blue study has impacted on cattle breeding procedures in the UK, with the British Blue Society introducing new rules for genetic testing. They also publish the results of this testing online. The Wolfhound genetic test is accessible to the general public via Laboklin[191] and has also had a positive impact on animal welfare.

Project reference number: G0601585

Research materials relevant to the 3Rs

The MRC considers the use of animals to be essential in biomedical research in order to better understand the living body and what goes wrong in disease, and to develop safe and effective ways of preventing or treating those diseases. The MRC is dedicated to animal welfare. As part of this commitment, the MRC plays a key role in developing and disseminating the three Rs (replacement, refinement and reduction of animals in research). The MRC is constantly evolving its practices to advance the 3Rs.

Adaptation of malarial parasite Plasmodium knowlesi to erythrocyte cells

Researchers at the **MRC National Institute of Medical Research (NIMR)** have successfully cultured the malaria-causing parasite Plasmodium knowlesi in human red blood cells, which means it is no longer necessary to use primate models[192]. P.knowlesi is a simian parasite; however it is closely related to Plasmodium vivax, the most important cause of malaria outside of Africa, so its study can provide insights into unique aspects of the biology of P. vivax. P. knowlesi has also recently been identified as a significant cause of often severe human malaria in southeast Asia.

Project reference number: MC_U117532067

New mouse model for CNV

Choroidal neovascularisation (CNV) is the development of new blood vessels in the retina, and is a common symptom of age-related macular degeneration. The condition is often modelled by inducing this growth using lasers. In 2012 **Dr Eric Ng** at **University College London** used a novel mouse model which develops the condition spontaneously and found that this is more consistent. The advantage is that these studies do not require the invasive laser procedure, and yield better quality data. This means both a refinement in the use, and reduction in the number, of animals needed for the work. The consistency of CNV observed in the model has opened up the potential to study vascular endothelial growth factor (VEGF) as a treatment.

Project reference number: G0901303

New cage systems for monitoring movement and feeding of mice

Research undertaken by **Professor Antonio Vidal-Puig** at the **University of Cambridge** in 2012 has led to a refinement of metabolic cages for monitoring movement and feeding in mice. The new caging system allows simultaneous assessment of food intake, energy expenditure, activity and water consumption. The equipment incorporates novel features such as having a food delivery system hook on the cover of the cage. The newly developed system to assess energy balance is also a refinement because more accurate measurements can be made in each experiment. The addition of a 24 hour camera system with Visual Sonics software enables secure systems to observe without interfering with measurements.

Project reference number: G0802051

New zebrafish model for arterial examination

Dr Sarah De Val's research at the **University of Oxford** is focused on the gene transcription dictating the growth of blood vessels during embryonic development and the development of cancer cells. Rapid growth of new blood vessels is a necessary step in the development and spread of tumours; the disorganised structure of these vessels presents is also a barrier to effective therapy. Abnormal blood vessel development in the eye is a major feature in diseases causing blindness. Prolonged and excessive vessel growth is also a feature of many inflammatory disorders and autoimmune diseases. Conversely, inadequate vessel growth also contributes to many disease states, including heart disease and pre-eclampsia.

In 2012, Dr De Val identified an enhancer that directs the expression of any linked gene specifically to the arterial endothelial cells in fish. This has been made available to other researchers, allowing people to generate transgenic zebrafish expressing their gene of interest specifically in arteries. Dr De Val has then used this enhancer to generate a transgenic zebrafish expressing green fluorescent protein (GFP) specifically in arteries, providing a mechanism to visualise arteries whilst the fish are still alive.

Project reference number: MR/J007765/1

Supply of macaque blood samples to assess welfare

In a project funded by the **National Centre for the Replacement, Refinement and Reduction of Animals in Research (NC3Rs), Professor Melissa Bateson** at **Newcastle University** is developing methods to better understand the emotional state of monkeys undergoing research procedures. The most appropriate guide to the symptoms that should be measured comes from the study of human patients with mood disorders such as depression.

Using this guide, Professor Bateson is measuring changes in the lengths of telomeres — protective caps at the end of chromosomes that are eroded during periods of psychological distress that can regrow when happy – and also the structural and functional changes in the brain using non-invasive brain imaging technology.

Dr Anna Mitchell at the **University of Oxford** has provided macaque blood samples to Professor Bateson to enable measurement of lengths of the macaques' telomeres.

Project reference number: G0800329

Drug development

Intellectual property: Styrene maleic acid lipid particle (SMALP) system

Professor Michael Overduin at the **University of Birmingham** has patented the SMALP system, a revolutionary new protein stabilisation technique which could lead to 30 per cent more proteins being available as potential targets for drug development, opening up exciting possibilities in drug discovery. Understanding the structure of proteins is a vital first step in developing new drugs, but to date, drug development has been slowed because proteins are difficult to work with in lab conditions due to their instability. However, the use of SMALP nanoparticles allows the intact preservation of membrane proteins, enabling detailed analysis of their structure and molecular functions.

Project reference number: G0601073

Research materials: Text-mining

The global research community produces more than 1.5 million articles each year[193]. Text mining, the process of deriving high-quality information from text through the devising of patterns and trends, was highlighted by the 2011 Hargreaves report as affording a real opportunity to support innovation and the development of new knowledge[194]. A 2012 report by Jisc found that text mining yielded wide-ranging benefits for research, from efficiency, unlocking hidden information and developing new knowledge to improving the research process[195].

Cancer risk assessments

There is now a large volume of scientific literature showing a strong link between environmental chemicals and cancer, and so there is a critical need to issue exposure limits on the use of harmful chemicals[196]. These limits are based on cancer risk assessments, which involve examining existing published evidence to determine the relationship between exposure to a substance and the subsequent likelihood of developing cancer. The task is however becoming increasingly challenging to administer manually due to the rapidly growing volume of risk assessment literature and the increasing complexity of experimental evidence. The process can be extremely challenging as the data required for the risk assessment of a single carcinogen may be dispersed across thousands of journal articles. Text mining technology could lead to considerably more systematic and efficient risk assessments.

Considerable progress has been made in the development of basic resources for text mining; however, more recent challenges have been to extend text mining techniques and to apply them to support particular needs in biomedicine identified by researchers.

Dr Anna Korhonen and colleagues at the **University of Cambridge**, in conjunction with researchers at the Institute of Environmental Medicine in Stockholm, have developed a taxonomy for cancer risk assessments based on the expert annotation of 1,297 abstracts downloaded from relevant PubMed journals[197]. It classifies 1,742 unique keywords into 48 classes, which specify core evidence required for the cancer risk assessment.

The researchers conducted annotator agreement tests, automatic classification experiments and a user test, which demonstrated that the taxonomy was accurate, well-defined and useful. The system can be used to support current manual cancer risk assessments in addition to facilitating the development of a more detailed approach based on text mining.

Project reference number: G0601766

Use of text mining in the FlyBase genetic literature curation workflow

FlyBase is the model organism database for genetic and genomic data on *Drosophila*, the fruit fly model organism. In the 20 years since its inception, the database has adapted to constantly evolving methods in research and database design. During this time, the number of *Drosophila*-related primary research articles published each year has steadily increased, from roughly 1,000 in 1980, to more than 2,000 a year since 2001. The website contains over 2.5 million pages covering 19 different data classes and 20 *Drosophila*-sequenced genomes.

FlyBase genetic literature curation is performed on an article-by-article basis and in 2011, FlyBase introduced a system whereby authors were asked to complete an online form to 'skim' curate their articles, extracting a minimal level of information from every article. Author-led curation has a completion rate of 57 per cent.

It is hoped that text mining can reduce the time necessary for manual paper triage and data extraction in skim curation to allow more time for the specialised task of full curation.

Dr Peter McQuilton and colleagues at the **University of Cambridge** have identified promising targets for effective text mining of *Drosophila* data[198].

They developed a 'natural language processing' (NLP) system that marked up html versions of an article for gene/allele mentions and associated phenotypes. This 'PaperBrowser' tool improved article navigation efficiency (the number of navigational events needed before the data are extracted) by 58 per cent. This has shown to be a good proof-of-concept, showing that text mining can work well with article-by-article curation.

They have also explored the use of support vector machine (SVM) methods to triage primary research articles into categories used in the author curation. The system has been trained to triage for new transgenes, new alleles and gene renames.

There are many genes still missing functional data and so text mining could also feasibly be used for the identification of articles with functional information about these genes.

The researchers also hope to be able to use text mining for other genetic disease associations and gene and allele symbols.

Project reference number: G1000968

researchfish

MRC Medical Research Council

Outputs, outcomes and impact of MRC research: 2013/14 report

SECTION 2.4: Industry interactions and other collaborations

Industry interactions and other collaborations

The MRC supports the most promising response-mode and strategic research, with the greatest potential for long-term advances. The MRC has a unique role in funding discovery science through to early clinical studies, and the training needed to deliver this, within a complex medical research ecosystem. It is the productive interactions between researchers globally and across all sectors that are essential for this research to be translated into wider impact. It is important that the MRC creates the optimal conditions for the right interactions to flourish. An analysis of approaches to track these productive interactions with particular focus on information about reported collaborations, sources of further funding and the creation of spin out companies is available in the quantitative analysis sections 3.2, 3.3 and 3.10.

Researchers providing feedback via Researchfish identify collaborations that can be evidenced (via activities such as joint funding, joint publication, and exchange of expertise, staff and/or facilities) as being productive and supportive of achieving their research goals. Each reported collaboration can include a number of partners already supported by funding from different sources (for example, charitable, public, and private sector) and are not confined to just the UK. Researchers reported a variety of purposes for engaging in a collaboration including provision of expertise, research materials and funding. Collaboration has been shown to be a driver of research excellence. In a period of constrained public finances it is even more important to have access to a wider range of facilities and equipment through a pooling of resources and expertise[199]. In addition to establishing and maintaining collaborations, researchers obtain funding to continue or expand their work. This "further funding" may be competitively won, at least in part, as a result of holding MRC support. Success in obtaining further funding may indicate that the research group has established a high quality track record and is therefore able to present attractive proposals for future research.

The MRC has also made an extensive contribution to the formation and growth of spin out companies[200]. The formation of spin out companies is one route to the commercialisation of discoveries, resulting not only in improved healthcare, but also in positive economic impact, such as employment and direct investment into the UK.

A number of case studies relating to the MRC's collaborations, impacts on the private sector and leveraging of further funding can be found throughout this chapter in the following areas:

- Cancer
- Metabolic diseases
- Obesity and nutrition
- Neurodegeneration and neurology
- Natural protection
- Infectious diseases
- Sexual development
- Rare diseases
- Global health
- Regenerative medicine
- Environmental exposures
- Musculoskeletal health
- Reproductive health
- Epigenetics

Further information on each piece of research can be found on the Research Councils UK (RCUK)'s information portal — *the Gateway to Research*[201] — by entering the project reference number listed under each case study in the search field.

Collaborations: Developing drug-like molecules for cancer

Professor Terence Rabbitts at the **University of Oxford** studies small molecules and peptides that mirror the inhibitory properties of antibodies with the aim of developing drug-like molecules for therapeutic application. MedImmune, the biologics research and development arm of AstraZeneca, has provided Professor Rabbitts with proteins to test *in vitro* and *in vivo* lung cancer molecules for an ability to enter cells and produce a therapeutic effect.

Project reference number: MR/J000612/1

Collaborations: Colorectal cancer screen

As a result of a Confidence in Concept award in 2012, **Professor Saul Tendler** at the **University of Nottingham** has embarked on a collaboration with Oncimmune, a company specialising in early cancer detection to identify new autoantibody biomarkers for colorectal cancer.

Project reference number: MC_PC_12019

Impacts on the private sector: Kesios Therapeutics Ltd

Kesios Therapeutics is a spin out company formed in 2012 by Imperial Innovations, originally founded as the technology transfer office of Imperial College London[202]. Kesios Therapeutics Ltd is focused on the development of small molecule drug candidates that are targeted at haematological malignancies, cancers of the blood, bone marrow, and lymph nodes. It builds upon the work of one of its founding directors **Professor Guido Franzoso**, head of the **Centre for Cell Signalling and Inflammation** at **Imperial College London**.

Project reference number: G0901436

Impacts on the private sector: Development of DNA damage assay

Chemotherapy for diseases such as cancer involves treatment with compounds designed to cause DNA damage, leading to cell death. However, resistance to these compounds and treatment failure can often occur. Repair of the DNA damage is the commonest cause of resistance.

Professor Simon Reed at **Cardiff University** has developed a method to detect, quantify, and localise DNA damage at high resolution throughout the human genome[203]. He has provided use of this to GlaxoSmithKline to determine the mechanism of genetic toxicity caused by drugs and the response of the epigenome to this damage. The epigenome describes complex chemical DNA modifications which can change gene expression. Understanding these responses could allow patients that are likely to respond well to particular treatments to be identified.

Project reference number: MR/K000926/1

Metabolic diseases

Collaborations: Structure and function of AMPK

AMP-activated protein kinase (AMPK) functions in the regulation of cell energy. Evidence suggests that it may therefore play a role in human diseases characterized by defects in energy metabolism. **Professor David Carling's** current research at the **MRC Clinical Sciences Centre** focuses on the regulation of AMPK using structure/function analyses and the physiological role of AMPK using transgenic models. Professor Carling has identified the mode of action of small molecule activators of AMPK and will use this in order to determine whether there are any natural ligands that activate AMPK by a similar mechanism. As part of an industrial CASE studentship in 2013, AstraZeneca have synthesised a number of small molecular activators of AMPK. They have also produced a fluorescent analogue molecule for one of these activators that will be used as a probe to screen for natural ligands that compete with the binding.

Project reference number: MC_U120027537

Impacts on the private sector: Targeting Nrf2 in the treatment of diabetes

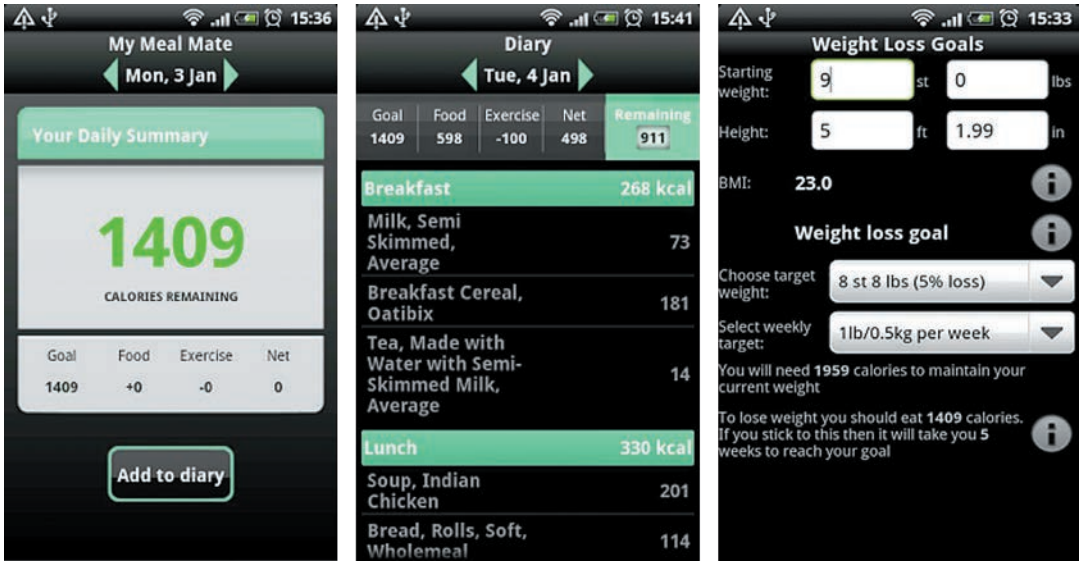
Professor John Hayes at the **University of Dundee** studies the regulation of the transcription factor Nrf2, primarily in relation to its role in cancer. Nrf2 increases the expression of antioxidant genes. In normal cells, activation of Nrf2 has strong anti-inflammatory effects and limits damage caused by oxidative stress, which results in the production of peroxides and free radicals that damage all components of the cell, including proteins, lipids, and DNA. Oxidative stress is thought to be involved in the development of many diseases, including cancer[204] and diabetes. Professor Hayes has acted as a consultant for Sanofi on a project led by Dr Dieter Schmoll to target Nrf2 in the treatment of diabetes.

Project reference number: MR/J001465/1

Obesity and nutrition

Collaborations: Smartphone app to monitor food intake

Researchers at the **University of Leeds** have developed a smartphone app in conjunction with Blueberry Consultants that enables users to monitor their food intake and exercise. My Meal Mate[205] also allows users to set a weight loss target and sends them a weekly update on progress via text message. In a pilot randomised controlled trial, the researchers, led by **Professor Janet Cade**, compared the app to other ways of monitoring food intake - an online food diary and a traditional paper version. Over the six months of the study, those using the app lost on average 4.6kg (10lbs), compared with the 2.9kg (6.5lbs) and 1.3kg (3lbs) lost by the paper-based and online diary users, respectively[206]. A link to the app has been placed on the NHS Choices website. Since its launch in 2013, there have been between 10-50,000 downloads[207]. This is the only weight loss app supported by published peer-reviewed evidence.



Smartphone app, My Meal Mate

Project reference number: G0802108

Further funding: Investigation of healthy eating and lifestyle during pregnancy

Around one in five pregnant women in the UK are obese. Obesity is linked generally to poor health and also to pregnancy complications, such as gestational diabetes, high-blood pressure and pre-eclampsia, and miscarriage. **Dr Sharon Simpson** at **Cardiff University** is conducting a clinical trial[208] to evaluate the effectiveness of a weight management intervention in pregnancy on gestational weight gain, pregnancy and birth outcomes and weight at 12 months following birth. This study has since attracted £72,000 from Slimming World to follow up on the trial results.

Project reference number: G0802038

Neurodegeneration and neurology

Collaborations: Parkinson's and antioxidant compounds

Parkinson's disease is associated with a loss of dopamine-containing nerve cells in the mid-brain area. Dopamine is a neurotransmitter that plays a central role in motor control. Also common in a number of age-related neurodegenerative diseases is the misfolding of aggregated — or accumulated — proteins. The link between the two has so far been inconclusively proven, however, it has been suggested that misfolded insoluble proteins are toxic to nerve cells and that the aggregation may be a defensive means of alleviating the toxicity by removing the misfolded proteins[209,210,211]. There is increasing evidence that oxidative stress plays a major role in the death of nerve cells[212]. Researchers have shown that the abnormal protein aggregates in Parkinson's contain oxidatively-modified α-synuclein — a protein found in the tips of nerve cells in the brain — which shows a greater propensity to aggregate compared to non-oxidised α-synuclein.

Professor Tilo Kunath at the **MRC Centre for Regenerative Medicine** at the **University of Edinburgh** is currently testing a new antioxidant compound developed by Antoxis Ltd in a cell-based model of oxidative stress and Parkinson's disease.

Grant reference number: MR/J012831/1

Further funding: Biomarkers to study the progression of Parkinson's and Alzheimer's diseases

Professor David Brooks' research at **Imperial College London** involves the use of positron emission tomography (PET) and magnetic resonance imaging (MRI) to diagnose and study the progression of Alzheimer's and Parkinson's diseases.

He was awarded £250k in 2011 to lead the UK research centre of the Parkinson's Progression Markers Initiative (PPMI)[213] — a major international study into the progression of Parkinson's disease. Coordinated and part-funded by the Michael J Fox foundation, the study will involve 400 patients in Europe[214] and the US in the earliest stages of Parkinson's to identify key biomarkers for the disease.

Reliable and robust biomarkers to monitor the progression of Parkinson's, which affects around 127,000 people in the UK[215], would improve patient care, lead to new drugs and enhance understanding of the condition.

In this study, blood, urine, and spinal fluid samples will be taken from the patients, and analysed, along with data on motor skills and brain scans to track the progression of the disease.

The programme is working closely with industry partners, and is receiving support, either financial, or in-kind, from 15 different pharmaceutical companies, including Roche, GlaxoSmithKline, GE Healthcare and Pfizer.

Project reference number: G1100810

Impacts on the private sector: Floceleris

Floceleris
Accelerating drug discovery and diagnostics

Floceleris is a spin out from the **University of Cambridge** formed in 2012 by **Dr Damian Crowther** and colleagues. The company is developing a pre-symptomatic test to capture and measure the aggregation of amyloid beta peptides that occurs during neurodegeneration from clinical samples. The test will be used to find new drugs that inhibit disease progression and serve as a companion diagnostics tool to stratify patients and personalise treatments for Alzheimer's patients. In 2013 Dr Crowther was awarded the Carpe Diem Life Science Award for the best start-up company for Floceleris, in the University of Cambridge's Entrepreneurs Business Creation Competition[216].

Project reference number: G0700990

Collaborations: Investigating calcium regulation in Alzheimer's disease

Alzheimer's disease is a neurodegenerative disorder characterised by plaques —accumulated clumps — of the protein ß-amyloid and 'tangles' of the protein tau within nerve cells, which are associated with neuronal (nerve cell) death.

There is evidence that increased intraneuronal calcium concentration mediates neuronal toxicity. Sodium calcium exchangers (NCXs) play an important role in regulating intracellular concentration and there is some evidence that reduced NCX function may contribute to neurodegeneration[217].

Professor Wendy Noble at **King's College London** has shown that ß-amyloids mediate the cleavage of a sodium calcium exchanger (NCX3) and therefore that reduced NCX3 activity could contribute to the sustained increase in intraneuronal calcium concentrations associated with nerve cell dysfunction in Alzheimer's disease[218]. The University of California, San Francisco provided specific NCX antibodies enabling Professor Noble to use these to screen post-mortem neurodegenerative diseased brain.

Project reference number: G0700355

£€$ Further funding: Identification of biomarkers for disease progression in Alzheimer's disease

Dr Stephen Newhouse is a senior bioinformatician at the **MRC Social, Genetic and Developmental Psychiatry Centre**. His research is focused on the biomarkers of disease, including dementia and cardiovascular disease, and in 2012 he was awarded £131k from Janssen-Cilag to identify biomarkers for progression in Alzheimer's disease.

In an international study, he reviewed 163 previously identified candidate biomarkers for the progression of Alzheimer's disease and conducted a replication study for 94 of these. The study found that nine of the 94 biomarkers — such as complement C6 and pancreatic prohormone — were associated with Alzheimer's disease characteristics, suggesting that Alzheimer's disease does affect the protein constituents of the blood and should be considered for further investigations[219].

Project reference number: G9817803B

Natural protection

Collaborations: Complement UK

Professor Steven Sacks at the **MRC Centre for Transplantation** at **King's College London**, in partnership with **Professor Paul Morgan** at the **University of Cardiff**, set up Complement UK in 2009. Complement UK is a group of 40 UK scientists and clinicians at 20 centres whose recent work involves complement – part of the immune system. The primary goal of the partnership, which brings together expertise in structural biology, chemistry, immunology, genetics, protein therapeutics and imaging sciences, is to facilitate collaborative interdisciplinary research, particularly in rapidly growing areas where investigators need access to technical and scientific expertise and to large groups of patients. As a result of this collaboration, Alexion Pharmaceuticals Inc has funded four four-year PhD studentships in this field.

Project reference number: MR/J006742/1

Collaborations: Critical Care Alliance

Professor Paul Morgan at **Cardiff University** is also part of the Critical Care Alliance, a network of clinicians, mathematicians and physicists across South East Wales, South West England and West Midlands. The aim of this interdisciplinary alliance, set up in 2010, is to facilitate translational research in the area of sepsis and the critically

ill patient. In 2012 the alliance was awarded two grants from the Technology Strategy Board (TSB): Sepsis I - Multi-pathogen detection and/or simple discrimination and Sepsis II - Advancing biomarker use in sepsis management.

Collaborations: Identification of a new amyloidogenic variant of ß2-microglobulin

ß2-microglobulin is part of the major histocompatibility complex (MHC) proteins, present on almost every nucleated cell in the body. The function of the MHC is to bind fragments of proteins from within the cell derived from pathogens and display these to T cells – triggering cells containing foreign proteins to be attacked by the immune system. Excess ß2-microglobulin is only cleared from the body through the kidneys, so patients on long-term dialysis have an abundance in their blood. This then aggregates into amyloid — a type of insoluble protein — fibres that are deposited in bones and joints, causing painful arthritis, cysts and pathological fractures.

In 2011, Dr Sophie Valleis at the Cochin Institute in Paris identified a new amyloidosis-causing variant of ß2-microglobulin in patients at her clinical centre[220]. The affected patients have normal kidney function; but develop rare visceral amyloidosis that leads to bowel disease. **Professor Vittorio Bellotti** and his research team at **University College London** have fully characterised the protein and identified its mechanism of amyloidosis, shedding light on the molecular mechanism of this poorly understood process[221].

Project reference number: MR/K000187/1

Impacts on the private sector: Sannox Therapeutics

Sannox Therapeutics is a spin out based on the research of **Professor George Baillie** at the **University of Glasgow**. Professor Baillie is developing novel therapeutic agents to treat a number of diseases which have an unmet clinical need. The ultimate aim is to progress potential drugs to such a stage that they would be attractive to pharmaceutical companies or investors to take forward to the marketplace. Professor Baillie's team have developed a system in which they can interpret the interfaces of protein:protein interactions and produce peptides that disrupt specific protein complexes. The lab uses screening techniques to convert peptides into conventional small molecules that could also disrupt protein:protein interactions. It is hoped that this platform will lead to drugs with fewer side effects as the compounds target the cellular location of a particular protein or enzyme rather than its overall activity.

Project reference number: MR/J007412/1

Unexpected impacts

Collaborations: Breed identification of dogs

Dr Carri Westgarth at the **University of Liverpool** embarked on a collaboration with researchers at Canisius College in New York to investigate the perceptions of dog rescue centre workers on breed identification of dogs resembling pit bull terriers – restricted by breed-specific legislation in the UK. The researchers concluded that participants did not strongly agree on whether a dog was a pit bull, bringing into question the validity of determining breed identity based on appearance alone.

Project reference number: G1002402

Infectious diseases

Collaborations: Investigating the emergence of novel MRSA strains in cattle and their transmission to man

Professor Mark Holmes at the **University of Cambridge** has formed collaborations with the Health Protection Agency (HPA) and Statens Serum Institut (SSI) in Denmark to investigate the emergence of a new MRSA strain in cattle and humans. In 2011 MRSA strains with a *MecC* gene — a new form of the *MecA* gene, the gene present in MRSA that encodes a penicillin-binding protein — were identified to be present in cattle and humans[222]. The strain was undetectable by current diagnostic tests, a concern when trying to identify the source and transmission of infection. Professor Holmes has exchanged *S.aureus* isolates with both organisations, who have also undertaken functional analyses on the samples. Professor Holmes has conducted whole genome sequencing on the samples, which has led to the HPA implementing a diagnostic test based on this data in order to incorporate screening for *MecC* MRSA as part of their surveillance activity[223].

Project reference number: G1001787

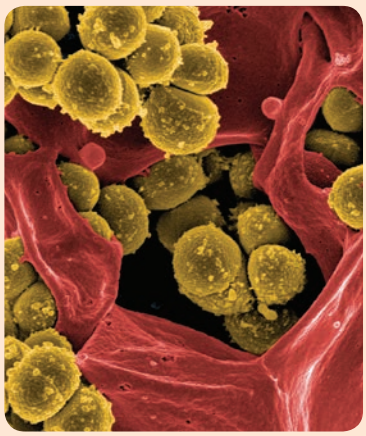
Impacts on the private sector: Prokarium

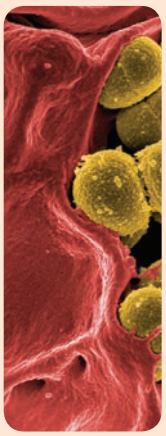
Professor Ian Henderson at the **University of Birmingham** sits on the scientific board of Prokarium, a spin out of Cobra Biologics. He is helping Prokarium develop a vaccine for Enterotoxigenic *Escherichia coli* (ETEC), the leading bacterial cause of diarrhoea in the developing world and which is responsible for between 300,000 and 500,000 deaths annually. In addition, every year more than 10 million travellers contract diarrhoea caused by ETEC, which costs €200m annually in medical resources within the EU, and accounts for €450m in lost productivity[231].

In 2013 the company received a £0.4m award from the TSB and BBSRC for the development of vaccines against ETEC and *Clostridium difficile* and the development of their oral vaccine platform Vaxonella.

Project reference number: G0900857

From cell biology to an MRSA vaccine





Impact summary

BBSRC and MRC-funded research contributed to the creation of spin out company Absynth Biologics by **Professor Simon Foster** and **Dr Jorge Garcia-Lara** from the **University of Sheffield**.

The company is developing vaccines against *S. aureus* and MRSA infection, and aims to enter preclinical development within three years.

The company also received further funding from the MRC and Technology Strategy Board via the Biomedical Catalyst to take forward the vaccine to a pre-clinical stage.

Fundamental research into the bacterium Staphylococcus aureus led to the creation of spinout company Absynth Biologics[1]. The company is now working to produce a vaccine against the bacterium, including methicillin-resistant *S. aureus*, or MRSA.

Absynth Biologics, founded in 2007 by Professor Simon Foster[2] and Dr Jorge Garcia-Lara from the University of Sheffield, has identified two promising protein targets for use in vaccines against *S. aureus*. The company aims to start preclinical development in the next few years.

"We had a finite number of targets, of which we've tested a number. We now have several lead targets, which are the basis of what Absynth is doing at the moment in terms of the *S. aureus* vaccine," says Foster.

Much of Foster's fundamental bioscience research, which led to the formation of Absynth Biologics, was funded by BBSRC. The MRC subsequently provided significant funding enabling Foster to study the interaction between *S. aureus* and humans, particularly how natural human defence mechanisms can be exploited to combat the bacterium's drug-resistance, and to develop the vaccine. Absynth has also obtained funding from the Technology Strategy Board[3]. Funded through the Biomedical Catalyst, these awards will help to take forward the vaccine to a pre-clinical stage.

The company is currently in a funding round with investors, which, if successful, will enable Absynth to grow and move to the next stage of product development.

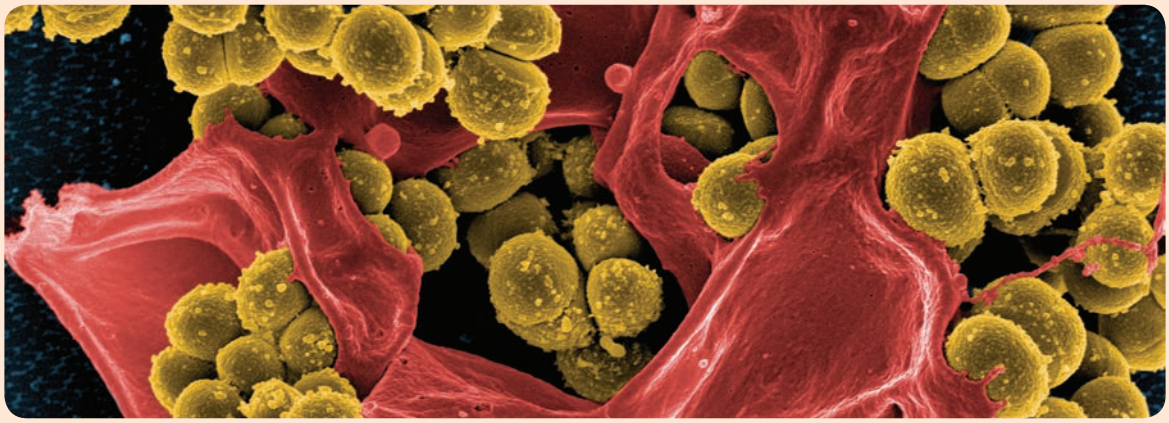
The superbug

S. aureus causes a wide range of infections, including septicaemia, endocarditis and wound abscesses. It is often resistant to antibiotics and one particular strain, methicillin-resistant *S. aureus* (MRSA), is the 'superbug' responsible for many hospital deaths.

It is a commensal organism, meaning that it lives alongside us all the time, and around one third of people carry it up their noses without suffering ill effects. Infections only occur when the bacteria are able to invade the body, for instance during a surgical procedure. In 2011 *S. aureus* was directly linked to 638 deaths in England and Wales, and MRSA killed 364 people in the same year[4]. MRSA was estimated to have killed over 11,400 people in the USA in 2010[5], and has led to many more infections and deaths around the world[7].

Antibiotics have been the conventional treatment for bacterial infection for 60 years. However antibiotic resistance is becoming a pressing concern[6]. Although some new antibiotics are being developed, it is likely that over time, a similar pattern of resistance will develop and so alternative strategies will be essential. One alternative is to generate protective immunity through vaccination.

A vaccine could help protect people in situations where they are most vulnerable to *S. aureus* and MRSA infections, particularly during elective surgeries such as knee, hip or heart valve replacements, reducing healthcare costs. It could also be used to vaccinate some groups against the



threat of 'community-associated' MRSA (i.e. an MRSA infection not associated with a medical setting); this includes people in care homes and prisons as well as the armed forces and hospital staff.

Ground-breaking research

Absynth Biologics arose from Foster's research into *S. aureus*. In particular, Foster's group had been studying genes in *S. aureus* that are essential to its survival, with support from BBSRC's Exploiting Genomics initiative; Garcia-Lara was the senior researcher on the grant.

The researchers used a genomics approach to identify over 200 potential essential genes in *S. aureus*. Several of the proteins encoded by these genes were associated with the cell membrane, but with loops or domains predicted to be on the outside, which could make suitable vaccine targets. However, the prevailing view was that these proteins were protected by the bacteria's impermeable cell wall so were unlikely to stimulate an immune response. Foster disagreed. "We had done a lot of work on cell wall structure and architecture over the years, and we knew the cell wall wasn't quite as impermeable as people might have thought."

With Follow-on funding from BBSRC in 2006, the team demonstrated that they could protect against *S. aureus* infection by vaccinating with a peptide derived from a loop of membrane protein, giving them a number of potential new vaccine targets. In particular, they focused on developing vaccines against proteins essential for the existence of *S. aureus* and its ability to cause disease. "The problem with many of the surface proteins is the bacteria alter them, or can do without them, so there is a lot of variability," says Foster. Absynth Biologics' initial funding enabled them to spend two years collecting more data. The researchers subsequently established a collaboration and license agreement with German company MorphoSys in 2010[7]. Subsequent funding from the MRC in 2011 allowed Professor Foster to test combinations of the vaccine targets and identify the most effective formulation for protection against *S. aureus*.

In 2012, Absynth received a feasibility award through the Biomedical Catalyst, a translational research programme run by the MRC and the Technology Strategy Board[8] to begin development of a vaccine. Following that, in 2013 Absynth received more than £2m from the Technology Strategy Board and the MRC, again through the Biomedical Catalyst and part-administered through the MRC's Developmental Pathway Funding Scheme (DPFS), to continue this work.

Notes and references

1. See: http://www.absynthbiologics.co.uk/
2. See: http://www.shef.ac.uk/mbb/staff/foster
3. £1,552,975 to Absynth and £460,731 to University of Sheffield for "Staphylococcus aureus Infections - Development of A Novel, Effective Vaccine"
4. See: http://www.guardian.co.uk/news/datablog/2012/aug/22/mrsa-related-deaths-fall-but-poor-still-worst-affected for an analysis of the data, and the ONS website for full details: http://www.ons.gov.uk/ons/publications/re-reference-tables.html?edition=tcm%3A77-266062
5. See: http://www.cdc.gov/abcs/reports-findings/survreports/mrsa10.html
6. See: http://www.who.int/mediacentre/factsheets/fs194/en/
7. See: http://www.absynthbiologics.co.uk/page/1n8x8/News.html#GRD%20award
8. Biomedical Catalyst: https://www.innovateuk.org/-/biomedical-catalyst#

Images: MRSA. *Image credit: National Institute of Allergy and Infectious Diseases (NIAID)*

Collaborations: Determining the structure of the *Plasmodium falciparum* cytosolic ribosome

In 2013 **Professor Sjors Scheres** at the **MRC Laboratory of Molecular Biology (LMB)** began collaborating with the Walter and Eliza Hall Institute of Medical Research (WEHI) in Australia to determine a preliminary structure of the *Plasmodium falciparum* cytosolic ribosome by cryo-EM single-particle analysis. The purified ribosome samples were provided by WEHI. Malaria is caused by infection with parasites of the genus *Plasmodium* and affects 300 million people each year, resulting in one million deaths. The ribosome is essential for protein synthesis and details of the parasite's specific ribosome structure may lead to the rational design of new treatments for the disease.

Project reference number: MC_UP_A025_1013

Sexual development

Collaborations: Molecular genetics of sexual development

Dr Andy Greenfield at **MRC Harwell** studies the molecular genetics of sexual development. In 2011 he embarked on a collaboration with researchers at the Pasteur Institute in Paris to assess the role of p38 MAPK signalling in mouse testis determination. The Pasteur Institute supplied Dr Greenfield with mouse mutant material and data concerning gene mutations in patients with disorders of sexual development.

Project reference number: MC_U142684167

Rare diseases

Collaborations: UK10K project

The UK10K project is a major collaboration among several leading academic and research institutions including the MRC, Wellcome Trust, Department of Health, Bristol University and King's College London.

The project, which started in 2010, aims to better understand the link between rare and low-frequency gene mutations and human disease by studying the genetic code of 10,000 people in great detail.

Several MRC researchers are involved in the project, including **Professor Peter Scambler** at **University College London** who has helped identify several new genes involved in ciliopathy spectrum disorders. These are genetic diseases of the cellular cilia, slender organelles that protrude from the larger cell body, such as those lining the windpipe, where they sweep mucus and dirt out of the lungs. Results include the identification of gene mutations causing jeune asphyxiating thoracic dystrophy (JATD), a sometimes lethal disease characterised by shortened ribs and long bones, accompanied by renal, liver and retinal disease[232], Mainzer-Saldino syndrome, characterised by retinal degeneration and kidney disease[233] and primary ciliary dyskinesia, that causes a defect in the action of the cilia lining the respiratory tract, fallopian tube in females, and the flagella of sperm in males, resulting in respiratory infections and infertility[234].

Project reference number: G9901217

Global Health

Further funding: African partnership for chronic disease research

Professor Manjinder Sandhu at the **University of Cambridge** and the **Wellcome Trust Sanger Institute** is the lead researcher for the African partnership for chronic disease research (APCDR), funded by the MRC until 2018. The APCDR is an international partnership comprising 18 centres from 12 different countries set up to assess the burden and causes of non-communicable diseases such as diabetes and heart disease in sub-Saharan Africa. Professor Sandhu's team is providing expertise in the genomics of chronic disease, informatics, and epidemiology, and providing access to high throughput next-generation sequencing. Expertise from the different centres ranges from the epidemiology of diabetes and cardiovascular disease in African populations to bioethics and population-based surveys and interventions. The African centres are also providing resources and infrastructure for sample collection (clinics and field stations) and analyses.

The collaboration has already attracted two further funding awards - £2.55m from the Wellcome Trust to study the burden, spectrum and cause of type 2 diabetes in sub-Saharan Africa and an additional MRC grant of £885k to assess the burden and cause of non-communicable diseases.

The partnership is also taking part in several on-going projects including the African Genome Variation project, led by the Wellcome Trust Sanger Institute, and an HIV/anti-retroviral therapy/non-communicable disease meta-analysis.

Project reference number: G0901213

Regenerative medicine

Further funding: Neural stem cell transplantation as treatment for multiple sclerosis

Dr Stefano Pluchino at the **Wellcome Trust-MRC Cambridge Stem Cell Institute** has previously shown that the systematic injection of adult neural stem cells protects the central nervous system (CNS) from the degeneration induced by inflammation in small rodents and non-human primates with experimental MS, ischemic stroke or spinal cord injury[235,236]. He is currently studying the cellular and molecular mechanisms regulating stem cell plasticity — the ability to give rise to cell types sited in a different location to where they are found — in pre-clinical models of complex CNS diseases such as multiple sclerosis and spinal cord injury. In 2011 Dr Pluchino was awarded £171k from Banca Agricola Popolare di Ragusa (BAPR) – the agricultural cooperative bank of Ragusa for the *"somatic neural stem cell transplantation as novel therapeutic approach for the treatment of multiple sclerosis."*

Project reference number: G0800784

Impacts on the private sector: DefiniGEN

DefiniGEN is a **University of Cambridge** spin out formed in 2012 to supply human induced pluripotent stem cells (hIPSC)-derived liver cells to the drug discovery and regenerative medicine sectors[237]. The company is based on the research of **Dr Ludovic Vallier** and his team at the **Anne McLaren Laboratory of Regenerative Medicine**. Dr Vallier's team developed the technology that has the ability to produce hepatocytes in a highly reproducible and scalable manner for commercial use. This is a major breakthrough in the costly and time-consuming process of

developing new therapies. Demonstrating that a new drug candidate is free from liver toxicity is a key part of the drug development process. Currently, either primary human hepatocytes or immortalised cell lines are used for toxicity testing. Primary hepatocytes have a high degree of batch-to-batch variation, are expensive and difficult to obtain in suitable quantities, while immortalised cell lines are an inferior model for toxicity testing. The hIPSC-derived cells produced by DefiniGEN, however, show many of the functional characteristics of primary cells, are highly reproducible and can be made in large quantities, making them ideal for toxicity testing. The technology has also been used to effectively model a diverse range of inherited liver diseases and has the potential to accelerate the development of new therapies for these conditions.

Project reference number: G0701448

Environmental exposures and child health

£€$ Further funding: Developing biomarkers for subclinical atherosclerosis

As part of the European Commission's Framework Programme 7 (FP7), the **MRC/DH Centre for Environment and Health** at **Imperial College London** has been awarded £641k for the study of novel tools to integrate early-life environmental exposures and child health across Europe and £2.5m to develop biomarkers for subclinical atherosclerosis, a potentially serious condition where arteries become clogged up by substances such as cholesterol.

Project reference number: G0801056

Musculoskeletal health

£€$ Further funding: Effects of musculoskeletal health on extended working lives

The current rises in life-expectancy, the subsequent increase in numbers of older people and increasing pension costs has prompted government policies to extend working lives. By 2034 the number of people aged 85 and over is projected to be 2.5 times larger than 2009, reaching 3.5 million and accounting for five per cent of the population[238]. However, working for an extended period of time may not be feasible for those with major, or chronic health problems. 58 per cent of those aged 60 and over report having a long-term condition, with 25 per cent of over 60s having two or more.

Information on the factors that influence work participation at older ages can be used to optimise government and employer policies to identify interventions to help older workers and to improve the design of work for older people.

Professor David Coggon leads a programme of epidemiological research on the inter-relation of work and health, aimed at informing policy and clinical practice, at the **MRC Lifecourse Epidemiology Unit, University of Southampton**. In 2012 he was awarded £180k from Arthritis UK to study the effects of musculoskeletal health on extended working lives.

Project reference number: MC_UU_12011/5

Reproductive health

Impacts on the private sector: Icthus Therapeutics

Icthus Therapeutics is a new spin out from the **University of Edinburgh's College of Medicine and Veterinary Medicine** focused on women's health, and in particular on endometriosis. The founders are academics and clinicians from the NHS's Centre for Reproductive Health and the Royal Infirmary of Edinburgh and include **Dr Andrew Horne**. The company is funding 'PURFECT' - a pilot clinical trial to determine whether purified fatty acids are effective in the treatment of endometriosis-associated pelvic pain.

Project reference number: G0802808

Epigenetics

Impacts on the private sector: Cambridge Epigenetix

Cambridge Epigenetix is a biosciences company based on oxidative bisulfite sequencing intellectual property that was spun out of **Cambridge University** in 2012. Bisulfite sequencing is the use of bisulphite treatment of DNA to determine its pattern of methylation. DNA methylation, whereby a methyl group is added to a cytosine or base, is an epigenetic mechanism that cells use to control gene expression. Treatment of DNA with bisulphite converts the DNA base cytosine to the RNA base uracil, but leaves 5-methylcytosine (5-mC), the methylated form of cytosine, unaffected. Thus, bisulphite treatment introduces specific changes in the DNA sequence that depend on the methylation status of individual cytosine residues, yielding single- nucleotide resolution information about the methylation status of a segment of DNA.

Recent studies have shown that at some sites in the genome, the level of 5-Hydroxymethylcytosine (5-hmC), a new mammalian DNA modification, can be comparable to the level of 5-mC, emphasising the importance of identifying these variants accurately. However, traditional bisulfite sequencing cannot discriminate between 5-hmC and 5-mC.

In 2013, the company published the results of a successful beta trial evaluating their pioneering TrueMethyl™ oxidative bisulfite sequencing technology[239]. TrueMethyl utilises a selective chemical oxidation that accurately distinguishes between 5-mC and 5-hmC. It enables analysis of the DNA methylome with unprecdented accuracy and opens new avenues for basic research, pharmaceutical discovery and diagnostics.

Playing a key role in the product validation process and assisting the company in the understanding of epigenetic science were 13 leading epigenetics labs around the world. These included **Professor Wolf Reik** at the **BBSRC Babraham Institute**.

Project reference number: G0801156

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MRC Medical Research Council

Outputs, outcomes and impact of MRC research: 2013/14 report

SECTION 2.5: Awards and recognition

Awards and recognition

The MRC values the 'measures of esteem' afforded to our researchers. Awards, prizes and other forms of acknowledgement are a worthy recognition of the quality of research undertaken by MRC scientists. Certain measures, such as being appointed to the editorial board of a journal or attracting visiting staff, can also be seen to have a wider impact on the research and teaching community. Measures of esteem are used internationally by some funders alongside citation analysis, peer review and research income as indicators of research quality[240].

The MRC seeks details of the prizes, awards and other types of recognition received by MRC researchers in order to better understand the ways in which researchers are recognised for their contributions to academia and the wider society.

It is quite clear that MRC researchers often work hard to enhance the science base and wider society far beyond pursuing their specific funded research interests. We cannot do justice in this chapter to the varied and important ways in which MRC researchers are quite properly recognised for this work.

A small selection of the ways in which our scientists have reported being recognised can be found throughout this chapter of the report, characterised by the following:

- Appointed to the editorial board of a journal or book series
- Membership of learned societies
- Attracted visiting staff or internships to laboratory
- Research prizes
- 2013 Orders of Chivalry

Appointed to the editorial board of a journal or book series

An engaged and expert editorial board is essential to the success of peer-reviewed journals[241]. Rost and Frey consider membership of the academic editorial board of a professional journal to be an integral indicator of research quality as it demonstrates a scholar's reputation and recognition among peers. It recognises their contributions to the research community in terms of reading and reviewing the work of others[243].

Researchers primarily reported appointments to the editorial boards of journals, including renowned publications such as *Science*, *Cell and Nature*, and a small number gave details of editing or producing content for a book. Such recognition yielded significant impact for researchers. This included:

- An increase in international profile for them and their research group.
- A subsequent increase in opportunities for international collaborations and networking.
- Being able to influence the strategic direction and scientific priorities of the journal in question
- Increasing the awareness of a particular scientific field by helping to disseminate the outputs of a particular study.
- Researchers also reported that this type of recognition enabled them to develop a greater awareness of the publication process and enhanced knowledge of the area of research in other regions of the world.

Professor Neil Ferguson at **Imperial College London** was a founding editor of *PLOS Current Outbreaks*, an Open Access publication channel for the rapid communication of new research in all aspects of infectious disease outbreaks.

Professor Ian Young at **Queen's University of Belfast** was appointed as a guest editor of the special issue of *Systematic Reviews* in 2013 to celebrate the 20th anniversary of The Cochrane Collaboration.

Dr Stephen Chapman at the **University of Oxford** was appointed, in 2013, joint editor-in-chief of new journal *BMJ Open Respiratory Research*, an online, open access, international respiratory medicine journal published by the BMJ in partnership with the British Thoracic Society.

Dr Lawrence Moon at **King's College London** was appointed to the advisory board of *Brain* in 2014 as a result of his membership of a working group and steering committee on the use of animals in research and design of experiments using animals. His aim is to improve experimental design using animals by persuading *Brain's* editorial board to require manuscript authors to report how experiments using animals were blinded and randomised, and if not, to justify why not.

Membership of learned societies

MRC researchers reported being made a Fellow of several learned societies, including Fellows of the Academy of Medical Sciences, the Royal Society, the Royal Society of Edinburgh and the Society of Biology. Being awarded a Fellowship of these societies is a testament to the researchers' exceptional contributions to, and eminence in, the research field.

Each year, the Royal Society elects up to 52 new fellows, from a group of more than 700 nominations made by the existing Fellowship, through a peer-review process that culminates in a vote by current fellows.

The Academy of Medical Sciences elected 44 new Fellows in 2013, bringing their total to 1,094; the Royal Society of Edinburgh elected 47 new Fellows in 2013, which brought their total to more than 1,500.

Researchers reported that this recognition also increased the profile of the individual and group, leading to increased opportunities for networking and collaboration and enhanced awareness of the scientist's particular field.

Attracted visiting staff or internships to laboratory

Many MRC researchers attracted visiting staff or internships to their laboratories – an indication of the wide reach of their reputation within their field. These included visiting researchers from around the world aiming to learn or refine techniques or scientific methods, and hosting those holding scholarships or fellowships and visiting collaborators.

Dr Eva Petermann at the **University of Birmingham** reported the visit of a PhD student from Germany to learn DNA replication methodology.

Dr Jonathan Powell at the **Human Nutrition Research Group** hosted a group of 10 visiting workers and students from various universities around the world who worked on specific projects within the research group.

Dr Peter Thelwall at the **University of Newcastle** hosted staff from the University of Edinburgh to observe and learn techniques for *in vivo* 13C magnetic resonance spectroscopy, with the aim of using the techniques in research

programmes at their university. This broadened collaborative network increased his profile in the field and yielded discussions regarding future research applications and directions.

Professor David Brooks at **Imperial College London** hosted a doctor from University Hospital Pisa who wanted to gain experience in PET imaging and dementia research.

Dr Jennifer Gregory from the **University of Aberdeen** reported the visit in August-September 2013 of a clinical research fellow from the United States as part of a three-year NIH award. The fellow learnt about bone analysis techniques which could be applied to her study. The visit led to a collaboration between the two institutions resulting in the development of a new model for examining the shape of ankle bones in osteoarthritis. Data from this visit has been used to apply for funding to develop this collaboration.

Research prizes

Award holders highlighted a large number of reports of prizes awarded either to the principal investigators personally or to a member of their team. Researchers reported prizes being awarded for a variety of reasons, including posters and presentations (often made by students or early-career scientists), good science communication, academic papers and lifetime achievement.

The primary reported impact of such recognition was the increased profile of the scientist and of their work. Others received grants or invitations to present at prestigious conferences and many reported increased career progression opportunities.

Professor Jim Smith, director of the **MRC National Institute for Medical Research**[242] was awarded the 2013 **Waddington Medal.** The Waddington Medal is the only national award in developmental biology and is awarded for outstanding research performance as well as services to the subject community.

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Professor Venki Ramakrishnan at the **MRC Laboratory of Molecular Medicine** was awarded the 2012 Federation of European Biochemical Societies (FEBS) **Sir Hans Krebs Lecture and Medal** for outstanding achievements in the field of biochemistry for his work on the structure and function of the ribosome.

Research led by **Professor Simon Griffin** and **Dr Rebecca Simmons** at the **MRC Epidemiology Unit, University of Southampton**, has won the British Medical Journal's prestigious **Research Paper of the Year** award in 2013. The paper presents the results of the ADDITION study which was the first robust evaluation of diabetes screening and suggested that its effectiveness may have been overestimated[244]. The authors concluded that screening is only likely to benefit the small minority of people with undiagnosed diabetes and is unlikely to reduce deaths in the general population.

The Cardiff University team. Image credit: BMJ

A team at **Cardiff University**, led by **Professor Alison Kemp** and **Dr Sabine Maguire**, was awarded the *British Medical Journal's* **Child Health Team of the Year** award in 2013. The team has developed an internationally-recognised methodology for systematically reviewing world literature with regard to child abuse and neglect. Over the past ten years, their focus has been on the recognition and investigation of suspected abuse or maltreatment, providing current and accessible literature, while also recommending a research agenda for those working within the field. The BMJ awards help to celebrate those who make a valuable contribution towards improving the quality of healthcare.

Professor Matthew Walker at **University College London** was made an **International League Against Epilepsy (ILAE) Ambassador** in 2013 in recognition of outstanding international contributions to activities advancing the cause of epilepsy, either internationally or with international impact. Professor Walker has organised international workshops in epilepsy and neuroscience and contributed to the SIGN epilepsy guidelines[245]. He also co-produced the BBC website's guide on epilepsy and wrote the British Medical Association educational module on status epilepticus.

Dr Conor Farrington at the **Open University** was awarded the Royal Statistical Society's **Bradford Hill medal** in 2013 for his development of the self-controlled case series method[246] and outbreak detection systems. Dr Farrington developed the world's first comprehensive, automated outbreak detection system which is capable of monitoring more than 3,000 infections and was used during the 2012 Olympics.

The Bradford Hill Medal is awarded every three years to a Fellow of the Society in recognition of 'outstanding or influential contributions to the development, application or exposition of medical statistics'[247].

Professor Cyrus Cooper, director of the **MRC Epidemiology Unit** was awarded the **International Osteoporosis Foundation (IOF) Medal of Achievement** for significantly advancing the field of osteoporosis through original and outstanding scientific contributions. Professor Cooper's key research contributions include: discovery of the developmental influences which contribute to the risk of osteoporosis and hip fracture in late adulthood; demonstration that maternal vitamin D insufficiency is associated with sub-optimal bone mineral accrual in childhood; characterisation of the definition and incidence rates of vertebral fractures; leadership of large pragmatic randomised controlled trials of calcium and vitamin D supplementation in the elderly as immediate preventative strategies against hip fracture.

Dr Liz Sampson at **University College London** was awarded the **William Farr medal** by the Worshipful Society of Apothecaries in 2014 for her contribution to the care of older people with dementia in the acute hospital, particularly with regards to pain and end-of-life care.

The William Farr Medal is for medical practitioners who have made a particularly significant contribution in any clinically related or research discipline to the management of elderly people as part of original work in the UK. The Worshipful Society of Apothecaries of London wishes to acknowledge innovations in the care of the elderly and particularly encourages the nomination of those in the middle of their career.

Professor Doug Higgs at the **MRC Molecular Haematology** Unit was awarded the Royal Society's **Buchanan Medal** in 2013. The Buchanan Medal is awarded biennially 'in recognition of distinguished contribution to the medical sciences generally.'[248] Professor Higgs was awarded the medal for his seminal work on the regulation of the human alpha-globin gene cluster and the role of the ATRX protein in genetic disease.

The **Grete Lundbeck European Brain Research Prize** – 'The Brain Prize' – is awarded to one or more scientists who have distinguished themselves by an outstanding contribution to European neuroscience. It was presented to **Professor Peter Somogyi**, director of the **MRC Anatomical Neuropharmacology Unit** in 2011, **Professor Gero Miesenböck** at the **University of Oxford** in 2013 and **Professor Trevor Robbins** at the **University of Cambridge** in 2014.

2011

With Professors Tamás Freund and György Buzsáki, Professor Peter Somogyi was recognised for his *'wide-ranging, technically and conceptually brilliant research on the functional organization of neuronal circuits in the cerebral cortex, especially in the hippocampus, a region that is crucial for certain forms of memory.'*[249]

2013

Together with fellow researchers, Professor Gero Miesenböck was awarded the prize for the *'invention and refinement of optogenetics. This revolutionary technique allows genetically specified populations of neurons to be turned on or off with light, offering not only the ability to elucidate the characteristics of normal and abnormal neural circuitry, but also new approaches to treatment of brain disorders.'*[250]

2014

Professor Trevor Robbins, alongside Professors Stanislas Dehaene and Giacomo Rizzolatti, was awarded the 2014 prize for his *'pioneering research on higher brain mechanisms underpinning such complex human functions as literacy, numeracy, motivated behaviour and social cognition, and for their efforts to understand cognitive and behavioural disorders.'*[251]

The **MRC Millennium Medal**, which recognises MRC-funded scientists for outstanding research, was awarded jointly in 2013 to **Professor Sir Philip Cohen**, former director of the **MRC Protein Phosphorylation Unit** and **Professor Sir Greg Winter**, formerly of the **MRC Laboratory of Molecular Biology**.

2013 Orders of Chivalry

Professor Nicola Cullum at the **University of Manchester** was appointed as a **Dame Commander of the Order of the British Empire** for **services to nursing research and wound care**. Professor Cullum is one of the UK's leading nurse researchers. She has led major multi-centre trials which have delivered significant impact on nursing practice and also founded the Cochrane Wounds Group, the world's first centre for evidence-based nursing[252].

Professor Anne Johnson was appointed as a **Dame Commander of the Order of the British Empire** for **services to the study of infectious diseases**. Professor Johnson has studied the epidemiology and prevention of HIV and sexually-transmitted diseases and other infectious diseases for over 25 years. She co-directed the MRC's UK Centre for Co-ordinating Epidemiological Studies of HIV and AIDS from 1985 until 1999 and has led the three National Surveys of Sexual Attitudes and Lifestyles.

Professor Carol Robinson was appointed as a **Dame Commander of the Order of the British Empire** for **services to science and industry**. Professor Robinson is widely recognised for her ground-breaking research in mass spectrometry and as a role model for female scientists.

Professor Stephen O'Rahilly has been appointed a **Knight Bachelor** for **services to medical research**. Professor O'Rahilly is a leading clinical researcher in the field of metabolic disorders and is renowned for combining clinical practice with scientific and clinical studies focused on understanding the causes and consequences of obesity and insulin resistance.

Professor Peng Tee Khaw at **University College London** was appointed as a **Knight Bachelor** for **services to ophthalmology**. Professor Khaw is a master of innovation in his field by developing new therapies, particularly for scarring. He has developed surgical techniques — such as the Moorfields Safer Surgery System — which have markedly improved the safety and outcome of glaucoma surgery and new anti-scarring regimens based on laboratory research, leading to large international clinical trials and use. These treatments and techniques have been successfully adapted for use in many parts of the developing world at minimal cost.

Professor Wendy Atkin at **Imperial College London** was awarded an **Order of the British Empire** for **services to bowel cancer prevention**. Professor Atkin led the flexi-scope study, a large trial of a bowel-screening technique which allows doctors to both detect the early stages of bowel cancer and remove precancerous polyps to prevent bowel cancer from developing.

Professor Jenny Donovan at the **University of Bristol** was awarded an **Order of the British Empire** for **services to social medicine**. Professor Donovan is the principal investigator of research grants valued at more than £45 million, including the NIHR-HTA programme-funded ProtecT randomised controlled trial – now the largest study in the world evaluating treatments for localised prostate cancer. She is involved in a wide range of other projects using molecular, clinical and social science approaches, as well as leading innovative qualitative research in randomised controlled trials.

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MRC Medical Research Council

Outputs, outcomes and impact of MRC research: 2013/14 report

SECTION 03: Quantitative analysis

3.1: Publications

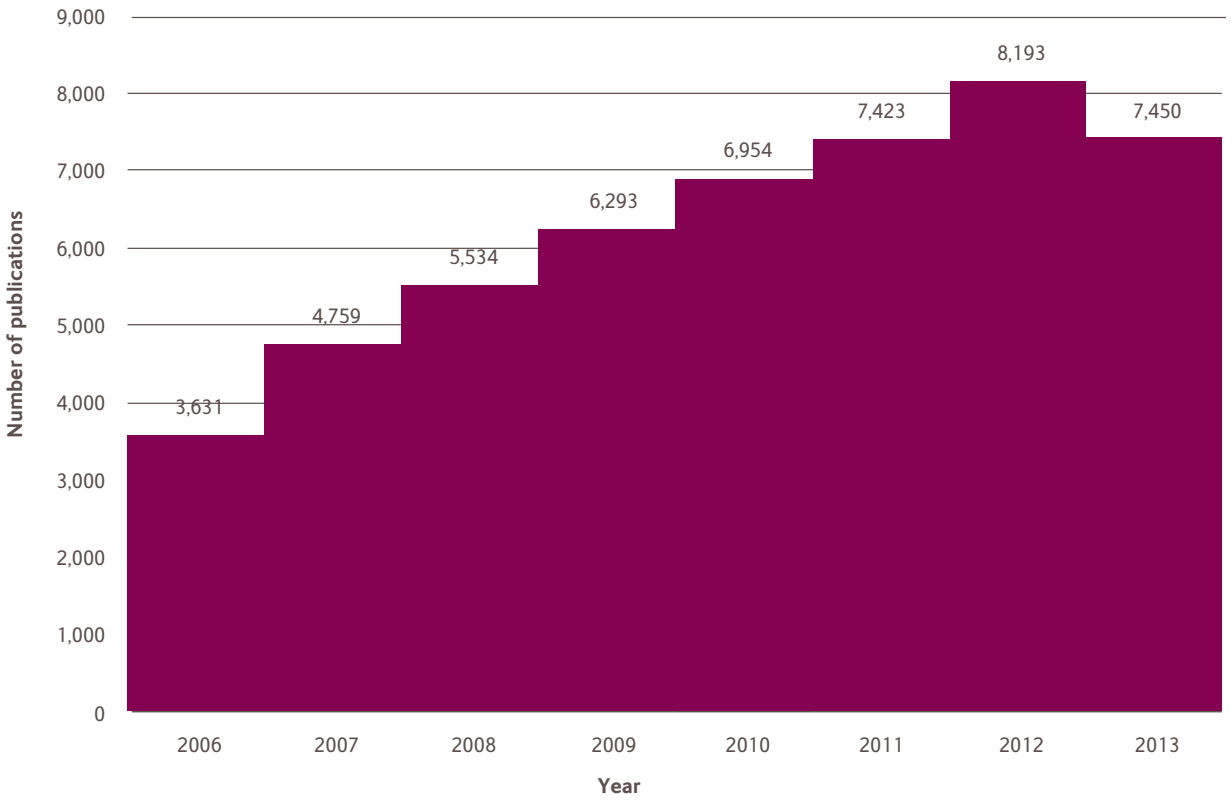
Summary

- MRC researchers reported publications[253] resulting, either wholly or in part, from MRC funding in 82 per cent of awards[254].
- There were 71,786 reports of publications, of which 51,520 are unique publications. Table 1 and figure 1 show the number of publications for each year since 2006. Please note that data for 2013 is partial.
- The average number of publications per award reporting at least one publication was 16 (15.81).
- A fifth of all awards (20 per cent) reported the generation of more than 16 publications.

Table 1: *Number of publications for each year since 2006*

2006	2007	2008	2009	2010	2011	2012	2013
3,631	4,759	5,534	6,293	6,954	7,423	8,193	7,450

Figure 1: *Number of publications for each year since 2006*



Publications by year

- 90 per cent of awards starting in 2006 or earlier have yielded at least one publication. Publications take time to produce and recent awards will naturally be less likely to have resulted in a publication. However, almost two thirds (60 per cent) of awards starting in 2012 and one third (33 per cent) of awards starting in 2013 have still resulted in at least one publication so far. Table 2 and figure 2 show the distribution of publications by award start year.
- Recipients of 25 per cent of awards reported their first publication within one year of the start of the award. This had increased to 82 per cent after five years. The time between the start of the award and report of first publication is shown in table 3 and figure 3.

Table 2: *Distribution of publications by award start year*

Start year	Number of awards	Number with at least one publication	Number with no publications	Percentage with at least one publication
2006 or earlier	2,076	1,864	212	90%
2007	466	425	41	91%
2008	569	517	52	91%
2009	565	505	60	89%
2010	470	418	52	89%
2011	410	340	70	83%
2012	525	316	209	60%
2013	481	156	325	32%

Figure 2: *Distribution of publications by award start year*

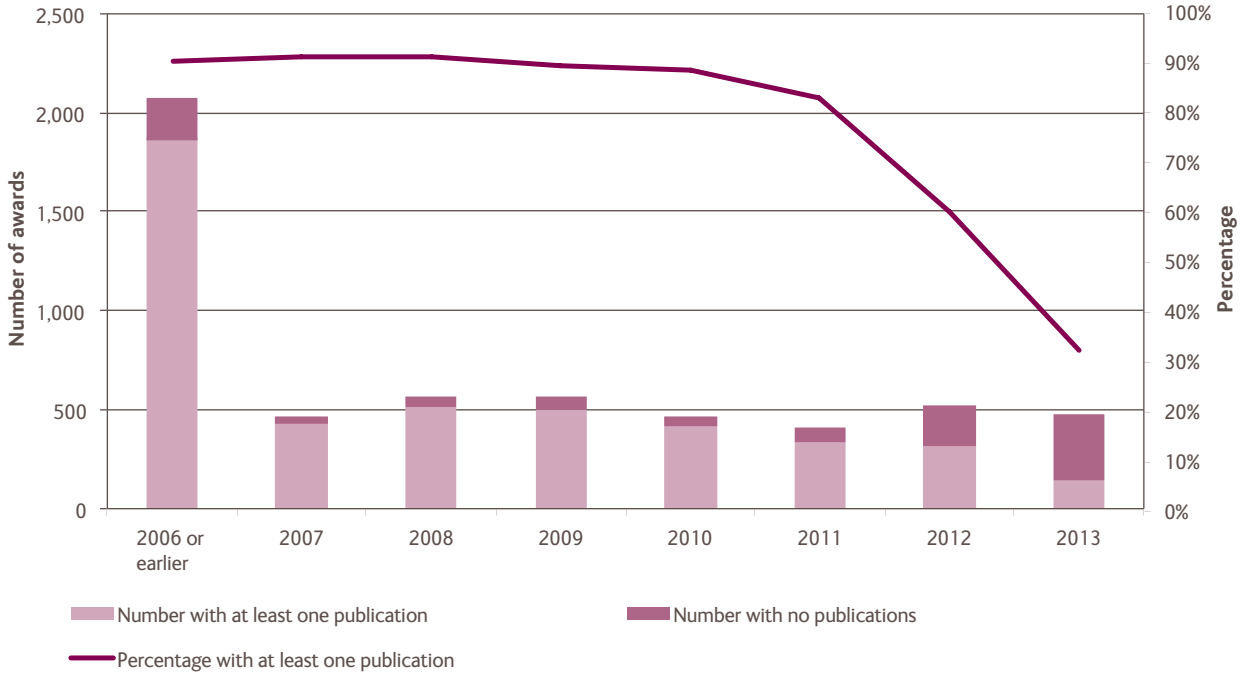


Table 3: *Time to report first publication by number of awards*

First publication	Number reporting	Cumulative number	Cumulative percentage
Within 1 year	1,378	1,378	25%
Within 2 years	1,150	2,528	45%
Within 3 years	758	3,286	59%
Within 4 years	461	3,747	67%
After 5 years	794	4,541	82%

Figure 3: *Time to report first publication by number of awards*

Publications by co-author

Co-authorship of publications provides an insight into the patterns of research collaboration; it can indicate the variety and even duration of collaborations. Thompson Reuters returns bibliographic information on MRC papers, including the names and addresses of all co-authors on a paper. The address data includes country information and this is used for basic geographic analysis. The address data however does not include information on the sector of the co-author. Further analysis on this is not currently available; however, a supplementary report on this will be published at a later date.

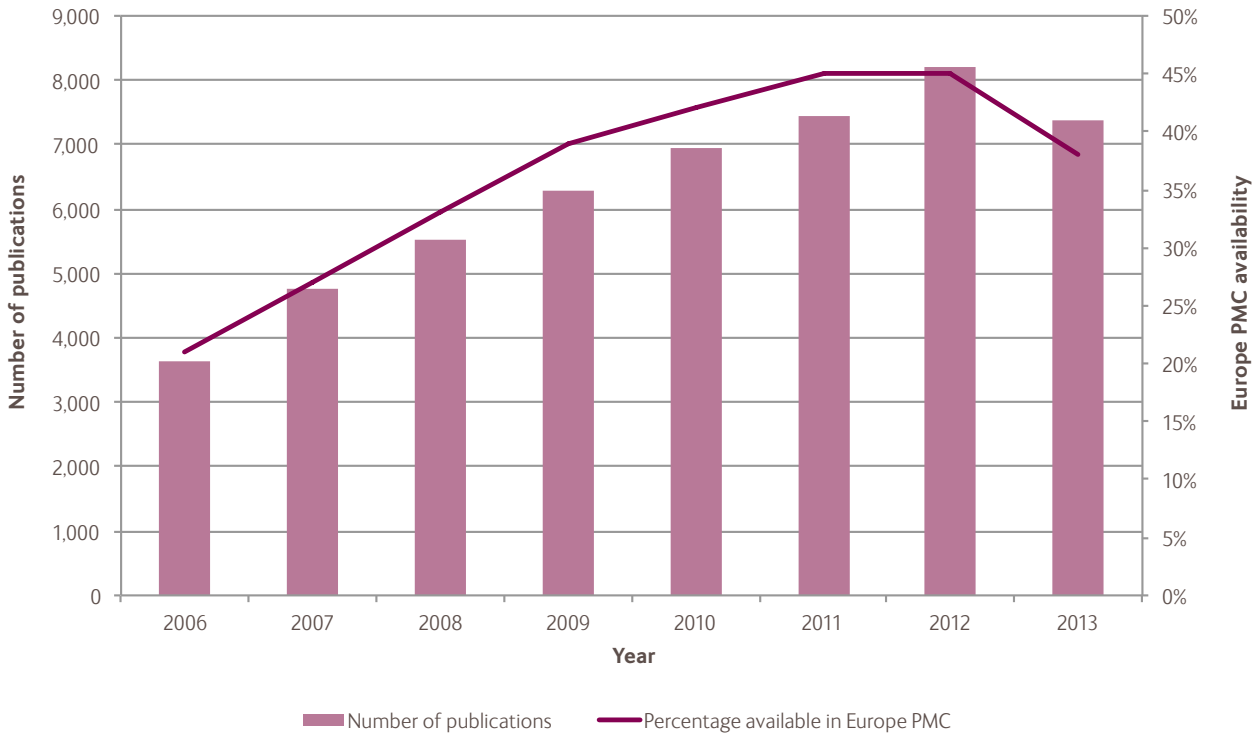
Open Access

Figure 4 shows the proportion of unique MRC publications produced each year that are currently available in Europe PMC (as at July 2014). The proportion of papers reported via Researchfish, published in 2013, that are openly accessible in Europe PMC is 38 per cent. It should be noted that this will include publications that are not subject to the Open Access policy (for example, books).

Due to time lags in publishing, ID assignment and Europe PMC processing, one would expect lower absolute numbers of publications and proportional compliance in the most recent year, and that these would increase with the next data gathering period.

We will work with Europe PMC to obtain further information about whether these papers were openly accessible within six months of publication, and to filter our results with respect to publication types that have to comply with the Open Access policy.

Figure 4: *Europe PMC availability by publication year*



3.2: Collaborations

Summary

- Recipients of 52 per cent (2,917) of awards reported that they had established a collaboration which they could evidence, for example with co-publications, co-funding or exchange of materials and expertise.
- The average number of collaborators[255] linked to awards reporting at least one collaboration was 5 (5.42), a slight increase on last year's figure (5.28).
- Six per cent (339) of awards were highly collaborative, with these recipients reporting at least 10 different collaborators.

Collaborators by year

- It takes time for researchers to set up collaborations and so there will naturally be fewer collaborations resulting from more recent awards. Recipients of 62 per cent of awards starting in 2006 or earlier had collaborations linked to them compared to 17 per cent of awards starting in 2013. The number of collaborators per award by starting year of the award is shown in table 1 and figure 1.
- 22 per cent of awards reported at least one collaboration within one year of the award starting, compared to 52 per cent after five years. The time between the award start date and collaboration starting is shown in table 2 and figure 2.

Table 1: *Number of collaborators by award start date*

Start year	Number of awards	Number with at least one collaborator	Number with no collaborators	Percentage with at least one collaborator
2006 or earlier	2,076	1,291	785	62%
2007	466	256	210	55%
2008	569	348	221	61%
2009	565	346	219	61%
2010	470	256	214	54%
2011	410	168	242	41%
2012	525	173	352	33%
2013	478	79	399	17%

Figure 1: *Number of collaborators by award start date*

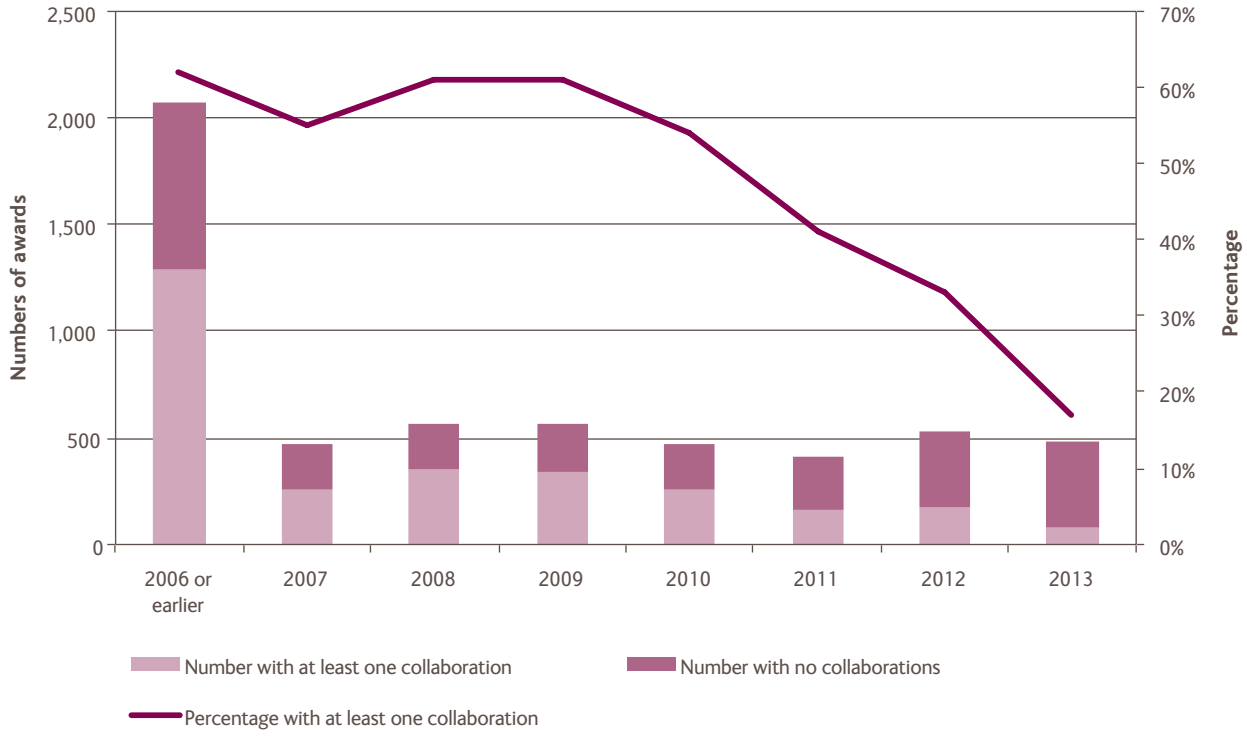
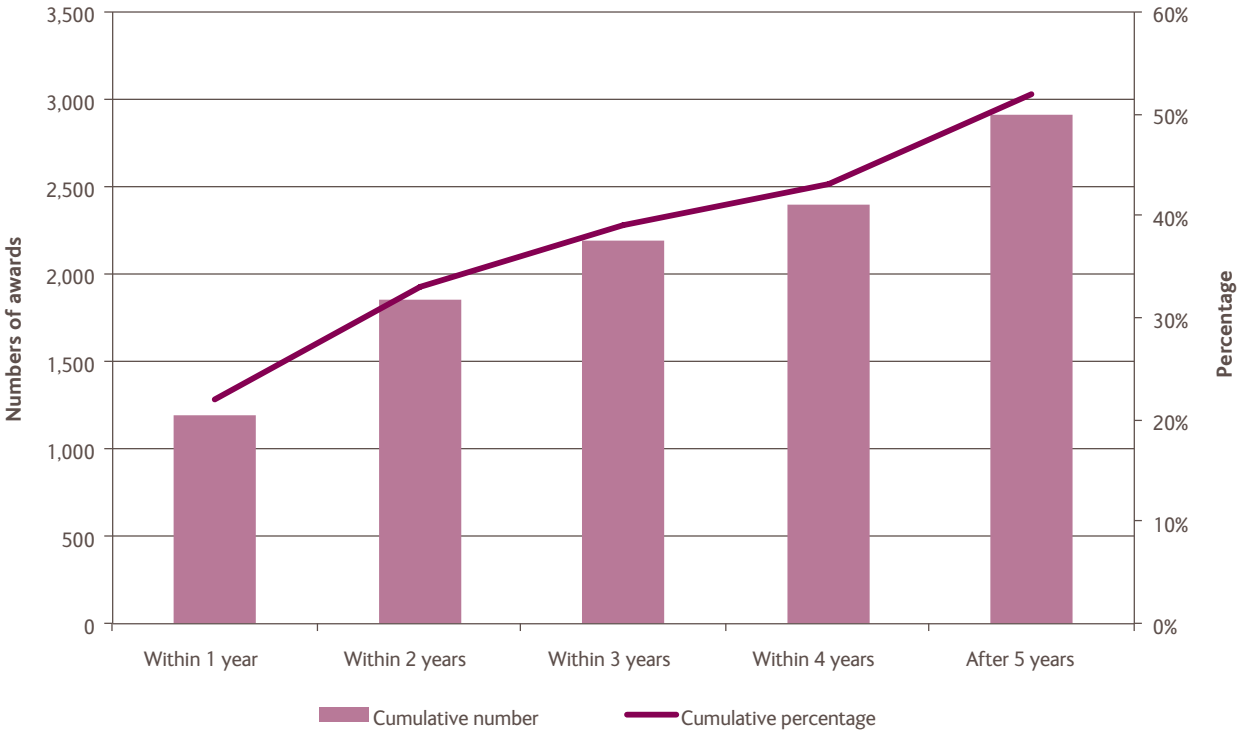


Table 2: *Time between award start date and collaboration*

First collaboration	Number reporting	Cumulative number	Cumulative percentage
Within 1 year	1,197	1,197	22%
Within 2 years	652	1,849	33%
Within 3 years	341	2,190	39%
Within 4 years	211	2,401	43%
After 5 years	516	2,917	52%

Figure 2: *Time between award start date and start of first collaboration*



Collaborators by location

- The majority of collaborators were from the United Kingdom (55 per cent), followed by the rest of Europe (17 per cent) and North America (12 per cent)[256].
- Table 3 shows the numbers of collaborators by location. Figures 3 and 4 illustrate the distribution of international (excluding Europe) and European (excluding UK) collaborators respectively[257].
- Figure 5 shows the top 25 location countries (excluding the UK) for collaborators. There is very little change from last year with just Italy and Canada swapping places, and Switzerland and Denmark swapping places within the top 15.

Table 3: *Number of collaborators by location*

Location of collaborator	Number of collaborators	Percentage of total
United Kingdom	8,162	55%
Europe	2,595	17%
North America	1,728	12%
South America	67	0%
Asia	408	3%
Africa	261	2%
Oceania	318	2%
Global	633	4%
Unknown	735	5%
Total	14,907	100%

Figure 3: *Distribution of international (excluding Europe) collaborators*

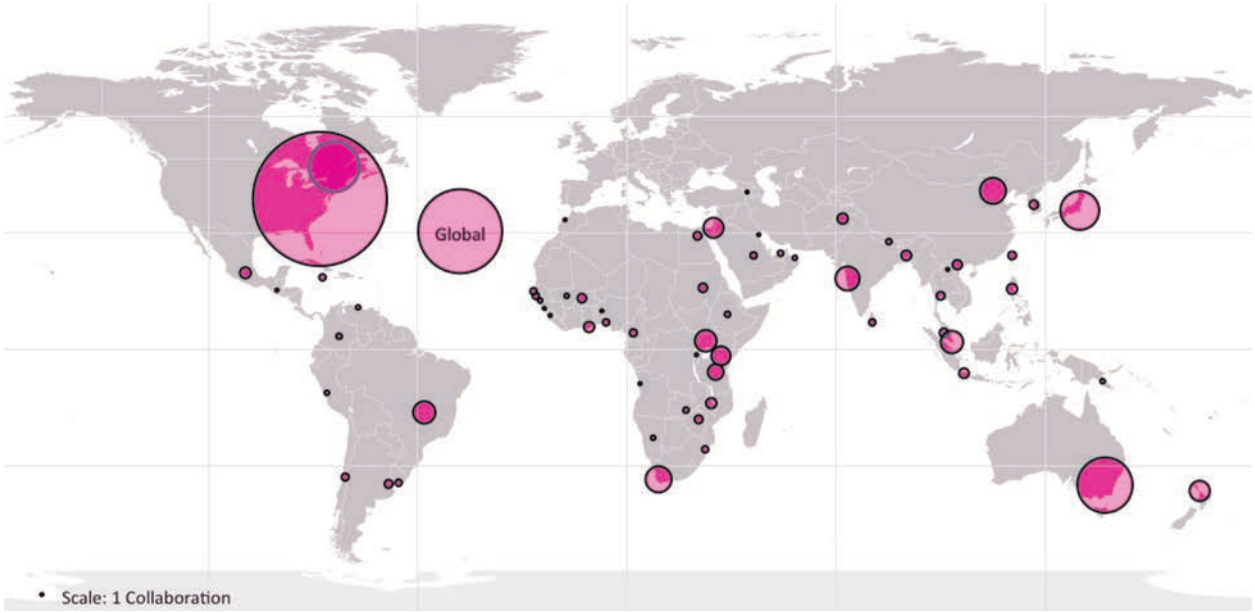


Figure 4: *Distribution of European (excluding UK) collaborators*

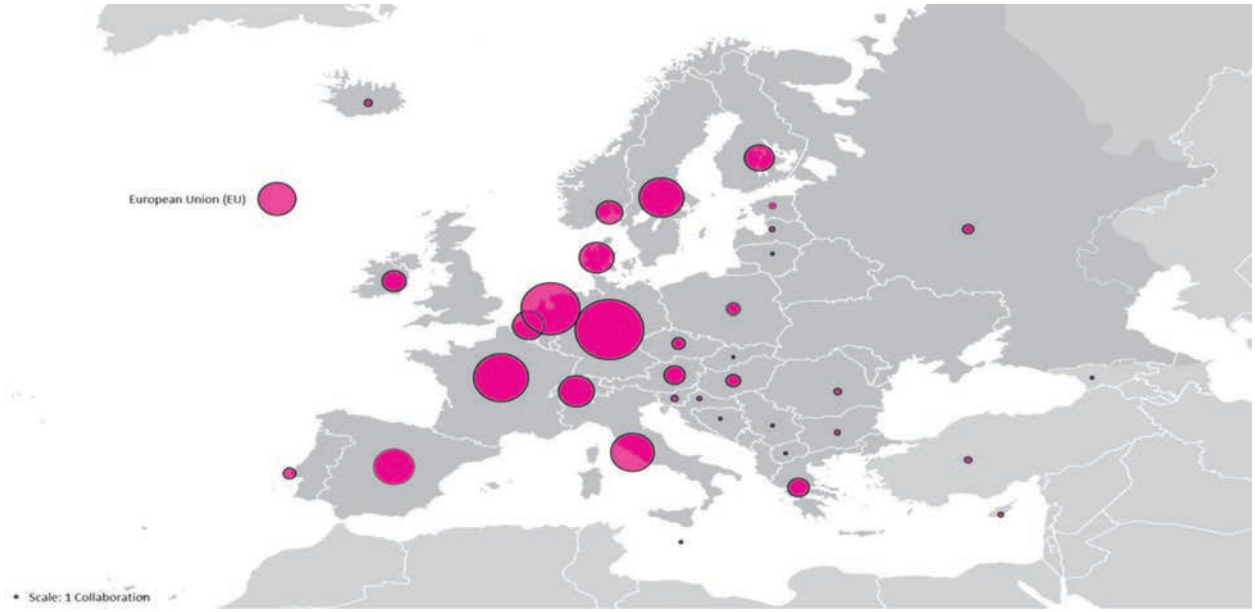
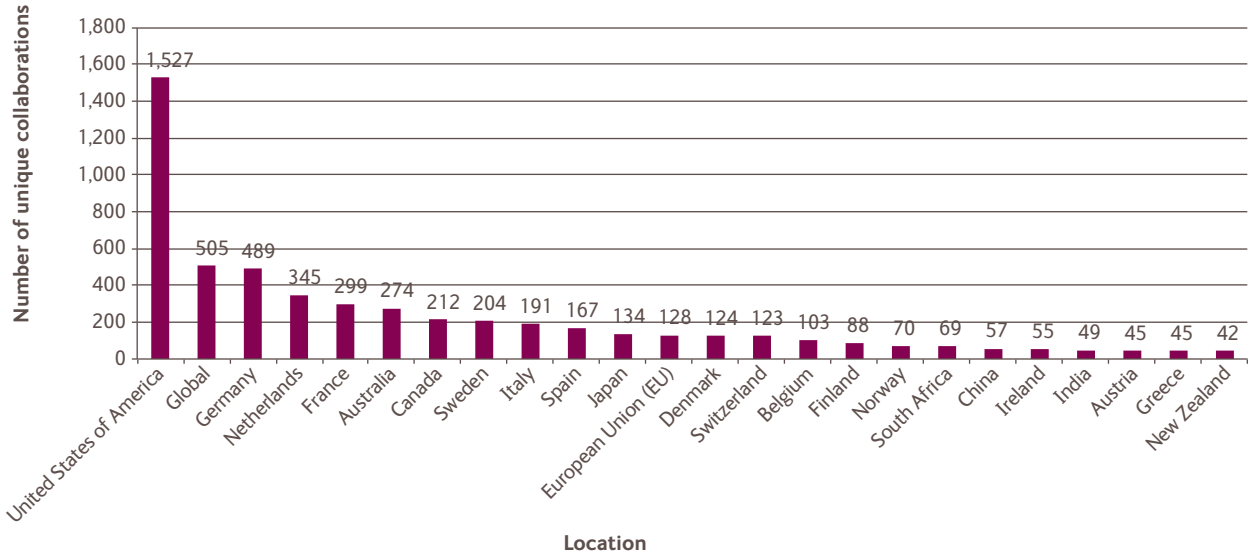


Figure 5: *Top 25 countries (excluding the UK) for collaborators*



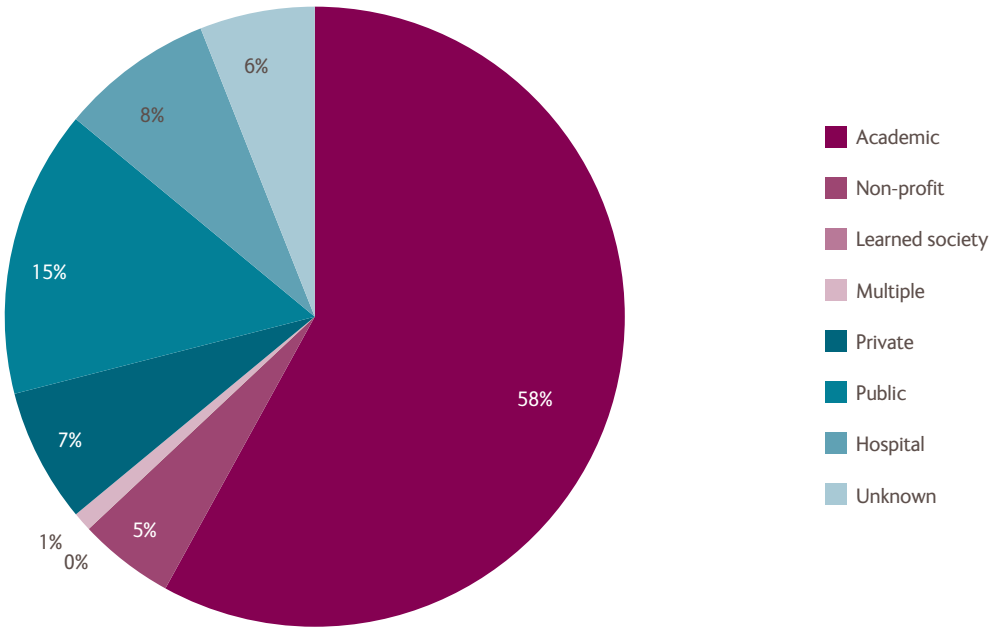
Collaborators by sector

- Researchfish data allows us to see the extent to which MRC researchers are engaging with collaborators from different sectors, including from the private sector.
- The majority of collaborators were from academia (58 per cent), followed by the public sector (15 per cent), hospitals (eight per cent) and the private sector (seven per cent). This is similar to the ratios reported last year. Table 4 and figure 6 show the number of collaborators by sector.

Table 4: *Collaborators by sector*

	Number of collaborators	Percentage of collaborators
Academic	8,599	58%
Non-profit	767	5%
Learned society	40	0%
Multiple	163	1%
Private	1,106	7%
Public	2,213	15%
Hospital	1,186	8%
Unknown	833	6%
Total	14,907	100%

Figure 6: *Collaborators by sector*



3.3: Further funding

Summary

- Researchers reported instances of further funding in 46 per cent of awards.
- 9,355 instances of further funding were reported.
- The average number of instances of further funding for those who had reported further funding was four (3.65).
- Recipients of 161 awards reported more than 10 instances of further funding.

Further funding by year

- As with other output types, it takes time to apply for, obtain and initiate new grants and so recent awards will be naturally less likely to result in instances of further funding. Recipients of 65 per cent of grants starting in 2006 or earlier had reported further funding, compared to 16 per cent of grants starting in 2013. The number of awards reporting at least one instance of further funding by the year the award started is shown in table 1 and figure 1.
- 11 per cent of awards reported instances of further funding within one year, compared to 54 per cent after five years. Table 2 and figure 2 show the time between the start of the award and when the further funding started by award.

Table 1: *Number of awards reporting further funding by award start date*

Start year	Number of awards	Number with at least one instance of further funding	Number without any further funding	Percentage with at least one instance of further funding
2006 or earlier	2,076	1,346	730	65%
2007	466	320	146	69%
2008	569	367	202	64%
2009	565	365	200	65%
2010	470	251	219	53%
2011	410	181	229	44%
2012	525	151	374	29%
2013	478	78	400	16%

Figure 1: *Number of awards reporting further funding by award start date*

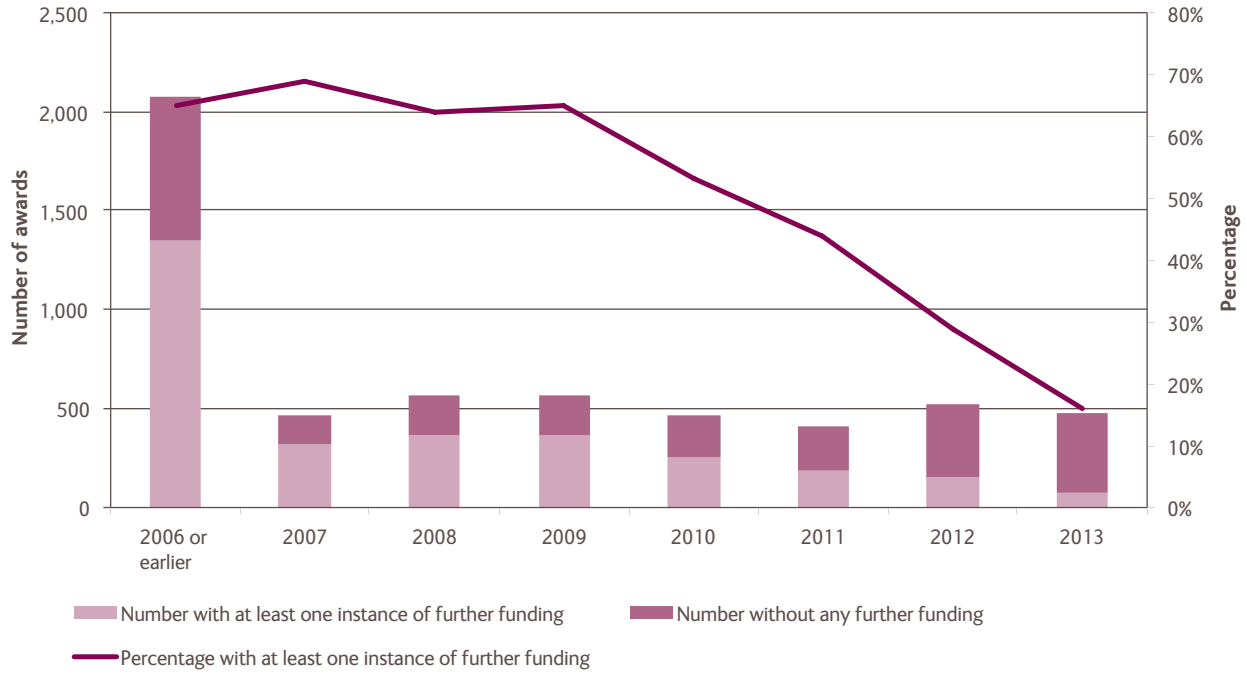
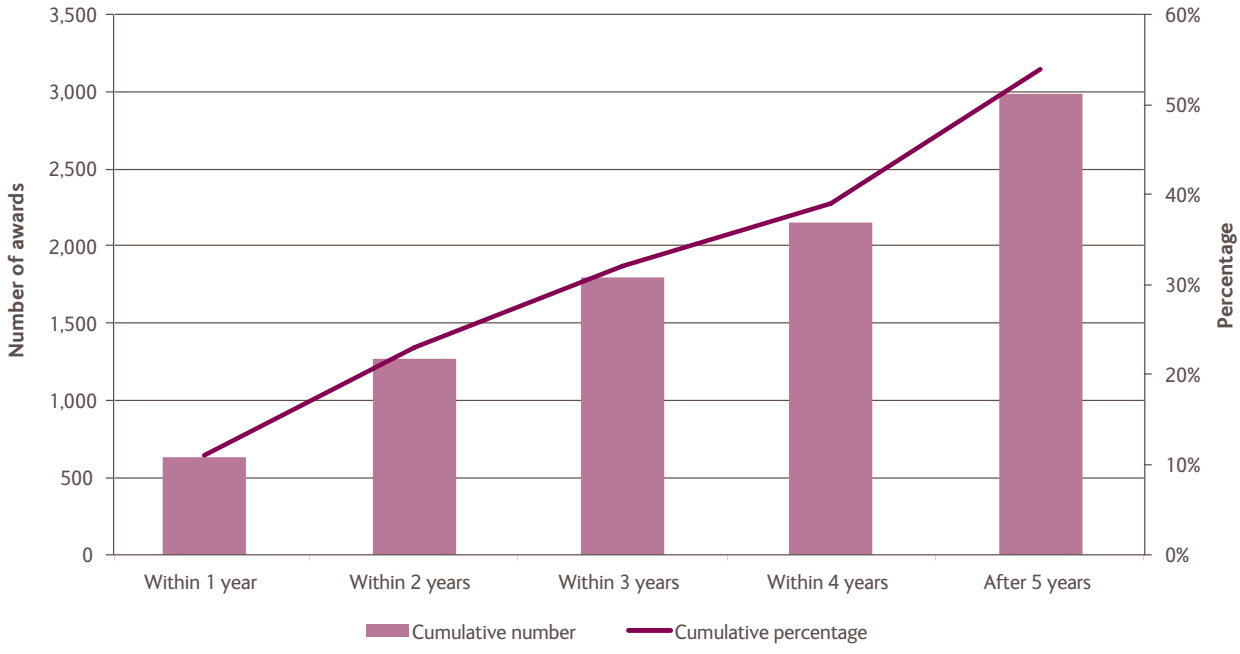


Table 2: *Time between start of the award and first instance of further funding*

	Number reporting at least one instance of further funding	Cumulative number	Cumulative percentage
Within 1 year	630	630	11%
Within 2 years	642	1,272	23%
Within 3 years	527	1,799	32%
Within 4 years	347	2,146	39%
After 5 years	845	2,991	54%

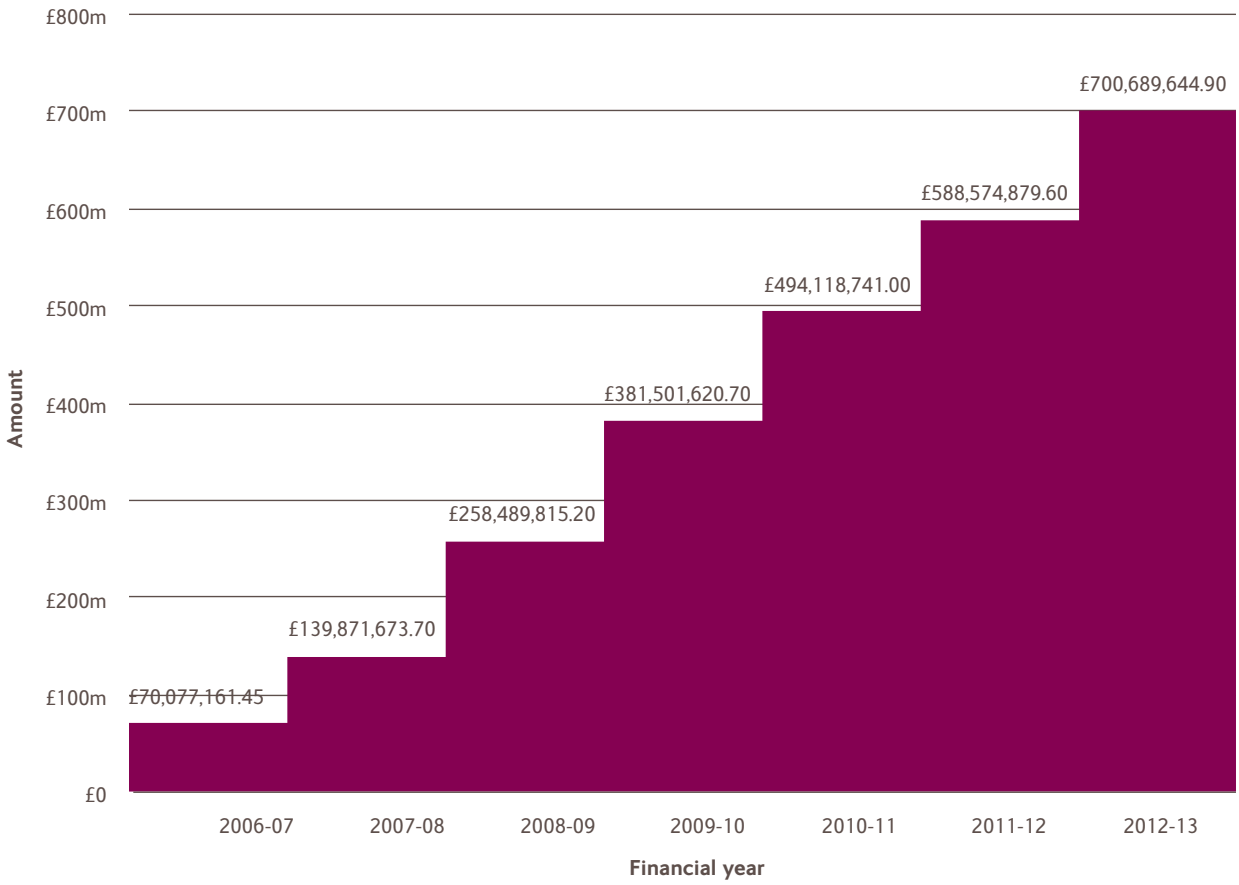
Figure 2: *Time between start of the award and further funding*



Further funding by value

- Researchers reported a total value of £3.2bn in further funding[258], with the average total value being £1.2m amongst those reporting further funding. 12 per cent of awards received more than £1m in further funding.
- A total value of £700.7m was reported to have been leveraged in 2012/2013, which is an increase on last year's total of £562m. The value of further funding by year is shown in figure 3.

Figure 3: *Value of further funding by year*



Further funding by location

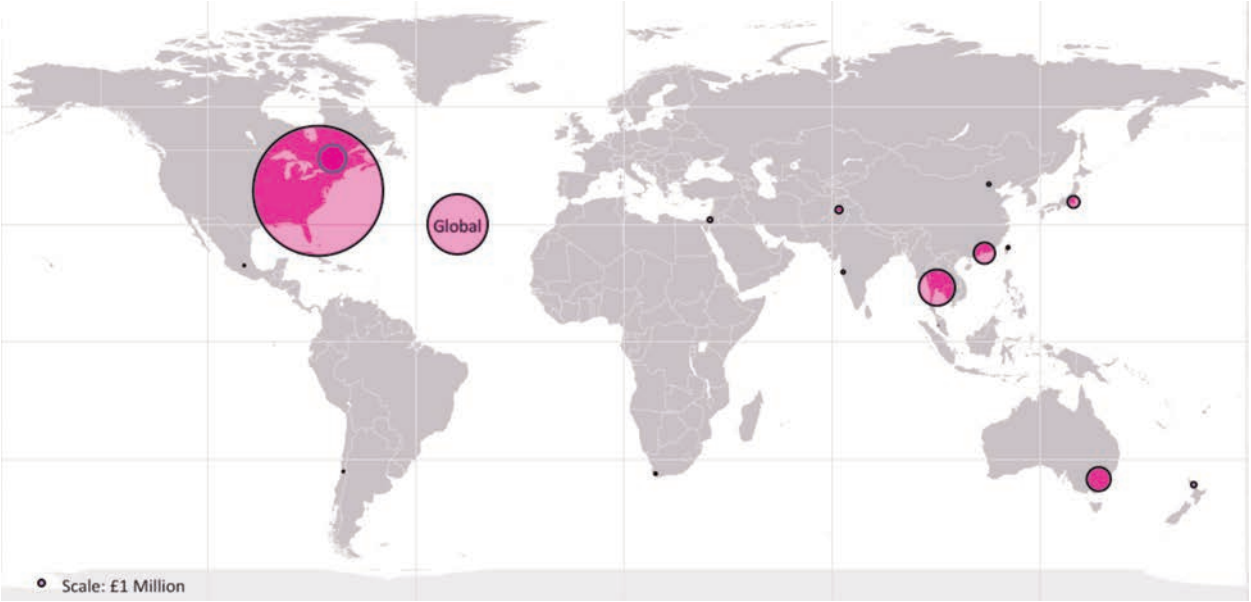
- The sources of further funding have been coded for country and sector to gain a greater understanding of the importance of other countries, governments, companies and non-profit organisations in funding the same research as the MRC.
- The majority of further funding reported in Researchfish was leveraged from the United Kingdom between 2006 and 2013 - 68 per cent of further funding (£2.1bn). 14 per cent of further funding (£447m) was obtained from the rest of Europe. Figures 4 (European, excluding UK) and 5 (International, excluding Europe) show the amount of further funding by location.
- The largest value of further funding between 2006 and 2013 came from the public sector (£1.4bn – 46 per cent of the total further funding reported). This was closely followed by non-profit organisations (£1.2bn – 37 per cent of the total further funding reported). Table 3 and figure 6 shows the value of further funding by sector.
- Six per cent of further funding (£197m) was leveraged from the private sector between 2006-2013. In 2012/13, this figure was £33.5m, seven per cent.

- The Wellcome Trust provided the largest value of further funding, contributing £435m between 2006 and 2013. This was followed by the National Institute for Health Research (£195m). The top ten funders by value is shown in table 4.
- The largest overseas funder was the European Commission, contributing £120m between 2006 and 2013, followed by the National Institutes of Health (£95m).
- The largest single private sector funder was Merck & Co Inc, providing around £88m in this period.

Figure 4: *Amount of further funding by location (European, excluding UK)*

European Union(EU):	*£246,217,331*
Austria:	*£833,874*
Belgium:	*£3,845,052*
Denmark:	*£6,382,612*
Finland:	*£648,680*
France:	*£28,461,651*
Germany:	*£14,457,002*
Greece:	*£565,029*
Ireland:	*£1,683,796*
Italy:	*£514,961*
Norway:	*£487,085*
Portugal:	*£1,137,572*
Russia:	*£145,000*
Spain:	*£4,798,854*
Sweden:	*£416,708*
Switzerland:	*£7,832,861*

Figure 5: *Amount of further funding by location (international, excluding Europe)*



Global:	£79,754,959
Australia:	£12,764,280
Canada:	£17,150,922
Chile:	£78,609
China:	£276,543
Hong Kong:	£10,025,487
India:	£279,885
Israel:	£546,581
Japan:	£3,224,431
Mexico:	£86,500
New Zealand:	£673,500
Pakistan:	£1,181,002
South Africa:	£159,480
Taiwan:	£215,562
Thailand:	£28,894,654
USA:	£371,545,335

Table 3: *Value of further funding by sector*

Sector	Value	Percentage
Academic	£105,314,414	3%
Non-profit	£1,184,518,846	37%
Learned society	£13,802,588	0%
Multiple sectors	£31,528,955	1%
Private	£197,204,966	6%
Public	£1,472,075,012	46%
Hospital	£111,292,741	4%
Unknown	£57,979,843	2%
Total	£3,173,717,367	100%

Figure 6: *Percentage of further funding by sector*

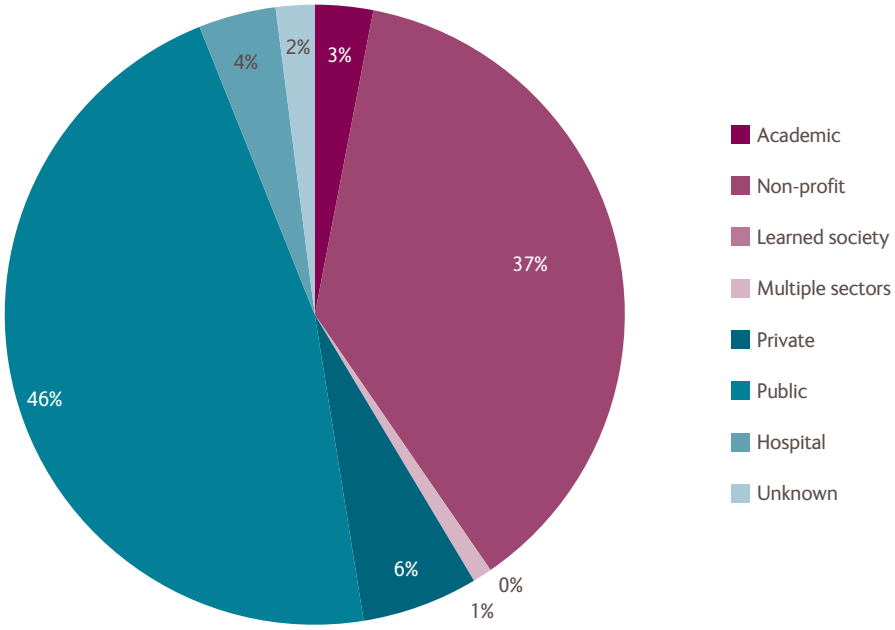


Table 4: *Top 10 funders by value*

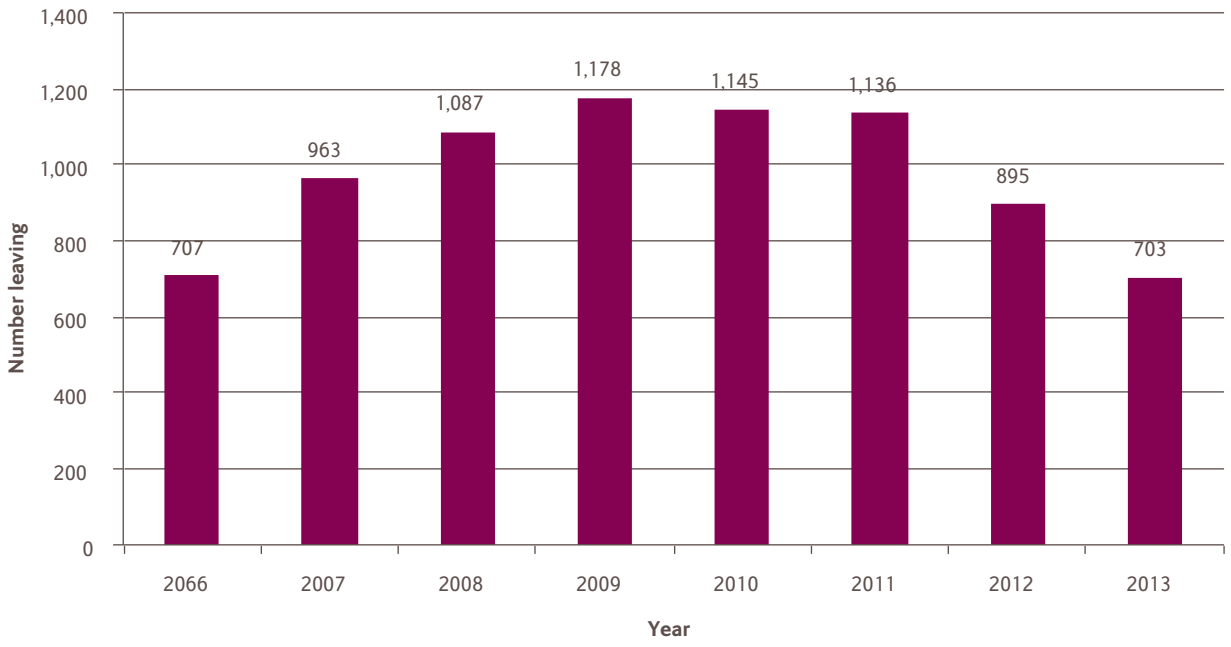
Top funders	Pro-rated spending
Wellcome Trust	£434,967,269
National Institute for Health Research (NIHR)	£194,571,599
Biotechnology and Biological Sciences Research Council (BBSRC)	£123,290,325
European Commission (EC)	£120,066,222
Cancer Research UK (CRUK)	£109,401,877
Engineering and Physical Sciences Research Council (EPSRC)	£101,287,979
National Institutes of Health (NIH)	£95,180,674
Merck & Co., Inc. (MSD)	£88,272,263
Bill and Melinda Gates Foundation	£77,528,405
British Heart Foundation (BHF)	£71,809,556

3.4: Next destination

Summary

- Principal investigators reported details of staff who had left MRC support in 47 per cent of MRC awards.
- On average, there were three instances (3.02) reported per award (for those awards where it was reported staff had left).
- Of the 7,814 reports of staff who moved from MRC support between 2006 and 2013[259], 20 per cent were research fellows and 13 per cent were research students.
- Figure 1 shows the number of staff leaving MRC support by year, as reported in Researchfish. The data includes people leaving MRC awards that have terminated, people leaving for opportunities elsewhere or retiring, and people leaving fixed-term positions such as studentships.

Figure 1: *Number of staff leaving MRC support by year*



Positions held at the MRC and future positions

- 35 per cent of staff leaving the MRC were in a post-doctoral position, 24 per cent held a researcher position and 20 per cent held a research fellow position. The distribution of all roles held is shown in figure 2.
- The majority of next destinations for research students leaving the MRC were described as 'post-doctoral researcher' (51 per cent), followed by 'student' (16 per cent). A breakdown of next destinations of research students is shown in figure 3.
- The majority of post-doctoral researchers left MRC support to take up a further post-doctoral position (51 per cent), followed by research fellow/project leader (16 per cent)[260]. A breakdown of next destinations of post-doctoral researchers is shown in figure 4.

» Overall, 61 per cent of staff remained in the academic (university-based) sector. 10 per cent of leavers moved into the private sector. Figure 5 shows a breakdown of next destinations by sector.

» These results are very similar to those published last year.

Figure 2: *Distribution of roles held by staff leaving the MRC*

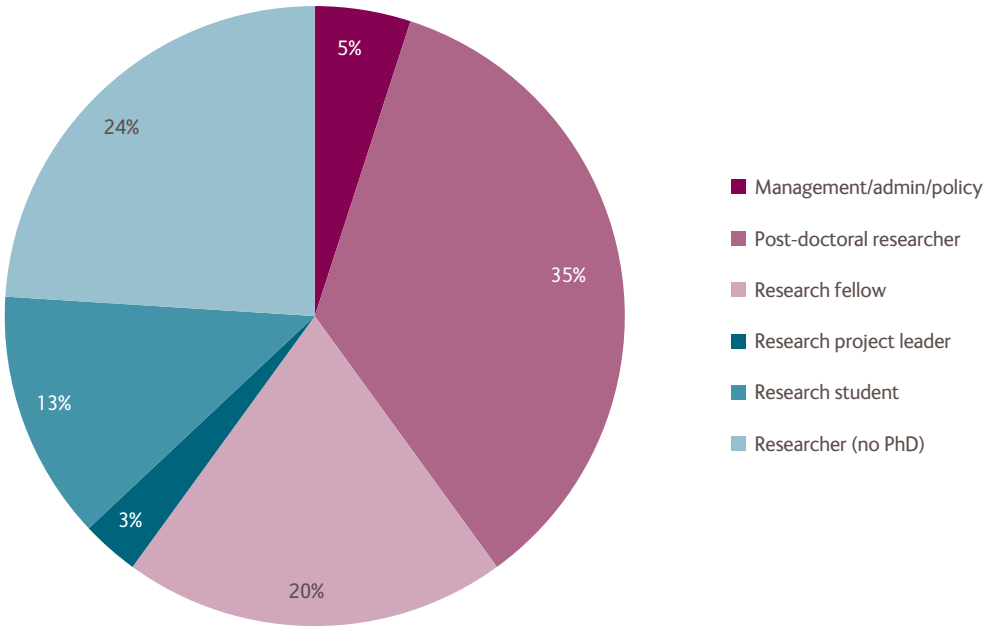


Figure 3: *Distribution of next destinations of research students*

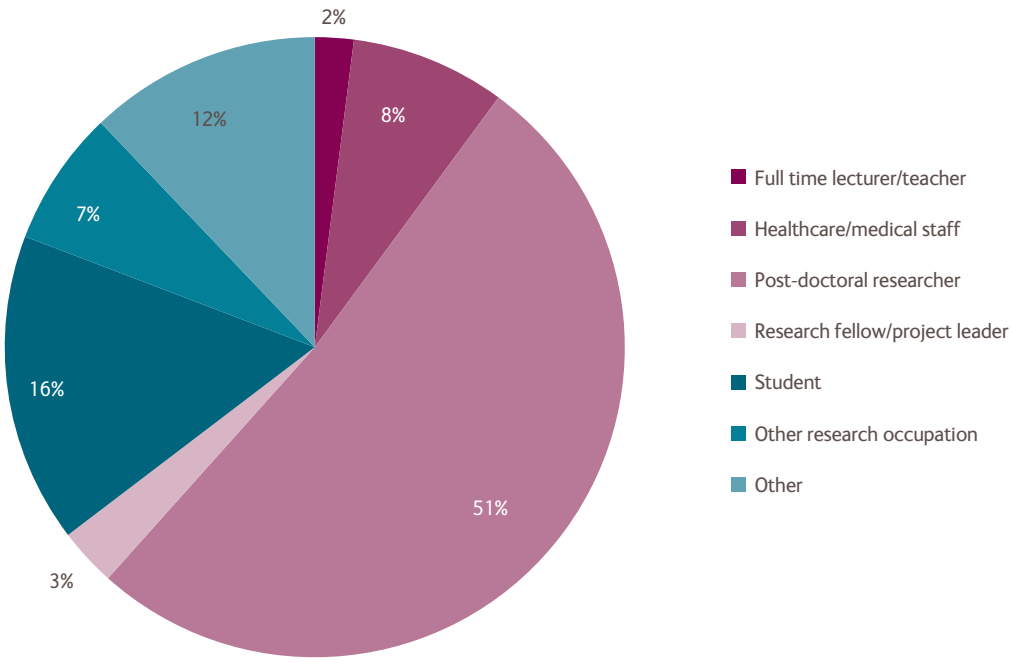


Figure 4: *Distribution of next destinations of post-doctoral researchers*

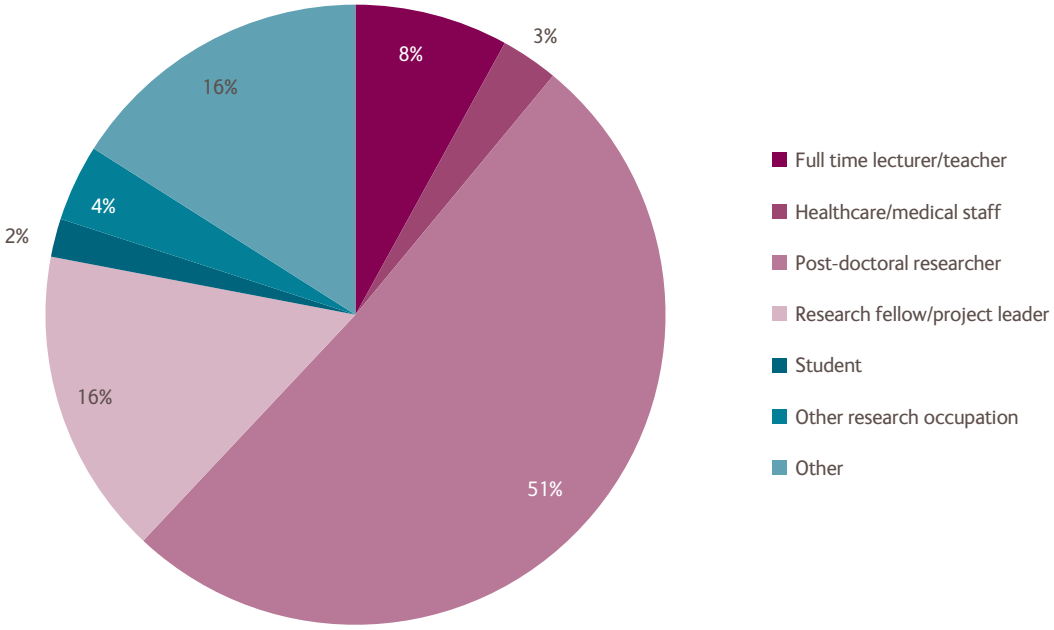
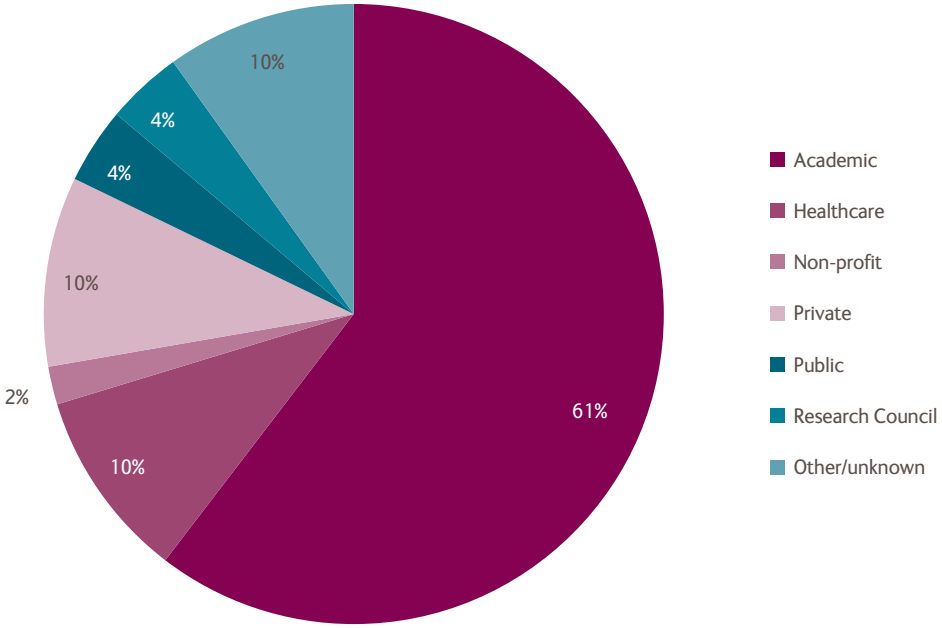


Figure 5: *Distribution of next destinations by sector*



3.5: Engagement activities

Summary

- Researchers reported participating in engagement activities outside of academia in 56 per cent of awards.
- The total number of engagement activities reported between 2006 and 2013 was 23,292[261].
- The average number of engagement activities per award (for awards reporting engagement activities) was seven (7.47).
- 11 per cent of all awards reported more than ten engagement activities.

Engagement activities by year

- There were 3,146 instances of engagement activities starting in 2013. A breakdown of engagement activities per year is shown in figure 1.
- The longer that an award has been running, the greater number of opportunities to participate in engagement activities there are. Recipients of 62 per cent of awards starting in 2006 or earlier reported at least one engagement activity, compared to 26 per cent of awards starting in 2013. The number of awards reporting at least one engagement activity by start year is shown in table 1 and figure 2.
- 19 per cent of awards reported at least one engagement activity within one year of the award starting compared to 56 per cent after five years. The time between the award starting and the engagement activity taking place is shown in table 2 and figure 3.

Figure 1: *Breakdown of engagement activities per year*

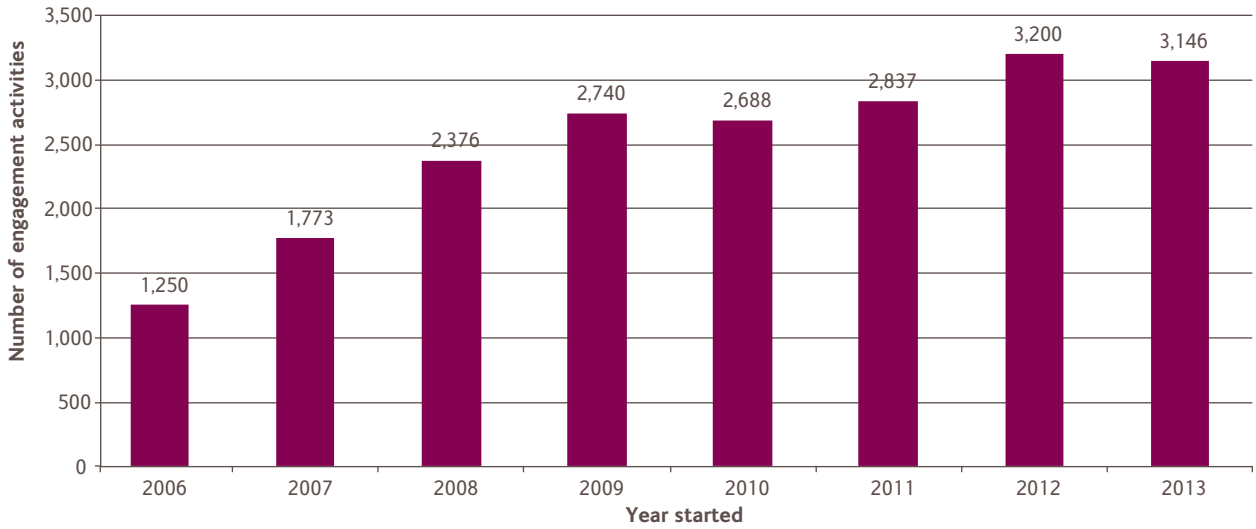


Table 1: *Number of awards reporting at least one engagement activity by start year*

Start year	Number of awards	Number with at least one engagement activity	Number with no engagement activities	Percentage with at least one instance of engagement activity
2006 or earlier	2,076	1,290	786	62%
2007	466	304	162	65%
2008	569	370	199	65%
2009	565	344	221	61%
2010	470	270	200	57%
2011	410	204	206	50%
2012	525	213	312	41%
2013	478	125	353	26%

Figure 2: *Number of awards reporting at least one engagement activity by start year*

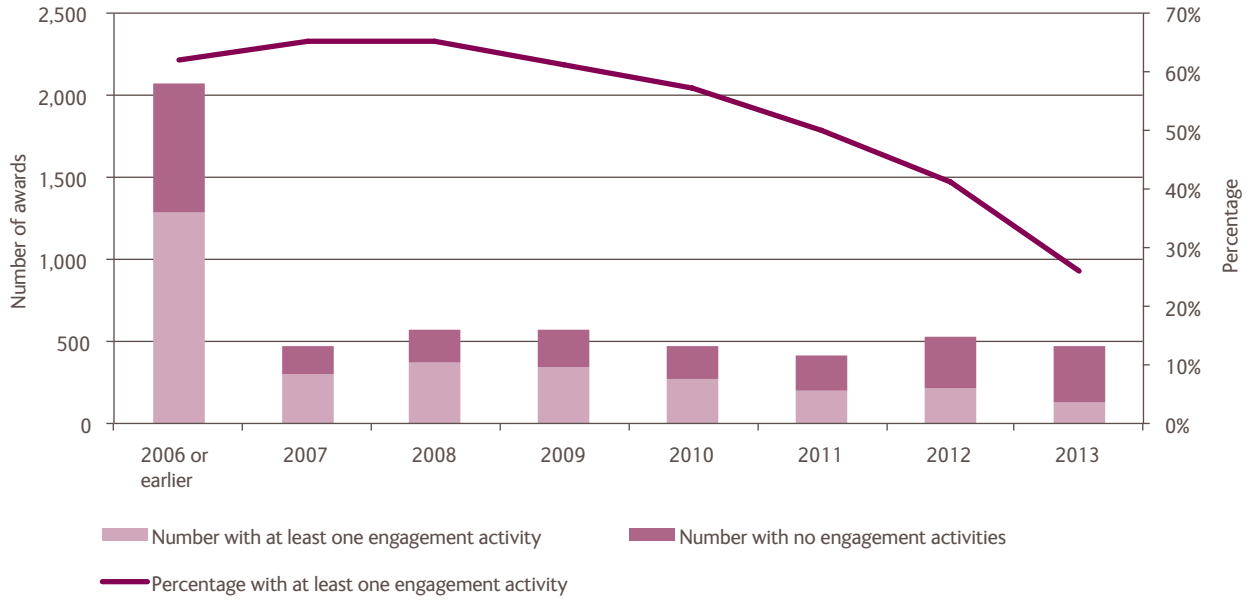
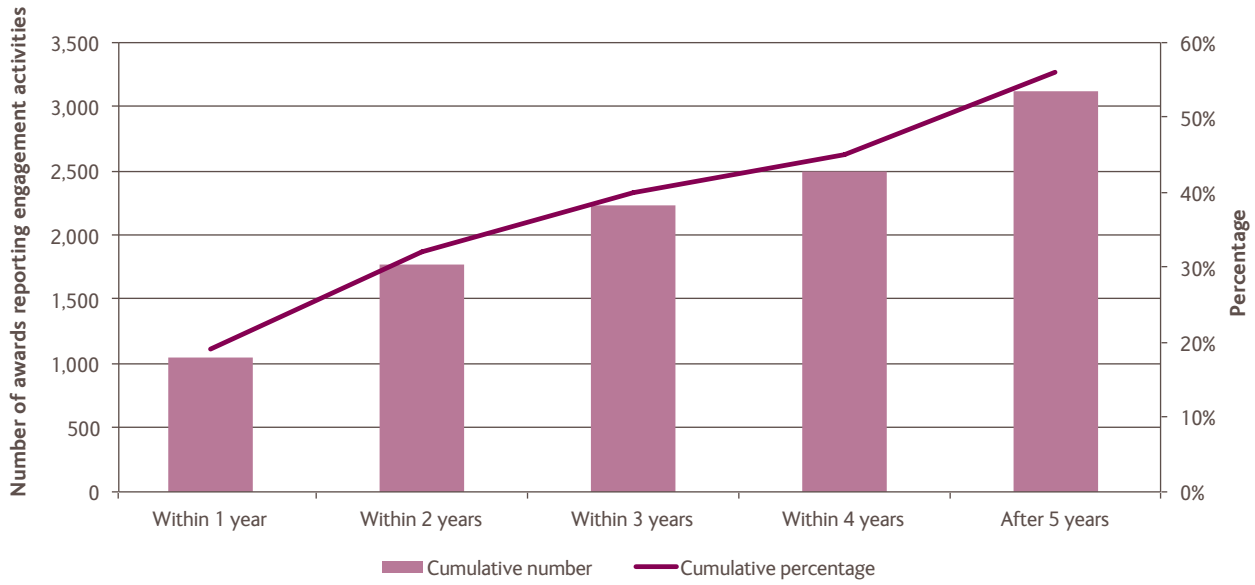


Table 2: *Time between the award starting and engagement activity taking place*

	Number reporting at least one engagement activity	Cumulative number	Cumulative percentage
Within 1 year	1,045	1,045	19%
Within 2 years	721	1,766	32%
Within 3 years	464	2,230	40%
Within 4 years	270	2,500	45%
After 5 years	620	3,120	56%

Figure 3: *Time between the award starting and engagement activity taking place*



Engagement activity by type and audience

- Engagement with audiences outside of academia[262] is an important part of the research process. It helps to enhance understanding of complex topics, communicate the importance of research carried out and inspire future careers in science.
- The most popular method of engagement reported was a talk or presentation (37 per cent), followed by participation in an activity, workshop or similar (17 per cent). A full breakdown of engagement activities by type is shown in table 3 and figure 4.
- Around a third of engagement activities were aimed at the public/other audiences (31 per cent), while 16 per cent were aimed at health professionals and 15 per cent at other academic audiences. A more detailed breakdown of engagement activities by audience type is shown in table 4 and figure 5.

Table 3: *Engagement activities by type*

Engagement activity	Number of instances	Percentage
A formal working group, expert panel or similar	1,992	10%
A magazine, newsletter or online publication	2,344	12%
A press release, press conference or response to a media enquiry.	1,854	9%
A talk or presentation	7,371	37%
Participation in an activity, workshop or similar	3,328	17%
Participation in an open day or visit at my research institution	1,371	7%
Scientific meeting (conference/symposium etc)	1,748	9%
Total	20,008	100%

Figure 4: *Engagement activities by type*

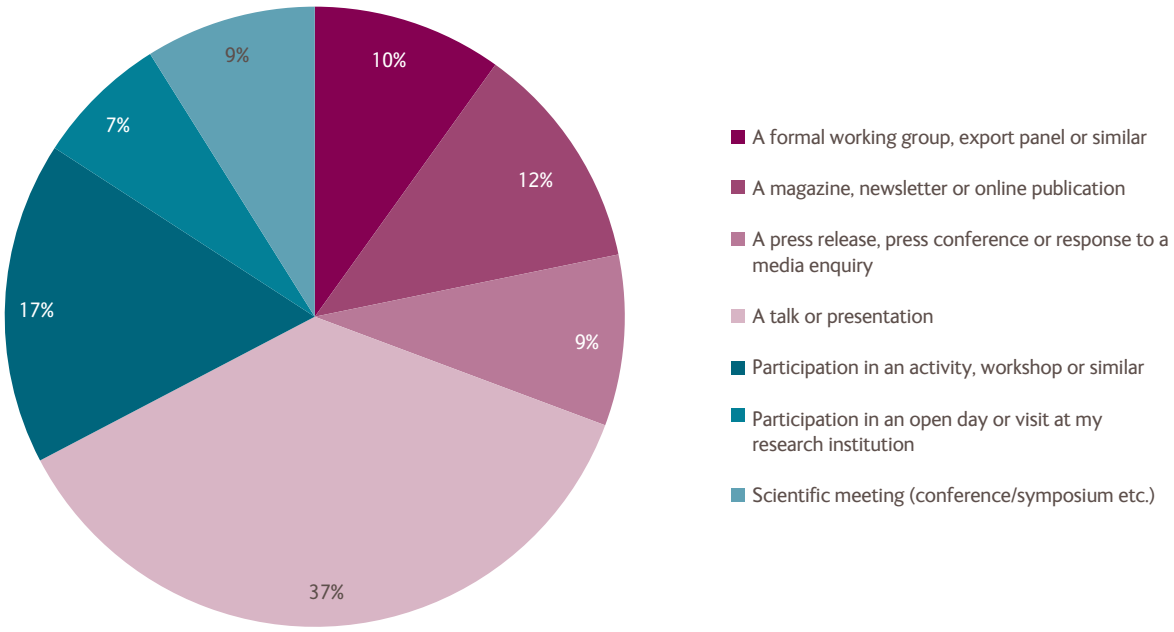
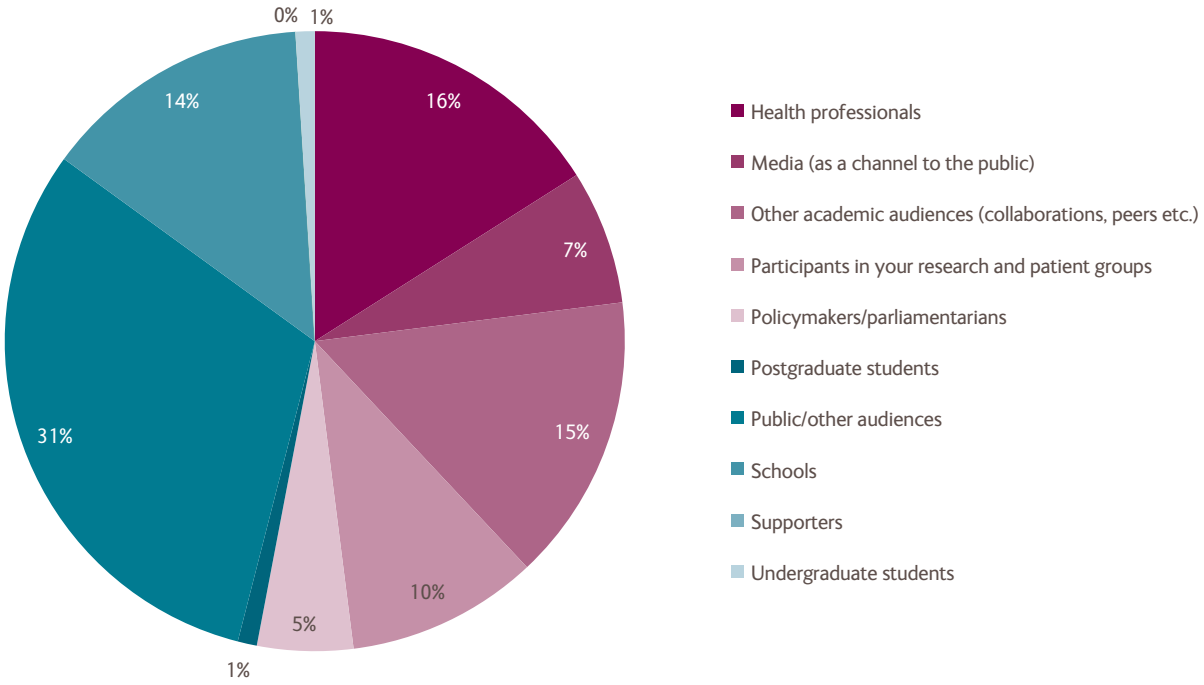


Table 4: *Engagement activities by audience type*

Audience type	Number of instances	Percentage
Health professionals	3,278	16%
Media (as a channel to the public)	1,418	7%
Other academic audiences (collaborators, peers etc.)	2,973	15%
Participants in your research and patient groups	1,929	10%
Policymakers/parliamentarians	976	5%
Postgraduate students	268	1%
Public/other audiences	6,223	31%
Schools	2,768	14%
Supporters	67	0%
Undergraduate students	110	1%
Total	20,010	100%

Figure 5: *Engagement activities by audience type*



3.6: Influence on policy

Summary

- MRC researchers reported 3,455 examples of influences on policy between 2006 and 2013.
- Influences on policy were reported in more than a fifth (22 per cent) of all awards. In these awards, the average number of influences on policy was three (3.2).

Influences on policy by year

- 460 policy influences started in 2013. A breakdown of policy influences by year is shown in figure 1.
- As with other output types, there is naturally a time lag between the award being made and the influence on policy being realised. More than a quarter (26 per cent) of awards made in 2006 or earlier reported at least one policy influence, compared to 18 per cent of awards in 2011 and six per cent in 2013. Table 1 and figure 2 show the number of policy influences by award start year.
- 22 per cent of awards reported at least one policy influence within five years after the award starting, compared to five per cent within one year. Table 2 and figure 3 shows the time taken to report the first policy influence.

Figure 1: *Policy influence by year realised*

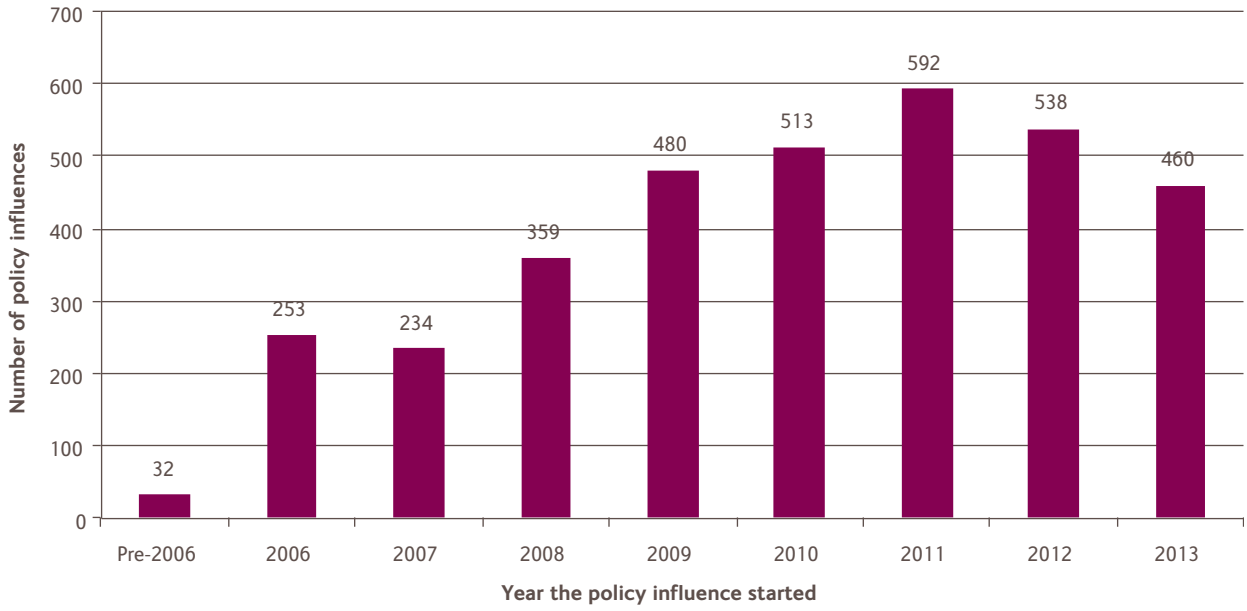


Table 1: *Policy influence by award start year*

Start year	Number of awards	Number with at least one policy influence	Number with no policy influences	Percentage with at least one policy influence
2006 or earlier	2076	543	1533	26%
2007	466	109	357	23%
2008	569	139	430	24%
2009	565	140	425	25%
2010	470	108	362	23%
2011	410	73	337	18%
2012	525	63	462	12%
2013	478	31	447	6%

Figure 2: *Policy influence by award start year*

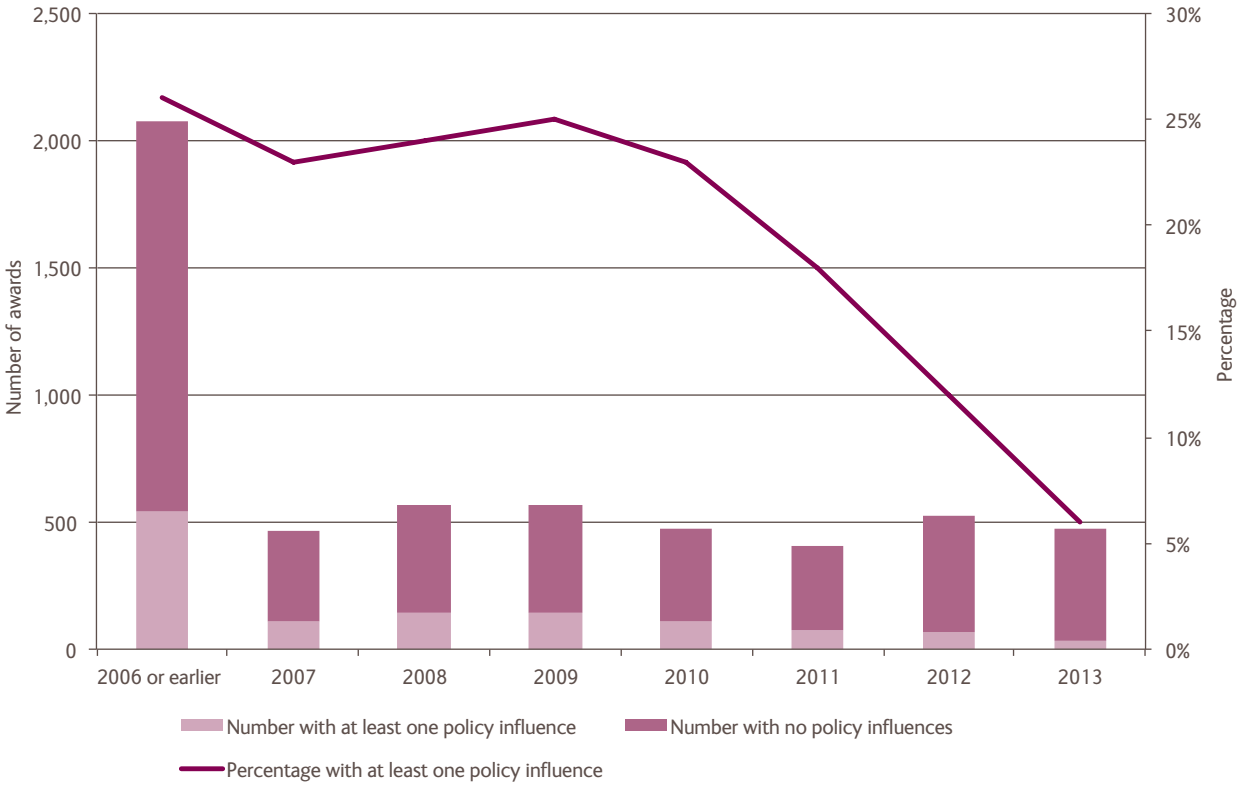
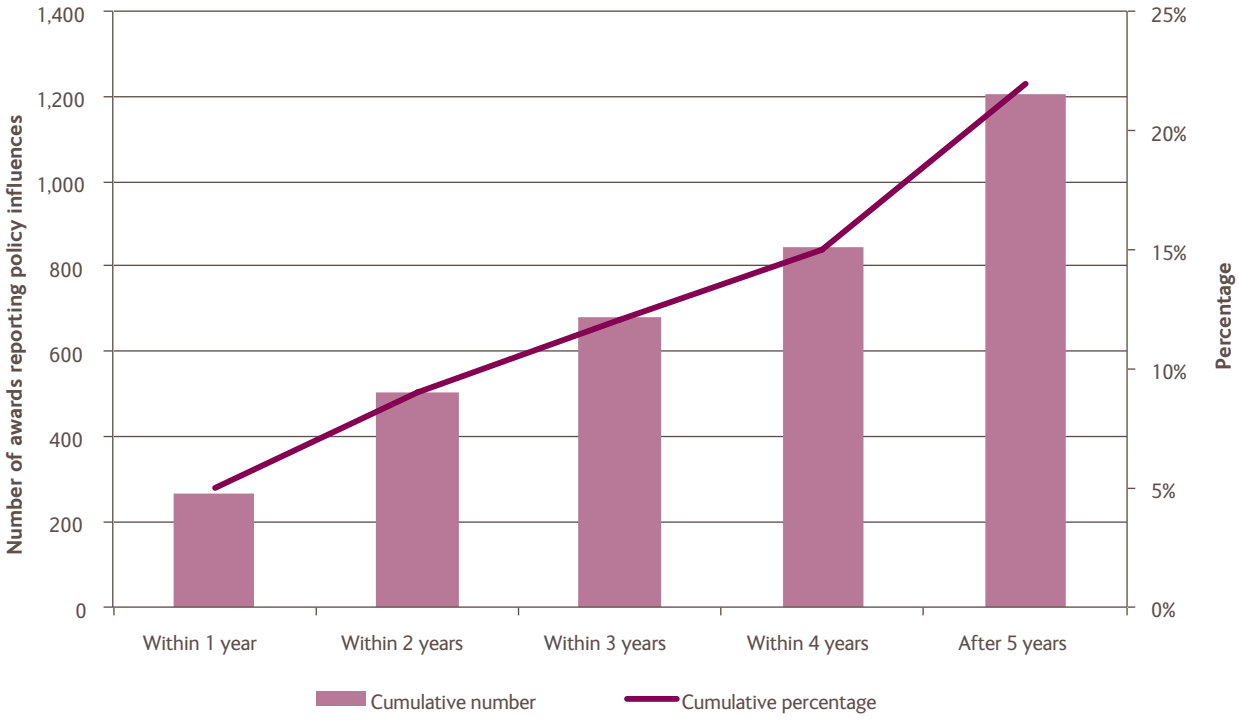


Table 2: *Time taken to report first policy influence*

	Number reporting at least one policy influence	Cumulative number	Cumulative percentage
Within 1 year	268	268	5%
Within 2 years	235	503	9%
Within 3 years	176	679	12%
Within 4 years	165	844	15%
After 5 years	362	1,206	22%

Figure 3: *Time taken to report first policy influence*



Policy influence by type and location

- Once unique policy outputs have been identified, the type of policy influence can be divided into citations in key policy documents (754/3,455 - 23 per cent of all policy influences) and influences on policy setting processes (2,701/3,455 – 77 per cent).
- A breakdown of policy influence by type is shown in table 1 and figure 4.
- Almost half of all policy influences (47 per cent) occurred in the UK. 27 per cent of policy outputs had an international influence. A breakdown of policy influences by location is shown in table 2 and figure 5.

Table 1: *Policy influence by type*

Influence Type	Number of instances	Percentage
Key policy documents		
Citation in clinical guidelines	376	11%
Citation in clinical reviews	94	3%
Citation in other policy documents	226	7%
Citation in systematic reviews	58	2%
Policy setting processes		
Gave evidence to a government review	186	5%
Influenced training of practitioners or researchers	762	22%
Membership of a guideline committee	422	12%
Participation in an advisory committee	1,005	29%
Participation in a national consultation	301	9%
Implementation circular/rapid advice/letter to eg Ministry of Health	23	1%
Other/unknown	2	0%
Total	3,455	100%

Figure 4: *Policy influence by type*

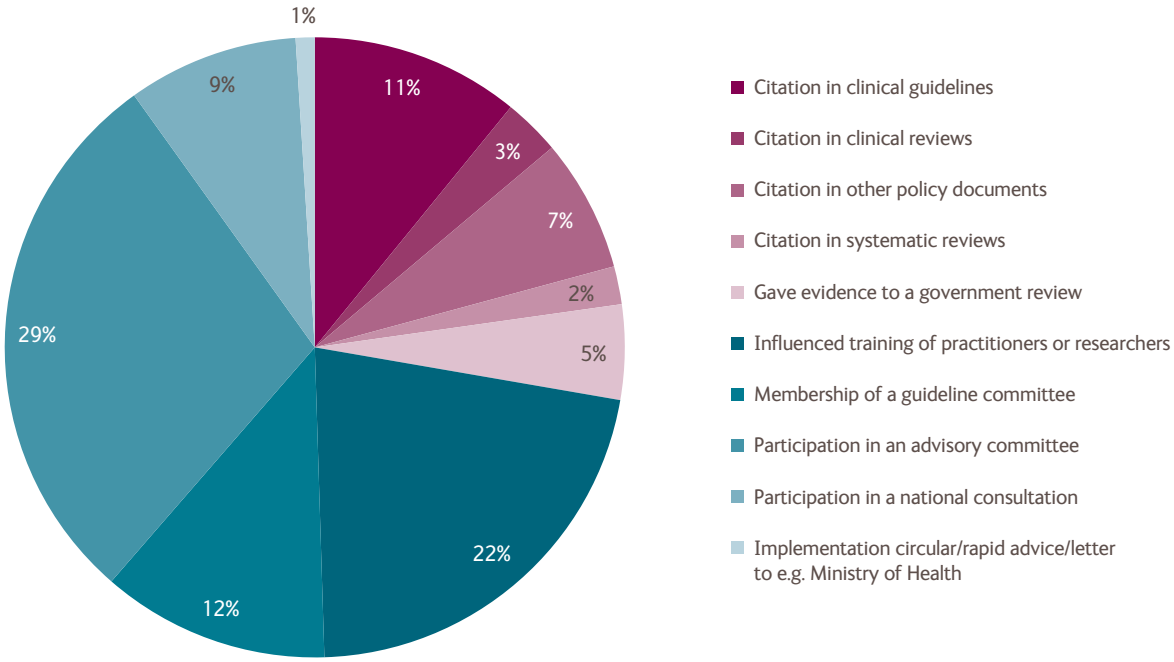
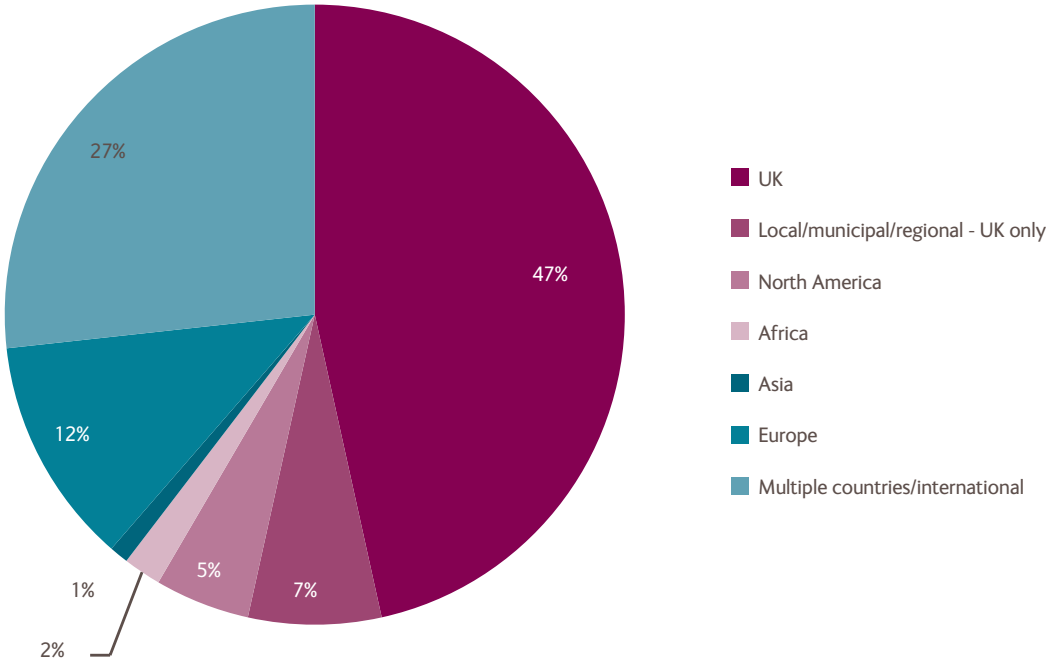


Table 2: *Policy influence by location*

Location of policy influence	Number of instances	Percentage
UK	1,607	47%
Local/municipal/regional - UK only	246	7%
North America	163	5%
Africa	59	2%
Asia	31	1%
Oceania	16	0%
Europe	415	12%
Multiple countries/international	916	27%
South America	1	0%
Unknown	1	0%
Total	3,455	100%

Figure 5: *Policy influence by location*



3.7: Research materials

Summary

- Recipients of 31 per cent of awards reported that their work had produced materials for others to use.
- The average number of research materials for awards reporting at least one instance was two (2.3).

Research materials by year

- The year when the research materials were first made available is shown in figure 1.
- The longer that an award has been running, the greater number of opportunities there are to create and share research materials. 47 per cent of awards starting in 2006 or earlier resulted in the production of a research material, compared to three per cent of awards starting in 2013. Table 1 and figure 2 show the number of materials reported by award start year.
- 31 per cent of awards reported at least one research material within five years[263], compared to just six per cent within one year. Table 2 and Figure 3 show the time taken to report the first research material.
- It should be noted that there is a large variety of materials produced and in future, as more data is captured, the time to produce research materials will be analysed by 'type' of research material.

Figure 1: *Distribution of when the research material was first made available*

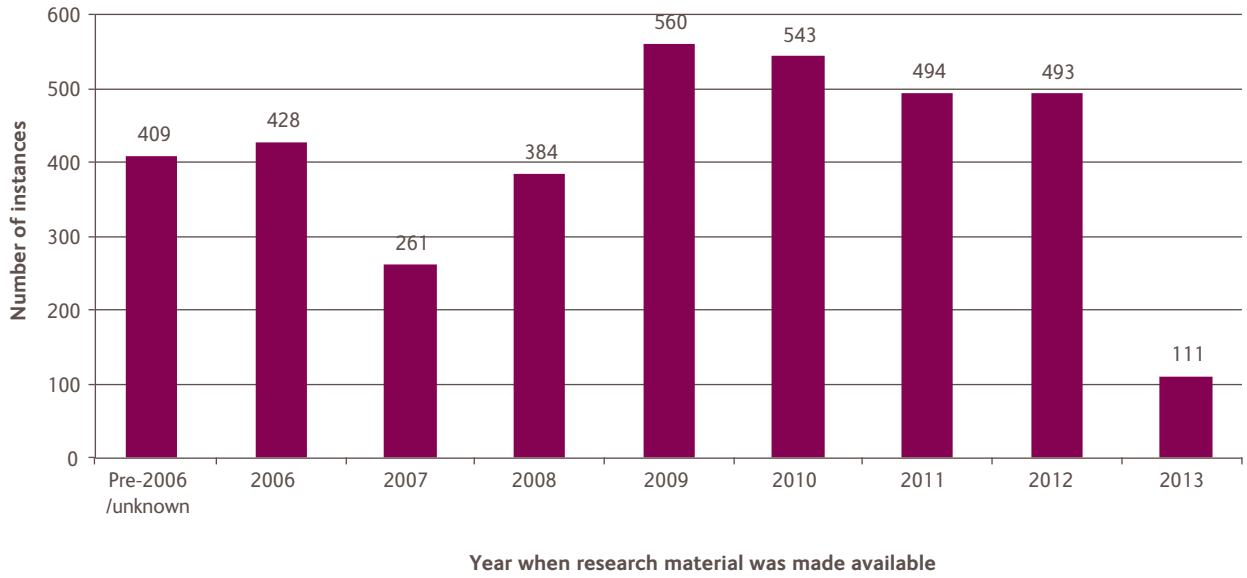


Table 1: *Research materials by award start year*

Start year	Number of awards	Number with at least one research material	Number with no research materials	Percentage with at least one research material
2006 or earlier	2,076	978	1,098	47%
2007	466	164	302	35%
2008	569	184	385	32%
2009	565	173	392	31%
2010	470	110	360	23%
2011	410	48	362	12%
2012	525	33	492	6%
2013	478	15	463	3%

Figure 2: *Research materials by award start year*

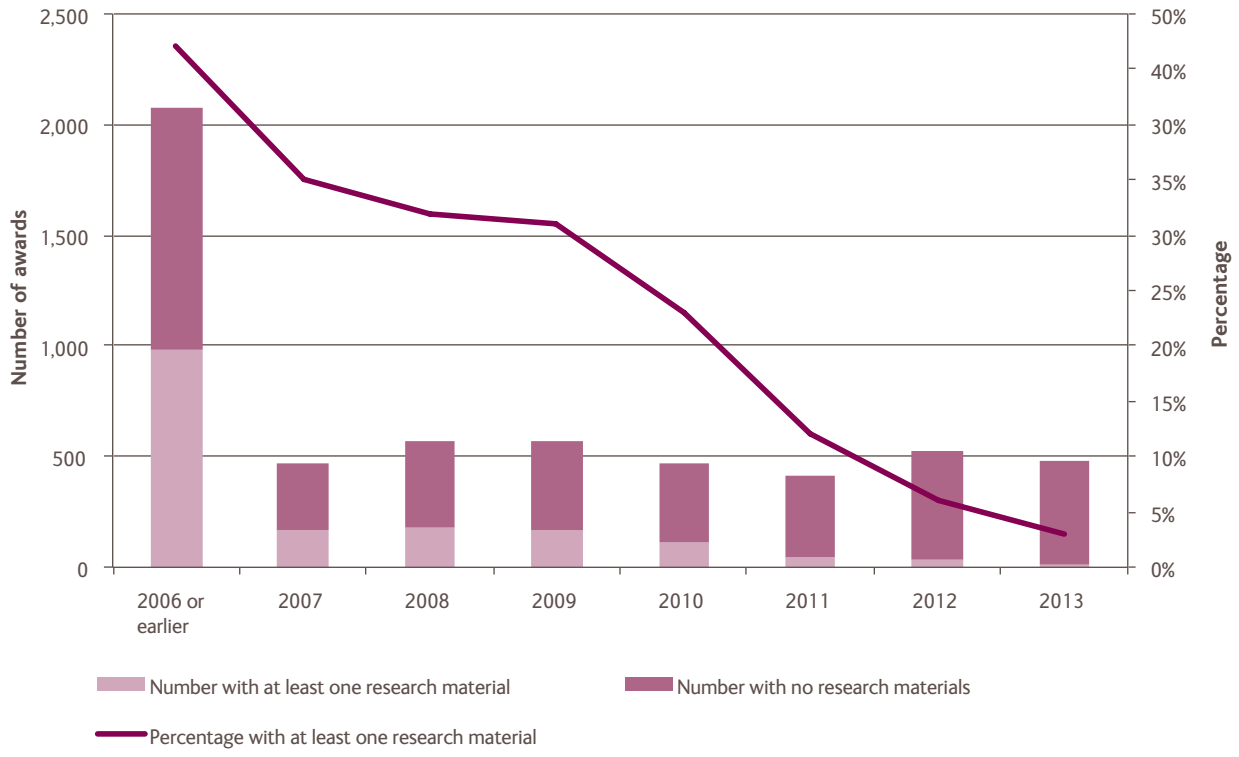
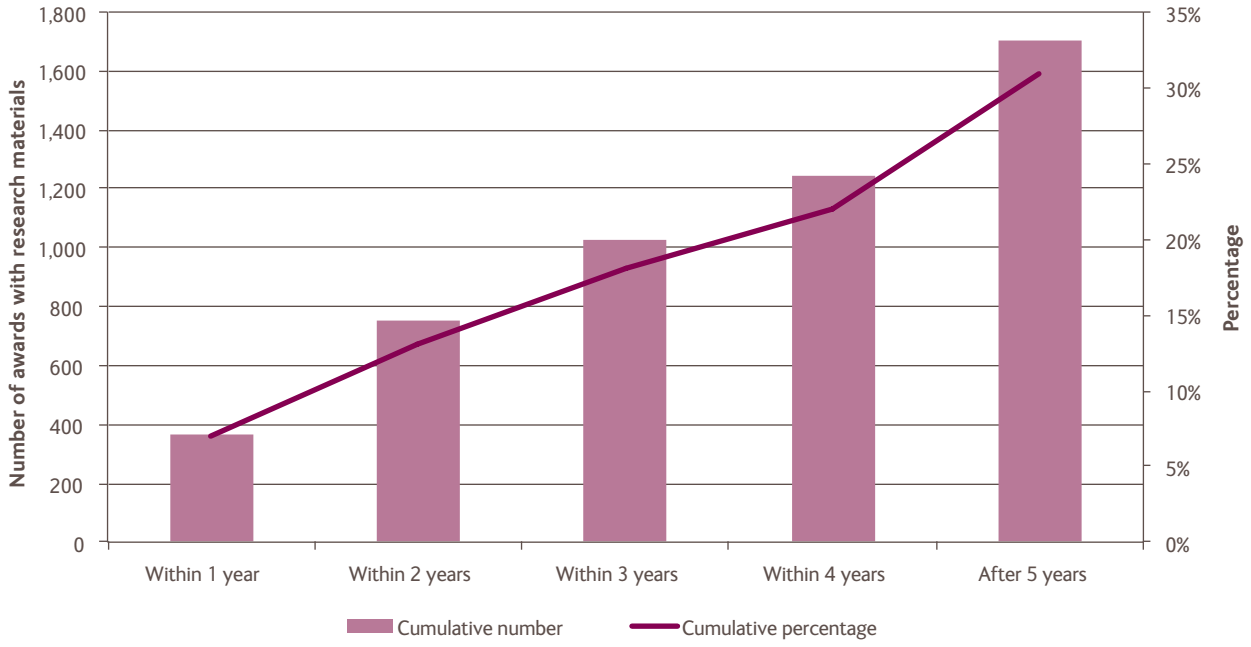


Table 2: *Time taken to report the first research material*

	Number reporting at least one research material	Cumulative number	Cumulative percentage
Within 1 year	369	369	7%
Within 2 years	381	750	13%
Within 3 years	275	1025	18%
Within 4 years	217	1242	22%
After 5 years	463	1705	31%

Figure 3: *Time taken to report the first research material*



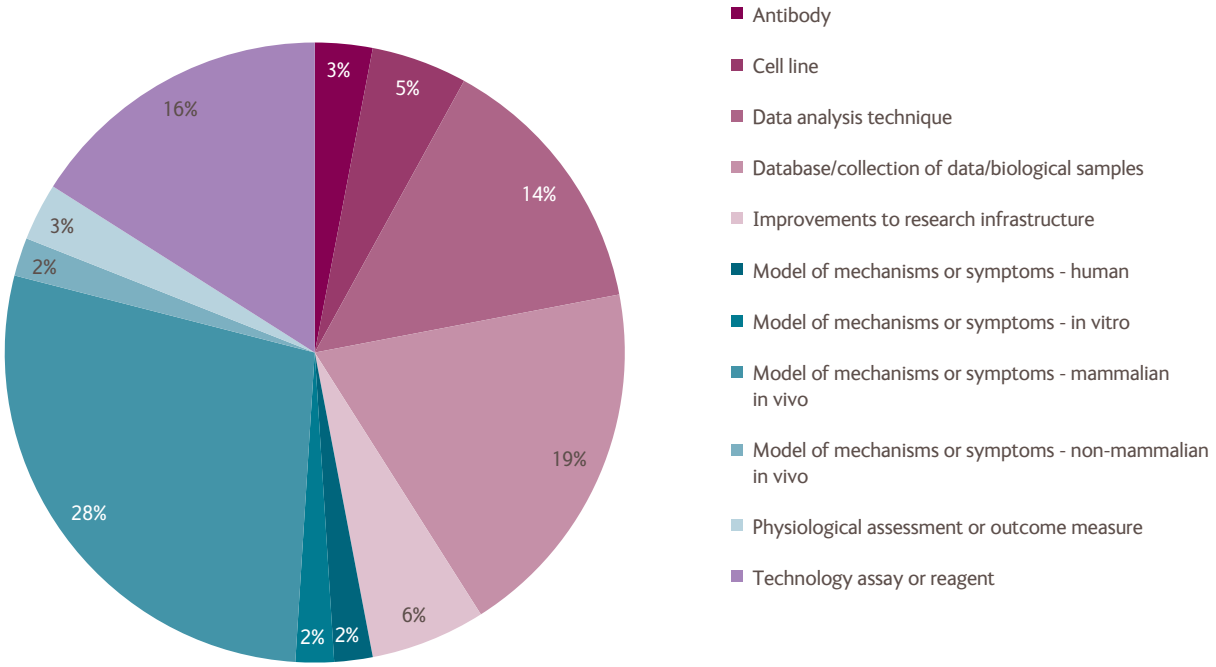
Research materials by type

» Models of mechanisms or symptoms – non-mammalian in vivo were the most common type of research material reported (28 per cent), followed by database/collection of data/biological samples (19 per cent). Table 3 and figure 4 show a breakdown of the type of research materials reported.

Table 3: *Research material by type*

Type of research material	Number of instances	Percentage
Antibody	126	3%
Cell line	173	5%
Data analysis technique	504	14%
Database/collection of data/biological samples	687	19%
Improvements to research infrastructure	235	6%
Model of mechanisms or symptoms - human	77	2%
Model of mechanisms or symptoms - in vitro	60	2%
Model of mechanisms or symptoms - mammalian in vivo	1,040	28%
Model of mechanisms or symptoms - non-mammalian in vivo	73	2%
Physiological assessment or outcome measure	110	3%
Technology assay or reagent	602	16%
Other/unknown	1	0%
Total	3,688	100%

Figure 4: *Research material by type*



3.8: Intellectual property

Summary

» The MRC dataset contains details of 849 discoveries in the intellectual property section. These include 74 reports of copyrighted works, 210 reports of discoveries for which formal protection was not possible or required, and 565 reports relating to published and granted patents.

Intellectual property by year

» Creating intellectual property can take a long time and therefore the longer that an award has been running for, the greater number of opportunities there are to create a patentable idea. 12 per cent of awards starting in 2006 reported at least one item of intellectual property, compared to one per cent of awards starting in 2013. Figure 1 shows the distribution of awards by start date and whether they have reported at least one item of intellectual property.

» Eight per cent of awards report at least one instance of intellectual property after five years[264], compared to one per cent within one year. Table 1 and figure 2 shows the time taken to report the first instance of intellectual property. In future analyses we will look to see if this elapsed time is different across the different 'types' of intellectual property.

» Supplemental analyses will be added in future to examine the way in which publicly-funded research is cited in these patents and the organisations that are noted as applicants on the patents. In 2014, Researchfish will add a patent lookup facility which will assist researchers in recording accurate patent details.

Figure 1: *Intellectual Property by award start date*

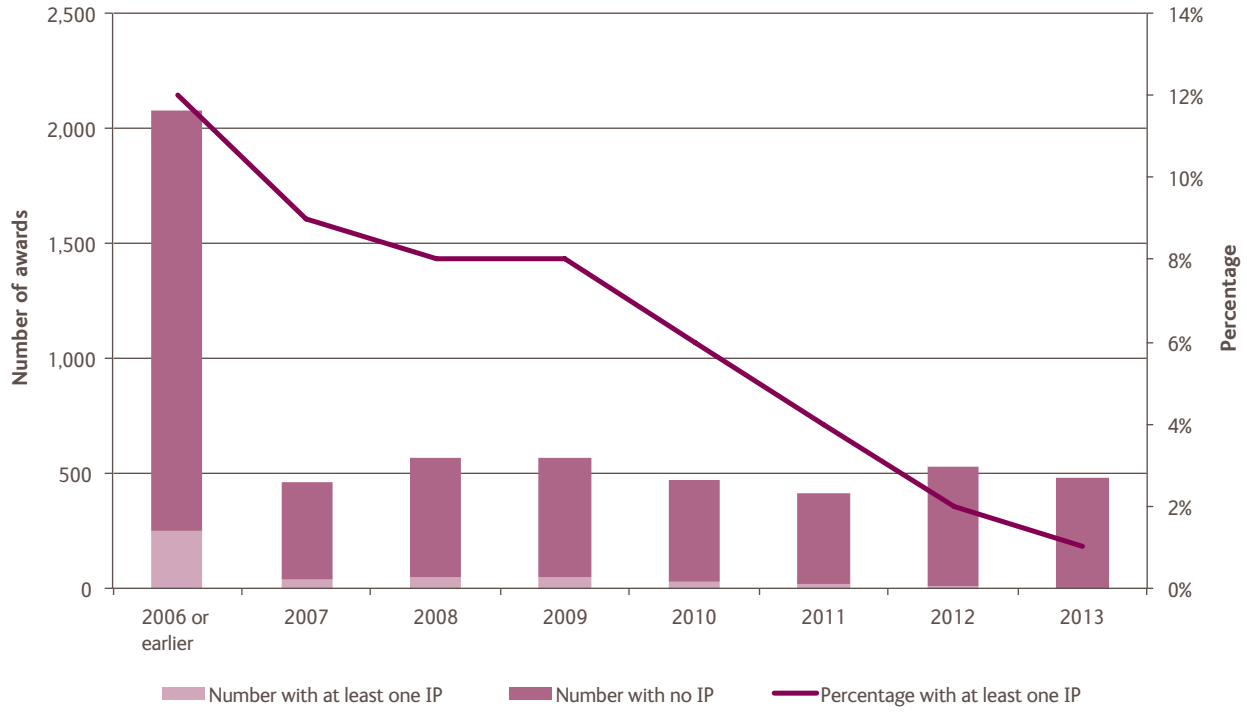
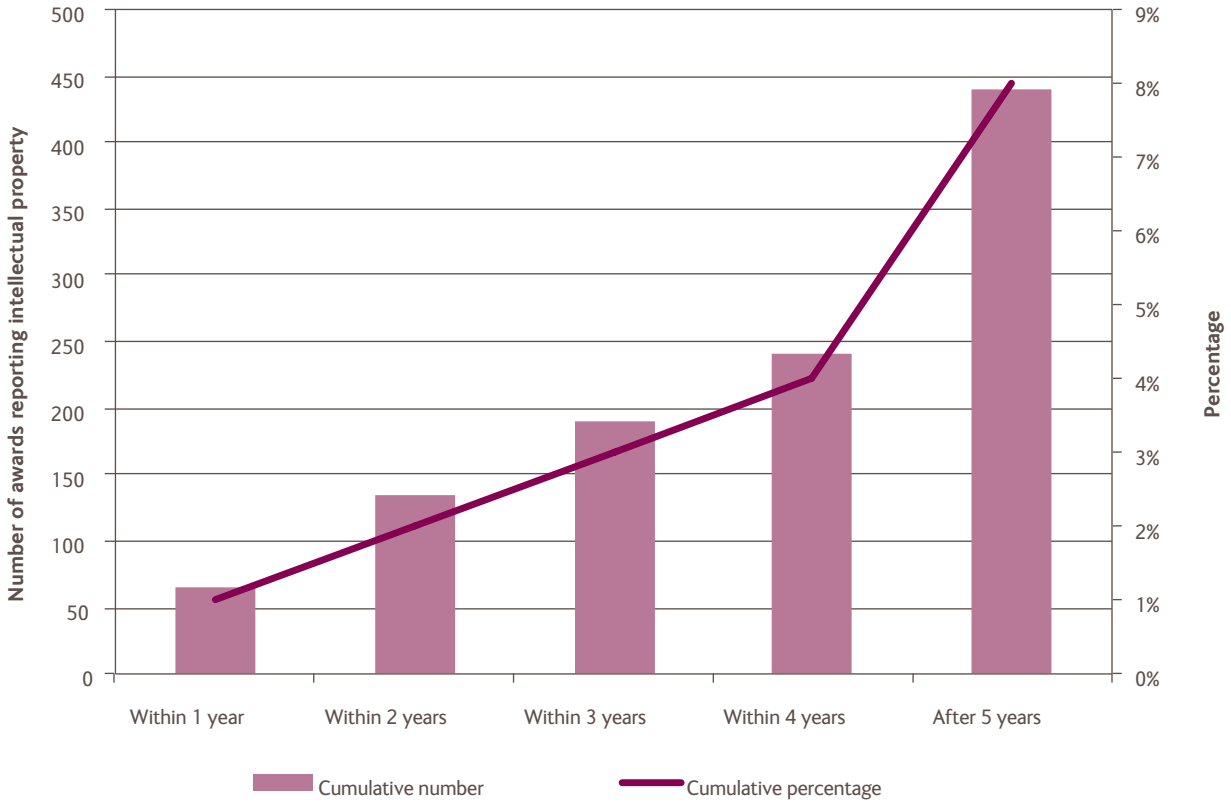


Table 1: *Time taken to report the first instance of intellectual property*

	Number reporting at least one IP	Cumulative number	Cumulative percentage
Within 1 year	66	66	1%
Within 2 years	68	134	2%
Within 3 years	55	189	3%
Within 4 years	51	240	4%
After 5 years	200	440	8%

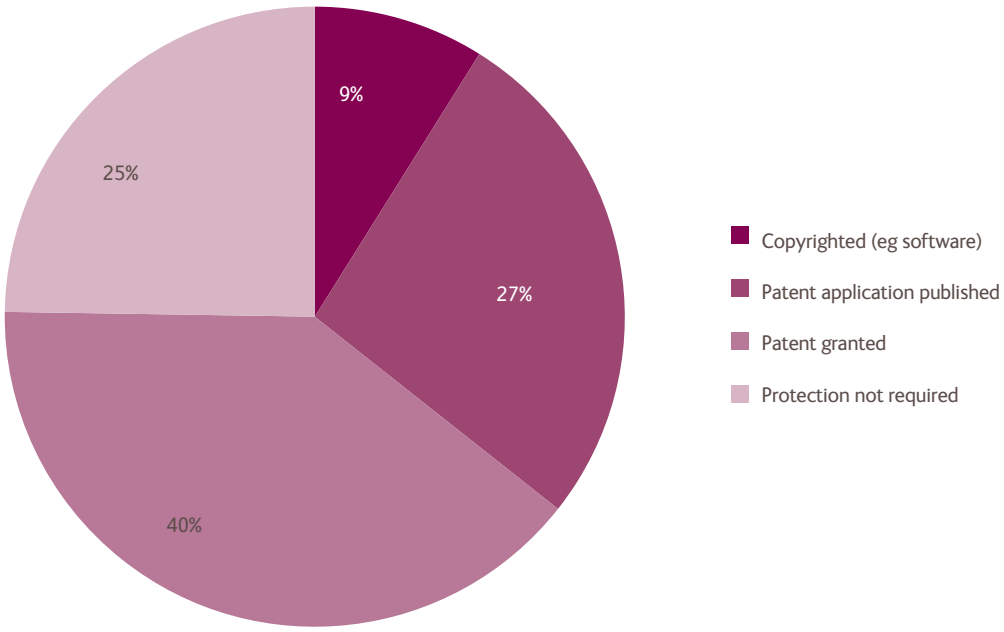
Figure 2: *Time taken to report the first instance of intellectual property*



Intellectual property protection by type

» 40 per cent of reports in this section were concerning a granted patent. Figure 3 gives a breakdown of the type of intellectual property reported.

Figure 3: *Type of intellectual property protection reported*



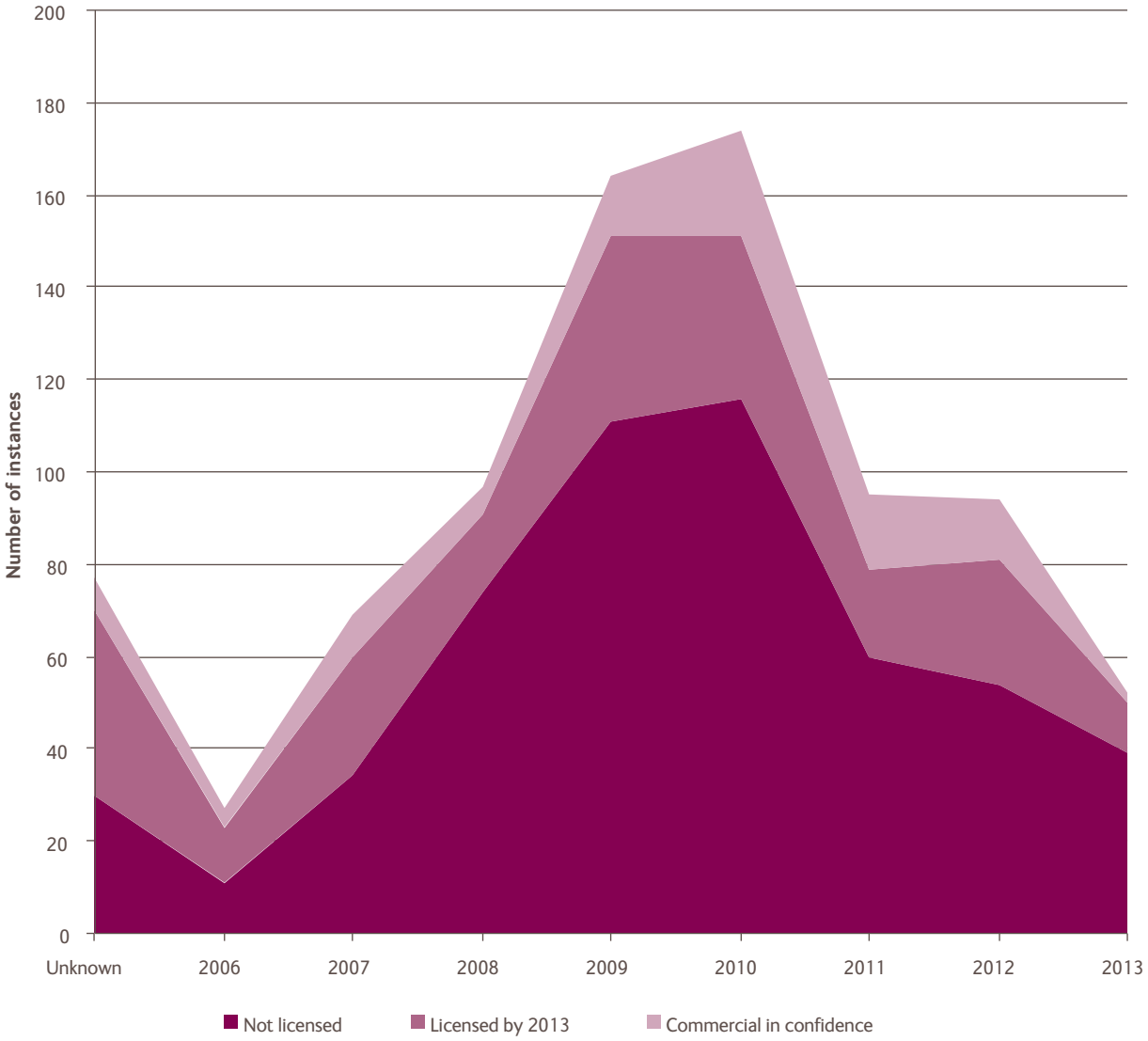
Licensing of intellectual property

- 27 per cent of discoveries overall (227/849) were reported as 'licensed' by 2013. The proportion is slightly higher for patented discoveries (31 per cent, 180/579). This is similar to the proportions reported in the last two years, and in our previous report from 2010, we suggested that this seemed reasonable in light of similar data from other organisations[265].
- This calculation does not include the 11 per cent of reports where researchers indicated that details were 'commercial in confidence' and could not be provided (93/849); it would be reasonable to assume that some of these cases will translate into new licenses in due course.
- The license status of intellectual property in 2013 by the year protection was granted is shown in table 3 and figure 4.

Table 3: *License status of intellectual property in 2013 by year of protection*

	Unknown	2006	2007	2008	2009	2010	2011	2012	2013	Total
Not licensed	30	11	34	74	111	116	60	54	39	529
Licensed by 2013	40	12	26	17	40	35	19	27	11	227
Commercial in confidence	7	4	9	6	13	23	16	13	2	93
Total	77	27	69	97	164	174	95	94	52	849

Figure 4: *License status of intellectual property in 2013 by year of protection*



3.9: Products and interventions

Summary

- Researchers reported that their work had led to the development of products or interventions in 12 per cent of awards (642/5,559), an increase on last year's data, in which recipients of 10 per cent of awards reported products or interventions.
- As can be seen by the chapter on case studies drawn from this section, this is a particularly important set of information with respect to the outcomes from research. We know from telephone surveys of MRC principal investigators that there is significant under-reporting of the developments arising from MRC research in this section, and so will be working to improve reporting in this area. A targeted effort to capture the details of trials linked to MRC research, which should be reported in this section, brought excellent results with more than 200 trials now linked to MRC research.
- There were 1,019 instances of products and interventions being reported in total; the average number of products and interventions reported per award (of those awards reporting products or interventions) was two (1.59).

Products and interventions by type

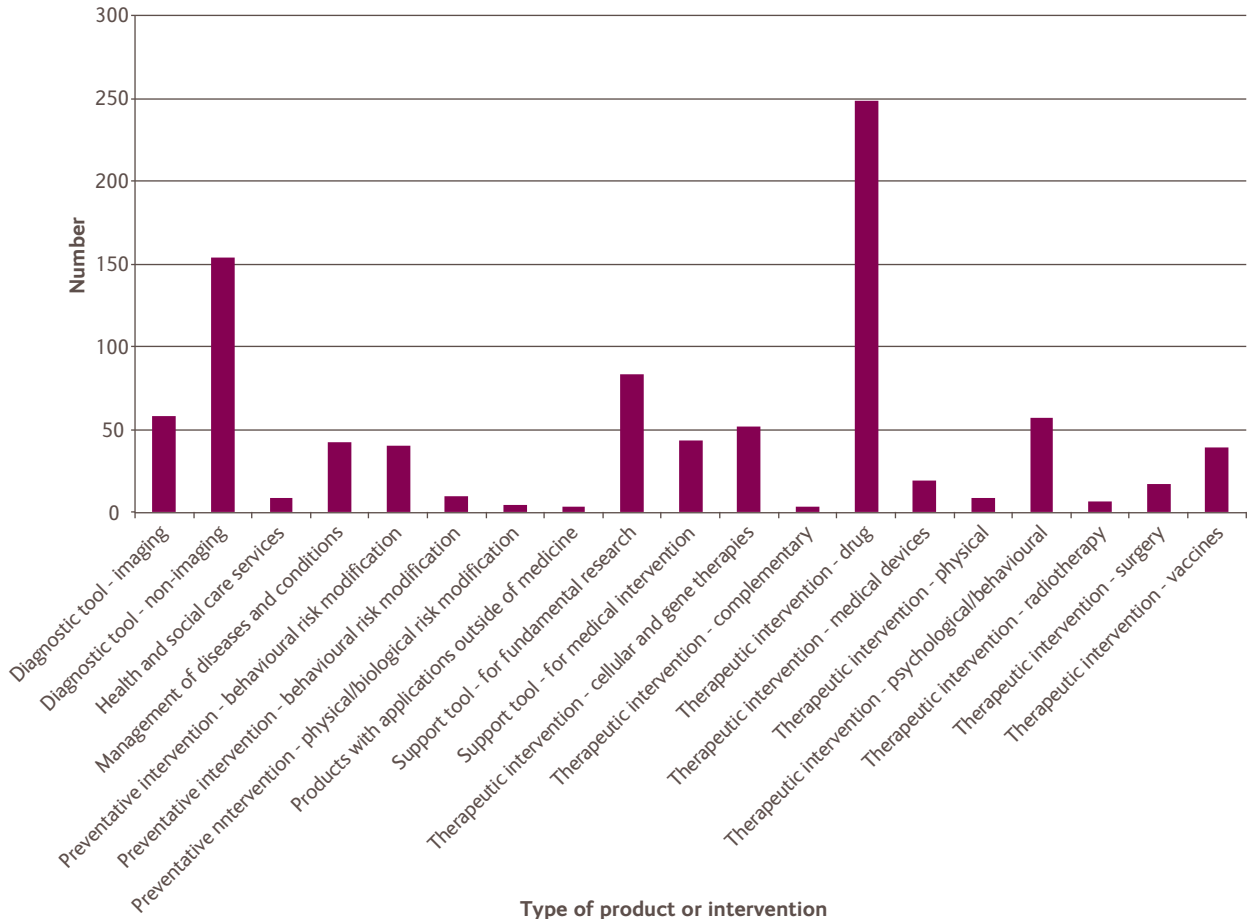
- The most common type of product or intervention in development was the therapeutic intervention – drug, reported by 249 awards (28 per cent of all products and interventions reported). This was closely followed by the diagnostic tool – non-imaging, reported by 154 awards (17 per cent of all products and interventions). The breakdown of products and interventions by type is shown in table 1 and figure 1.

Table 1: *Breakdown of products and interventions by type*

Type of product or intervention	Number of instances	Percentage of total
Diagnostic tool - imaging	58	6%
Diagnostic tool - non-imaging	154	17%
Health and social care services	9	1%
Management of diseases and conditions	43	5%
Preventative intervention - behavioural risk modification	40	4%
Preventative intervention - nutrition and chemoprevention	10	1%
Preventative intervention - physical/biological risk modification	5	1%
Products with applications outside of medicine	4	0%
Support tool - for fundamental research	83	9%
Support tool - for medical intervention	44	5%
Therapeutic intervention - cellular and gene therapies	52	6%
Therapeutic intervention - complementary	4	0%
Therapeutic intervention - drug	249	28%
Therapeutic intervention - medical devices	19	2%
Therapeutic intervention - physical	9	1%

Therapeutic intervention - psychological/behavioural	57	6%
Therapeutic intervention - radiotherapy	7	1%
Therapeutic intervention - surgery	17	2%
Therapeutic intervention - vaccines	39	4%
Total	903	100%

Figure 1: *Breakdown of products and interventions by type*



Products and interventions by development stage

- A total of 125 awards reported products and interventions as being launched onto the market since 2006, with a further 18 awards reporting products and interventions currently undergoing the process of market authorisation.
- There were 287 reports of products and interventions in early- or late-stage clinical evaluation demonstrating the strengthening pipeline of developments supported via MRC's investment in experimental medicine.
- There were 473 reports of products in initial or refinement stages, demonstrating the strength of MRC's investment in discovery and translational science. The inclusion of DPFS projects in 2011 has significantly added to the number of projects in early developmental stages.
- Table 2 and figure 2 show the distribution of products and interventions by development stage. Figure 3 shows the distribution of products and interventions by type and development stage.

Table 2: *Products and interventions by development stage*

Stage of development	Number of instances	Percentage of total
Initial development	277	31%
Refinement, non-clinical	113	13%
Refinement, clinical	82	9%
Early clinical assessment	180	20%
Late clinical evaluation	107	12%
Market authorisation	18	2%
Small-scale adoption	71	8%
Wide-scale adoption	54	6%
Total	902	100%

Figure 2: *Products and interventions by development stage*

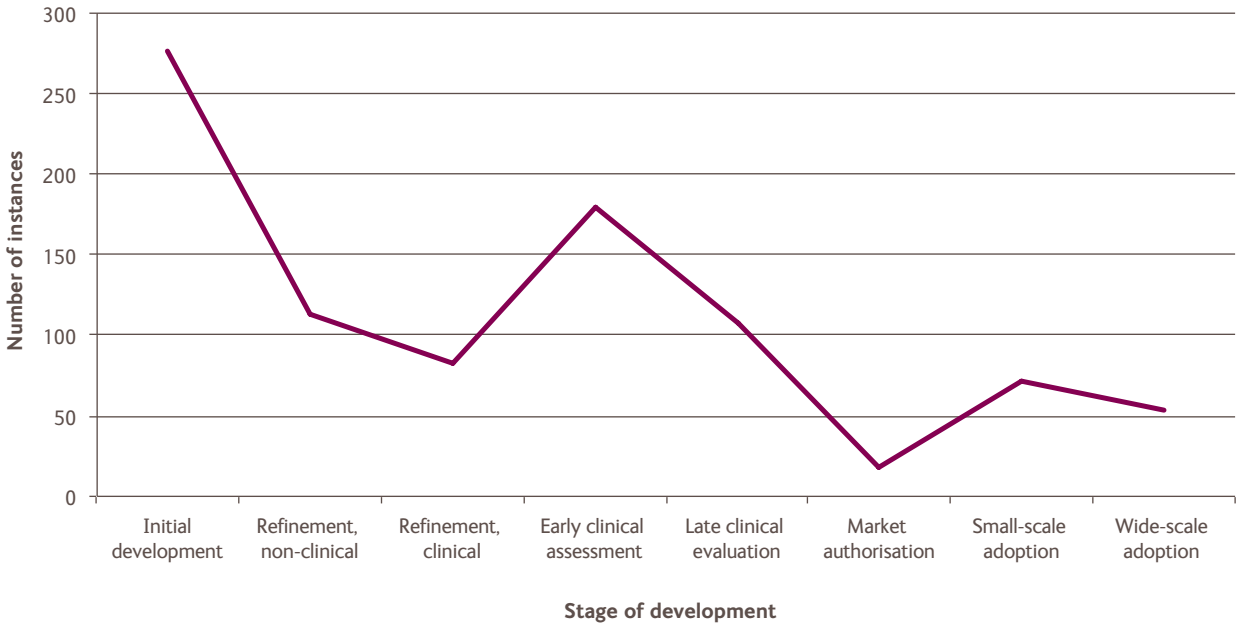
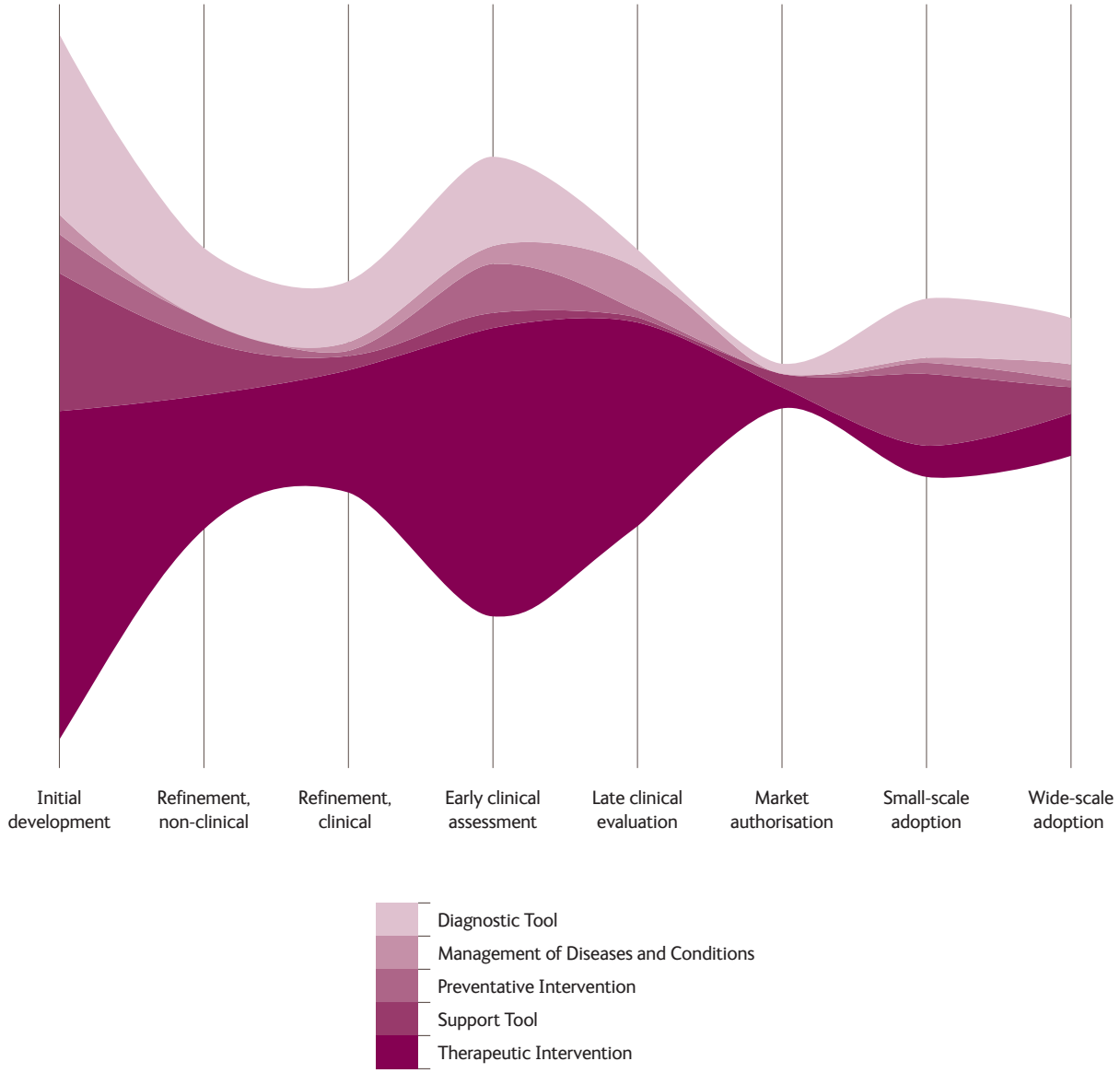


Figure 3: *Distribution of products and interventions by development stage and type*



3.10: Impacts on the private sector

Summary

- The MRC now has evidence of MRC-supported research leading to the creation of 109 companies, 82 of which have been formed since 2006. It is estimated that these companies represent at least 500 new highly skilled jobs in the UK.
- Further details on each of the spin out companies are on the MRC website[266].

3.11: Awards and recognition

Summary

- Recipients of 50 per cent of awards reported that their work had resulted in formal recognition or award for them personally or members of their team.
- The average number of reports per award (of those reporting recognition) was six (5.93).
- In total, researchers made 16,317 reports in this section; a large increase on last year's figure of 11,338.

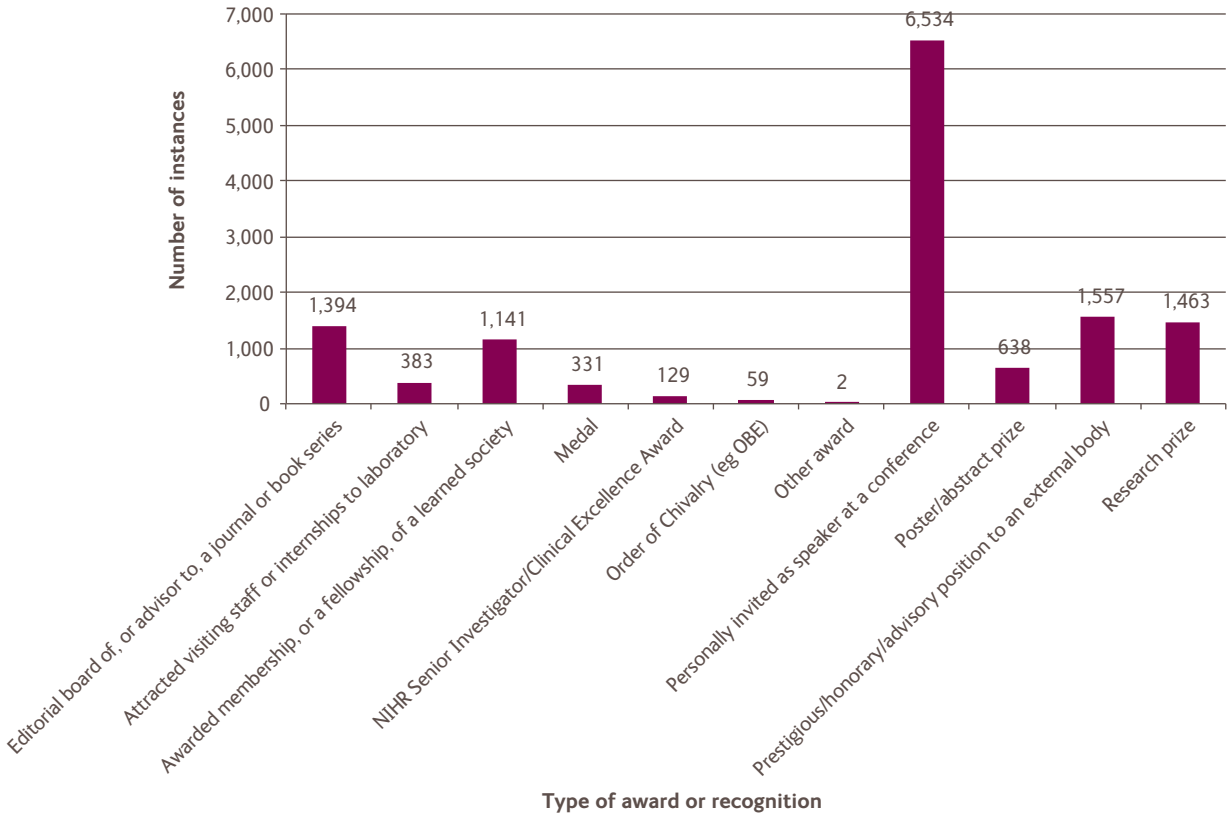
Awards and recognition by type

- The most common form of award or recognition was being personally invited as a speaker at a conference (47 per cent), followed by being appointed to a prestigious/honorary/advisory position to an external body (12 per cent) and appointed to the editorial board of, or as an advisor to, a journal or book series (11 per cent).
- Table 1 and figure 1 show the distribution of types of award and recognition.

Table 1: *Awards and recognition by type*

Type of awards and recognition	Number of instances	Percentage of total
Appointed to the editorial board of, or advisor to, a journal or book series	1,394	10%
Attracted visiting staff or internships to laboratory	383	3%
Awarded membership, or a fellowship, of a learned society	1,141	8%
Medal	331	2%
NIHR Senior Investigator/Clinical Excellence Award	129	1%
Order of Chivalry (eg OBE)	59	0%
Other award	2	0%
Personally invited as speaker at a conference	6,534	48%
Poster/abstract prize	638	5%
Prestigious/honorary/advisory position to an external body	1,557	11%
Research prize	1,463	11%
Total	13,631	100%

Figure 1: *Distribution of type of award and recognition*



Endnotes

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MRC-funded research has played a significant role in the establishment of some of the earliest biotechnology companies. Biogen was formed in 1978 and one of its founders was Research Council scientist Professor Sir Kenneth Murray, whose work, jointly with that of Heinz Schaller, provided the basis for the Hepatitis B vaccine launched in 1989. The vaccine is now marketed by GlaxoSmithKline and Merck as Engerix-B™/ Recombivax™, and has achieved $1bn in annual sales.
Some of the MRC's more recent successes include Oxford Nanopore Technologies, Heptares Therapeutics, Pentraxin Therapeutics, Bicycle Therapeutics, and Thiakis Ltd, an Imperial College London spin out based on the obesity research of Professor Steve Bloom, and which was acquired by US-based Wyeth Pharmaceuticals for £100 million in 2008.
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253. All primary, peer-reviewed publications that were published in refereed journals from 01.01.06 onwards, in which the PI or members of their research group were named as authors.
254. Where more than one award claims to have contributed to a publication, each is credited equally. This means that several thousand publications are counted multiple times.
255. Researchers reporting a collaboration via Researchfish can list any number of partner organisations as party to that collaboration. For the purposes of this summary analysis all partners across all collaborations are referred to as 'collaborators' linked to an award. So if two collaborations, each involving two partner organisations, are attributed to an MRC award, it is noted that four 'collaborators' are linked to this award.
256. In this analysis, the occurrence of non-unique collaborators from different locations is counted, so for example, if three MRC researchers indicated that they collaborated with the same partner in North America, this would be counted three times. Collaborators with more than one location, for example, the United Nations, or multi-national companies, are categorised as 'global'.
257. Each map has a number of circles and each circle's size represents the number of non-unique collaborators reported with each particular country. Global collaborations are also listed and the scale is noted.
258. This is the estimated expenditure of further funding during the time frame of Researchfish, rather than a reported commitment of further funding. Estimates of expenditure are based on the assumption that the spending is distributed evenly over the period reported. For example, if a researcher reported £100k of funding from 1 December 2012 until 1 December 2014, it is estimated that 50 per cent of this award or £50k will have been spent in the period covered by the 2013 data-gathering period.
259. Reported in Researchfish.
260. Discounting the 'other' category.
261. Researchers are advised to report any recurring activities only once.
262. The range of options in this section changed in 2012 to include activities where the audience was primarily academic, however, MRC researchers are still advised not to report these.
263. The time between the start of the award and the influence being reported.
264. The time between the start of the award and the intellectual property being reported.
265. A study of over 1200 patents published by the University of California and the University of Columbia in all disciplines between 1980 and 1994 found that 41 per cent of these were licensed by 1992. A similar study of 686 patents published by the Memorial Sloan-Kettering Cancer Centre and Dana Faber Cancer Institute between 1983 and 2003, also found that 41 per cent of these were licensed by 2007. Other studies have indicated a lower proportion of patents licensed (for example, 25 per cent of NASA patents published between 1994 and 2002 were licensed by 2007).
266. www.mrc.ac.uk/documents/xls-csv/spin-out-company-list/

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