MRC Medical Research Council

MRC Translational Research 2008-2018

Evaluation Report: Evaluation Framework (Annex A2.1)

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Annex A2.1: Evaluation framework

This annex sets out the overarching framework used to guide the evaluation of the last 10 years of the Medical Research Council's (MRC) translational research portfolio. The framework set out a theoretical causal process by which the MRC's investments in translational research might be expected to deliver their intended outputs, outcomes and impacts. The purpose of the framework was to identify the key outcomes that needed to be examined in the evaluation, highlight issues that may be encountered in establishing the evidence for these outcomes, and wider issues that may need to be explored to interpret the findings.

1 The MRC's translational research portfolio

1.1 Objectives

The MRC's translational research portfolio (the translation of basic scientific findings observed in laboratories into clinical application in humans) has developed considerably over the last 10 years, to address a broad range of perceived challenges in relation to the translation of basic or fundamental knowledge into health and wellbeing benefits for society. The overall translational objectives of the MRC are to:

- Encourage and support research to improve human health;
- Produce skilled researchers;
- Advance and disseminate knowledge and technology to improve the quality of life and economic competitiveness of the UK; and,
- Promote dialogue with the public about medical research.

The MRC also produced a set of strategic aims:

- To increase the scale and speed of progress from discovery into new clinical studies
- To strengthen R&D in areas which underpin and enable translation where there are currently bottlenecks
- To strengthen the quality and scale of infrastructure for translational research
- To define and support priority research areas effectively
- To develop a strong, internationally unique, programme in research methodology
- To improve progression of innovative interventions into late phase ii and phase iii clinical trials
- To improve peer review and evaluation of research proposals and projects with translational elements
- To improve partnership working
- To enhance skills and capacity underpinning of all these areas.

1.2 Rationale

Following the Cooksey review[1] in late 2006, the MRC and other funders invested significant resources to bolster UK translational research to address gaps in translation (primarily the process of taking ideas and developing them into products that can be disseminated into wider healthcare practice potentially through commercialisation) and improving the coherence and coordination of publicly funded support for translating basic scientific research (or discovery science) into health interventions.

A mix of views were offered by stakeholders regarding the degree of funding made available by the MRC for translational research at the time. However, there was a degree of consensus regarding the factors holding back the level of translational effort within academic institutions. Career progression in academia was linked to (a) the quality

[1] https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/228984/0118404881.pdf

of research produced by academics (as inferred from the impact factor of journals) and (b) the level of funding attracted. The strength of incentives to engage in translational research were limited by both the absence of targeted funding and the likelihood that the translational research would not lead to publications in the highest profile journals. The economic crisis of 2008, as well as concerns that reduced profitability stemming from the anticipated 'patent cliff' was reducing appetite for risk in the life science sector, was also limiting private funding for early and late stage translational research. The Government sought to act to maintain investment in R&D in the life science sector to stimulate economic growth.

Responding to this issue, the Office for Strategic Coordination of Health Research (OSCHR) tasked the MRC and NIHR to develop their translational research portfolios to help address these barriers. This led to the introduction of the MRC's Departmental Pathway Funding Scheme (DPFS) which provided targeted funding to support the development of translational research projects led by academic research teams at early stages of the development pathway, as well as a range of other targeted programmes aiming to either address issues and barriers encountered by translational researchers in developing new products or interventions or to provide further support for translational research projects.

1.3 Evaluation scope

The evaluation is intended to cover the following components of the MRC's portfolio of translational research projects funded over the last 10 years. This portfolio can be grouped into the following categories:

- **Directed translational projects:** These are projects funded through the MRC's directed translational initiatives, where the core intent of the funding is translation. There have been 608 grants awarded through these initiatives since April 2008, that completed their MRC funding by March 2018, and these account for £337 million of MRC spending over this period. These initiatives vary in terms of their underlying objectives, and can be grouped as follows (though there is some overlap between these categories):
  - **Focussed translation:** Several programmes (the DPFS, Confidence in Concept, Regenerative Medicine Platform) have been funded with a central objective of accelerating the development of new products. The DPFS programme accounts for the greatest share of spending under this theme. DPFS applications are assessed against additional criteria not normally emphasised by the MRC. For example, panels may consider factors including the level of medical need being addressed by the underlying product, the benefit of a proposed technology relative to competing alternatives, and the freedom of the research team to operate. DPFS projects, in contrast to open-ended discovery work, have predefined technical goals and are monitored against technical milestones.
  - **Enabling research:** Other programmes and funding calls have the objective of producing knowledge that may not result directly in a medical product but can be used by others to unblock or otherwise enhance the translational research process. This could include efforts to improve basic understanding of disease biology – such as validating the presence of human disease pathways in animals or identifying biological properties that indicate the presence of disease. This group of projects also include those aiming to develop tools or methodologies that enhance or enable translational research initiatives – such as research into optimal clinical trial design. The translational impact of these projects will be largely in terms how the knowledge produced enables other researchers to progress, rather than directly supporting the development of an underlying translation concept, product, or technology.
  - **Networking:** A third group of programmes involve a stronger focus on putting in place the conditions to allow academic and industry to collaborate more effectively. These projects may lead to the genesis or initiation of activity described above, but do not involve any direct funding for research.
- **Non-directed translational projects:** In addition, the MRC funds projects through its research boards that state an intention to translate clearly in their proposed work. The MRC has identified 964 awards with translational intent (detected by text mining of application abstracts), awarded since April 2008 and completed by March 2018. These awards total £713 million of expenditure. The translational component of these projects will vary and may only be a relatively limited strand of activity in some cases. Funding arrangements also give researchers flexibility to change direction during delivery, and the importance of translational objectives to the underlying project may increase or decrease as the project evolves. This group of projects may include projects with no translational objectives (but have abstracts that are worded in a way that creates a false positive result) and overlooked projects with translational objectives (but with no concepts that the automated coding approach will identify).

- **Other awards:** The remaining MRC portfolio (all other MRC awards funded after April 2008 and completed by March 2018, excluding fellowships), totalled 2624 awards and approximately £2.2 billion. Although there was no translational intent in the abstracts of these proposals, detectable using the text mining approach, some of these projects nevertheless had reported outputs via Researchfish® that suggested that translational work had taken place. Outputs of interest included a link to spin-out companies, the development of new products or clinical trials, private sector follow on funding, and patent applications. Given the nature of response-mode funding, where the applicant has flexibility to explore research avenues that arise, these translational outcomes may have been unexpected, and / or the original abstract not detailed enough in this respect to indicate that part of the work would be translational, or indeed this translation may have occurred subsequent to the research in the project. We also could not rule out occurrences where the self-reported Researchfish® information may have been attributed to these projects in error, and so indicate false positives. A small number of other awards, where there was evidence of reported translational outcomes, were included in this evaluation. There seemed no reason to investigate any awards from most other awards that had no evidence of any translational outcome at all.

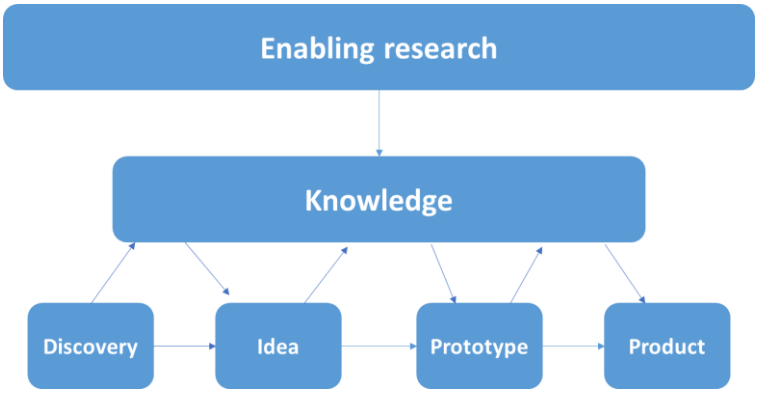
For the purposes of this evaluation, we are not including projects that support the delivery of late phase clinical trials (beyond Phase IIa) and implementation or efficacy studies which occasionally involve combined funding from other research funders (e.g. NIHR), 218 of these late translational awards, totalling £294 million were identified.

Typology of interventions

The portfolio of interventions funded can also be understood in terms of the following stylized model of the translational research process in Figure 1.1. below:

- **Product development:** The model describes the translational process in terms of a progression from fundamental research or discovery research to product launch through stages of idea and prototype development. 'Product development' projects (as defined above) map onto this this process.
- **Enabling research:** This process draws on (and contributes to) a broader body of knowledge generated through fundamental science and could potentially be blocked if there are fundamental gaps in this knowledge. 'Enabling research' projects (as defined above) primarily seek to address these gaps.
- **Networking:** Networking projects have the potential to facilitate the translational process in numerous ways. For example, collaboration could lead to new ideas for potential prototyping or product development (including repurposing of existing products) or better understanding of the key gaps in fundamental science, methodologies or tools that are acting to hold up translational research – leading to the initiation of new research programmes. However, collaboration could also act to improve the transmission of existing knowledge between groups, enabling activity to progress.

Figure 1.1: Translational process model



2 Theory of change

This section sets out the expected causal process by which the MRC's translational research portfolio will deliver its intended results.

2.1 Inputs

Projects within the MRC's translational research portfolio will (or may) draw on a wide variety of inputs:

- **MRC funding:** Translational research projects will draw on MRC funds to progress the programme of activity and achieve the aims and objectives that are defined in the application form. In the case of product development projects, this funding may help the researchers involved to refine the underlying translational concept, technology, product or intervention, but will not be enough to bring a new product to market. As flagged below, one metric of translational success will be in terms of how far the academic research teams have secured additional funding secure onward funding following completion of the project. Follow-on funding is potentially available through the MRC, and there are number of examples of academic research teams being involved in a sequence of closely related projects.
- **Funding from other research funders:** In addition to MRC funding, projects may receive funding from other public or charitable research funding organisations (e.g. NIHR, Wellcome Trust, Cancer Research UK, British Heart Foundation, Arthritis Research UK, European Research Council).
- **Private investment and in-kind support:** Projects may receive funding from private investors to support development of specific products (or methodology or best practice underlying infrastructure to promote translation into the clinic). If the product has commercial potential, industry invest of further development would require a university to establish a commercial vehicle to receive private funds (or alternatively, the underlying intellectual property could potentially be licensed to an external firm).
- **Applicants own resources:** Researchers may also draw on resources from their own organisation to support the delivery of a project, including financial, technological, infrastructure and human resources, as well as knowledge. Academic research teams are likely to draw on the resources of their Technology Transfer Office, and where applicable, the Translational Research Office, to support project management, collaboration with industrial partners, understanding of regulatory pathways, or commercialisation.

2.2 Development of medical products and health-influence interventions (Focused translational research)

Funding has been channelled through a range of initiatives (see Annex A for specific initiatives) aiming at supporting projects in the development of new products and interventions. These activities focus on accelerating the development of novel therapeutics, diagnostics, medical devices and public health interventions:

2.2.1 Activities

- **Project delivery:** Funding is used to resource research activity at variety of different stages in the product development process. Funding tends to be focused on early stage work, such as exploratory paper studies to help validate a potential target for a new therapeutic, or experimental proof of concept studies seeking to identify candidate molecular compounds that modulate the target disease pathway and explore the properties of those compounds. However, funding is also available to fund activity at later stages including pre-clinical laboratory studies (such as toxicology testing or tests in animal models of the disease pathway), and in some cases, clinical trial activity involving tests in humans. Late stage clinical evaluation (e.g. Phase III trials) is outside of the remit of the MRC.
- **Formation of collaborative relationships:** Research that bridges the pre-clinical and clinical spheres of discovery and development typically requires multidisciplinary teams that may span academic, clinical and industrial researchers, requiring many different skills and sector perspectives to identify opportunities and overcome challenges. From a transactional point of view, teams will need to draw on a breadth of skills to facilitate project delivery, including basic scientists, project managers, regulatory experts, clinicians and statisticians, addressing the many facets of drug development, such as target selection and validation, safety, exposure, statistical significance and commercial opportunity. Collaboration may also enable the delivery of projects by facilitating access to complementary resources (e.g. intellectual property) or capabilities needed to support

progression. Collaboration with end-users, such as medical professionals or patients, may be vital in understanding customer needs or constrains and how a new product might ultimately be integrated into health users. The MRC has also developed a specific contractual agreement (the MICA) which is specifically designed to facilitate collaboration between industry and academia. Academic research teams may also draw on internal resources within their TTO or Translational Research Office to support the design or delivery of projects or the later commercialisation the underlying translational concept or technology.

While the collaboration forming around a specific project to develop a translational concept or technology may have a transactional dimension, the relationships involved may have been formed in advance of the application for funding and may endure beyond the funding provided by the MRC. As such, on-going interactions between researchers may have been critical in the gestation or refinement of the hypotheses underlying the translational concept. As highlighted above, the MRC funds a range of activity with the aim of engendering a broader platform of collaboration between academic researchers and other communities of interest (such as the MRC/ABPI Inflammation and Immunity Initiative). The MRC also funds the Proximity to Discovery Fund to support exchange of staff between academia and industry – not just at the level of post-doctoral researchers, but also staff involved in project management and/or commercialisation activities (e.g. TTO staff). These wider activities aim to feed into wider objectives to facilitate cultural changes in the approach to translational research adopted by academic institutions (described further below).

In turn, these activities are expected to lead to the following **intermediate outputs and outcomes**:

- **Development of knowledge:** Projects funded will involve implementation of a research protocol which at its core will produce new knowledge regarding disease biology and/or the properties of the translational concept, technology and product being developed. This knowledge will be translationally relevant – producing results that confirm the initial hypotheses and supporting progression to subsequent tests to further develop the project, or disconfirming hypotheses – requiring an assessment of the underlying causal explanations for those results, revisions to hypotheses, and where feasible, refinements to the underlying technology or translational concept (or alternatively concluding that the underlying approach is not viable). Projects may also add to the stock of basic knowledge of disease biology with the potential to spill-over into parallel programmes of research as described below (or in the case of technical failures, discouraging others from pursuing similar avenues).

  The value of this knowledge be connected to the quality of the underlying science forming the focus of the project and/or the research design. For example, researchers may not draw useful conclusions if the projects deploy animal models that are an inadequate representation of the relevant disease pathways in humans, if compounds or cellular materials being tested have been imperfectly manufacturing, or if trial designs do not offer enough statistical power to support the desired conclusions. The ability of research teams to generate useful knowledge may also be hindered by practical issues encountered in the delivery of the research programme – for example, if there were unexpected difficulties in recruiting patients, required skills absent in the research team assembled, and gaps in infrastructure needed to support the project. While the research process may allow the researchers to acquire new types of understanding, it may also highlight specific gaps in fundamental knowledge that may need to be addressed to enable further progression (e.g. the absence of an appropriate biomarker or validated animal model of the disease pathway being studied).

- **Academic publications:** Translational projects have the potential to lead to research publications in academic journals expressing the knowledge acquired through the study and will be a key mediator of any spill-over effects. While academics may have wider incentives to publish the results of their research, the publication of the results of clinical trials and similar also acts to encourage the adoption or consumption of any new products developed (as national health systems will typically require evidence that the treatments involved are both effective and cost-effective). While Researchfish provides lists of academic publications that have reportedly arisen from the projects, a review suggests that in some cases, the publications listed are only tangentially (if at all) connected to the underlying research. As such, interviewers will require a critical review of the relevance of the publications cited in advance of the review.

- **Informal dissemination and engagement:** Those involved in the project may be invited to participate in workshops, meetings, and other similar activities, and information related to the project could be picked up by local media for example. The distribution of knowledge in this way has the potential to have wider impact, for example within the academic and industry communities, but also more widely across the NHS, government and even the public domain.

While the above results might be expected during an MRC award, further results can be anticipated beyond the lifetime of the grant:

- **Onward progression:** In many cases, the translational concept or technology will follow a highly structured and regulated development pathway involving a sequence of tests to determine its safety and effectiveness in producing its desired clinical results in humans. The MRC funded project will only cover a subset of the activities to be undertaken on this journey, and key measure of success or impact will be in terms of any onward development that has been taken forward by the research team (or others) beyond the lifetime of the grant. There is a wide array of both technical and non-technical barriers that might encountered in achieving this progress, of both an avoidable and unavoidable nature – which are given further consideration in the following subsection. There are also variable product development pathways across different types of product (e.g. the regulatory requirements involved in bringing a Class I medical device to market are substantially less onerous and costly than those associated with new medicines). Additionally, the investment cost and time associated with reaching the next stage of technical progress broadly grow exponentially as the product gets closer to market.
- **Leverage further research funding:** To take the project outputs further along the translational pathway, it is anticipated that research teams will need to attract further funding. Follow-on clinical trials based on original research will likely factor significantly here. Funding could be available from public or private sources. It will be possible to determine how successful teams have been securing additional public funding through databases of grants awarded by research funders (e.g. Gateway to Research). To attract private funding, it is anticipated that research teams will need to establish an external commercial vehicle – potentially with the support of the TTO – as described below. Such a commercial vehicle would then be capitalised by external investors (typically VC funding – at least in the short run – though in the longer term, other options may open to companies – such as raising funds on capital markets through an IPO or via management buy-outs / private equity).

  The MRC's rigour in how it approaches its translational research funding can also help to de-risk investment from the point of view of external investors. For example, the scientific due diligence provided by the MRC's activities (e.g. the strict requirements projects must meet to obtain DPFS funding – which places great emphasis on the scientific underpinning of projects) may send positive signals to external investors (e.g. venture capitalists) providing assurances around the underlying scientific basis of a project (e.g. the likelihood that the project will produce the intended outcomes). This may raise the confidence of external investors to invest in the project, potentially reducing their own due diligence or search costs (sometimes referred to as a 'certification effect') when deciding where to invest their capital.
- **Impact of collaboration:** An expectation of more academic researchers working in collaboration with industry is that this may lead to greater exposure to the industry 'mind-set' and facilitate a deeper understanding of how to progress their research along the translational pathway. A range of skillsets common to industry are not well established in academia, such as medicinal chemistry, drug metabolism and pharmacokinetics, and safety evaluation (toxicology). By combining expertise, collaboration can 'prime' academic research for uptake for further development, e.g. by ensuring robust target validation, and decrease the risk of failure. This may also enable greater mobility across sectors (between academia and industry) and career progress (i.e. benefits of the experience gained from collaborating with industry may support academics in furthering their career). Collaboration may also lead to other impacts, supporting the sustainability of cultural changes within academia (in relation to translational research - see below for more detail). Similarly, some projects are expected to support greater collaboration between academics and clinicians (those who will use medical products), and this may lead to improved understanding of the needs of clinicians (and their patients) as how best to tailor medical products to meet user needs. It may also assist academics in 'discovering' new research projects, i.e. opportunities or approaches to tackle a health issue or facilitate multi-disciplinary research combining the skills of academics and clinicians within a research project. However, collaboration may not always produce beneficial results – there will inevitably be uneven returns to collaboration across partners, potentially leading to variable levels of commitment to the project, which could undermine the onward progression of the underlying translational concept or technology if key partners do not make the anticipated contributions (or withdraw their involvement altogether).
- **Registration of intellectual property:** Projects might lead to the development of new scientific or clinical knowledge that can be protected through patents or other intellectual property. The level of patenting will also depend on baseline levels of technical development and the extent of any foreground IP at the start of the project. Such effects might plausibly be observed for projects at earlier stages of technical development. Though it is important to note that timing of patenting is a strategic decision as the holder of intellectual property will need to both maximise the lifetime of the patent to maximise commercial returns, while being alert to the risk that others

may patent technologies with similar features (reducing the size of the property right acquired). It should also be noted that research teams may hold back academic publications if there is a risk that this may jeopardise the underlying IP position. Foreground IP issues could also act to block the onward development of the underlying translational concept – for example if the IP on which the project was based was licensed from a third party with restrictions on how it could be ultimately be exploited. The absence of intellectual property protections could also act as a block on onward progression through the private sector – e.g. investors will have limited incentives to invest if they are unable to acquire monopoly power on any resultant technologies. TTOs and Translational Research Offices may also have a significant role in decision making around patenting decisions and will need to trade off the costs involved against the (future) commercial value of holding the patent.

- **Licencing deals:** The marketing and logistical costs associated with onward development may also be externalised through licensing agreements with industry, where firms assume responsibility for further R&D, manufacturing, logistics and marketing. Such a strategy may deliver lower pay-offs for projects but would also externalise the risks associated with managing a complex set of operations which may require greater resources than can be brought to the project than can be marshalled by the team. The MRC holds little information on licences, however, and therefore a requirement of this evaluation will be to explore the number of licences (this may be possible through data sources, such as Gateway to Research or via TTOs). Interviews will also be critical in determining the licensing outcomes associated with the initiative, though it is also important to acknowledge that where licensing deals have been agreed – the researcher may not have full details of the agreement (which may have been put in place by the TTO), or a detailed understanding of the onward development of the technology. As such, it will be important to review whether interviews are producing enough detail on outcomes where licensing deals are concerned – and whether it would be feasible to undertake interviews with licensees to provide additional information. It is important to note that most products being investigated by MRC-funded projects will be unlikely to have progressed this far and the responsibility for licensing negotiations often lies beyond the that of the PIs but to university TTOs.
- **Spin-out activity:** A key indicator of progress towards commercialisation will be the propensity for the researchers involved to 'spin-out' or create a new entity with the objective of commercially exploiting the intellectual property generated. However, there is some ambiguity as to the possible direction of the impacts that may be observed in this area: one possibility is that the availability of MRC funding for translational research helps protect the researchers from the need to commercialise too rapidly (with possibly damaging effects on the commercial prospects of the project under development), which could lead to a reduction in the propensity to spin-out in the short term (though the spin-outs themselves may ultimately prove more sustainable). It is assumed that in many cases, the Principal Investigator will be part of the management team (in roles such as Chief Scientific Officer), but without responsibility for the commercial management of the firm. As such, it may be beneficial to include interviews with commercial management staff to help understand the importance of the originating research to the firm's product pipeline. Additionally, it will be important to consider the success of the spin-out – which may be
- **Commercialisation of new products**: The funding arrangements described above will be used to fund research activity aimed at further progression through the translational pathway. In the long term, this may eventually result in market authorisation (e.g. European Medicines Agency orphan designation), approval by health systems, and the commercialisation of new products. It is important to note that this is a long-term process and it is unlikely that the interviews will reveal significant outcomes of this nature (though medical devices and diagnostics have a much shorter time to market authorisation). It is also highly unlikely that a spin-out could marshal the depth of resources required to take a product through the highly costly process of Phase III clinical trials (except perhaps in the case of some cell and gene therapies where trials typically involve smaller number of participants than for small molecule pharmaceuticals). This may be evident where large pharmaceutical companies have taken equity stakes in or acquired spin-outs (and anecdotally, some large companies have transformed their business model to focus on the acquisition of late stage biotechnology companies to de-risk their R&D activities). Again, this is unlikely to be a frequent occurrence.
- **Policy influence**: As a result of a project, those involved (either directly or indirectly) could end up participating in activities which have much wider impact, for example being invited to be part of an advisory committee, or a national consultation. As well, knowledge produced as a result of the original project could make its way into training or course material for students, practitioners or researchers thus the impact could be much wider in reach.

- **Economic value:** The long-term nature of the product development cycle creates some challenges in understanding the economic value of translational research projects that have been funded, as the impact of MRC funding is unlikely to be visible in turnover and economic output (GVA). As such, it may be more instructive to focus on firm valuations which are implicitly observed each time an equity investment is made. The value of the firm – in perfect financial markets – will represent investors (risk-adjusted) expectations of the firm's future profits (and is also a measure that can be relatively unproblematically treated as a 'benefit' under HMT Green Book guidelines for cost-benefit analysis).
- **Human health:** The main social benefit associated with the MRC's programme of translational research will be the impacts on human health resulting from the introduction of new products or interventions, enabling diseases to be treated or diagnosed more effectively (or cost-effectively). Given the long-term nature of these types of outcomes, it may be difficult to capture these effects in a systematic way. However, the findings of clinical trials will at least provide measures of the potential early health benefits accruing to trial participants (and their economic value, should the trial include a health economic analysis).

2.2.2 Barriers to translation

The simple representation of the translational research pathway implies that it is a straight-forward passage of innovations, such as drug candidates, unchanged from discovery to clinical development and on to regulatory approval. However, this is in stark contrast to the diverse network of iterative learning loops, with potential failure at every step:

- **Scientific failure:** Scientific failure of progress along the translational research pathway can be thought of in terms of three broad – and to some degree overlapping - categories:
  - **'Hypothesis failure'** happens when research conducted to the highest standards results in negative results, e.g. the drug candidate was conclusively shown to lack efficacy in early TR phases, or a different approach tested elsewhere is proving to be superior. This type of failure is part of the nature of research. The earlier in the translational pathway this failure is recognised, the better, as later costs and efforts can be avoided. Findings from 'experimental failure' projects can feed back to inform and improve further research. However, if this feedback loop remains open, it can lead to 'avoidable failure' (see below). For example, a project had already uncovered issues with a certain approach, but restricted access to research results led to a duplication of the (fruitless) research effort. This problem is exacerbated by a lack of interest from journals to publish negative results.
  - **'Knowledge & skills failure'** occurs when important known factors were not considered in preceding TR phases, leading to 'avoidable' research failure, e.g. insufficient/sub-optimal target validation leading to failed clinical trials, or a lack of attention to implementation, regulatory or manufacturing issues which render the innovation unusable. Knowledge resulting from early translational research needs to be 'translatable', i.e. matched to requirements for moving to later stage clinical trials and then into real-world settings, and hence requires some consideration of these aspects from the outset. Avoidable failure also includes issues with reproducibility of academic research in industry settings (Freedman & Mullane 2017).
  - **'Experiment failure'** is caused by a current methodological or technological gap in the field, e.g. a lack of suitable animal models or biomarkers, or 'unrealistic' clinical trial designs given the complexity of the indication and limited size of (stratified) patient population. The research was guided by the highest standards in the field, but the tools employed fell short in some way. While one might question why these types of projects are attempted at all, it must be considered that researchers are likely aware of the known experimental shortcomings and the enhanced risk of failure (compared to a hypothetical 'optimised' R&D protocol) but need to balance this risk against the desire to address an unmet health need.

    Some of these issues relate to the artificiality of experimental set ups. For example, many of drugs are approved based on indirect ('surrogate') measures; however, these do not always reliably predict whether the therapy will result in an improvement for the patient. Experiment failures are beyond the remit of the individual project and may extend to an entire research community (e.g. lack of animal models in neurological disease). They can in principle be addressed through additional research.
- **Non-scientific barriers:** Research translation can also be hampered by a number of non-scientific barriers, such as operational and economic obstacles (van der Laan & Boenink 2015). These external factors can occur along

all stages of the translational research pathway, and can be the cause of, or at least contribute to, 'knowledge & skills failure' described above.

- **Within the R&D domain (from academic researcher point of view):**
  - **Cost: e.g.** lack of funds for expensive clinical trials; lack of gap funding between grants; lack of follow-on funding (public or private)
  - **Collaboration:** lack of communication/collaboration between academic researchers, clinicians, and industry; distrust between collaborating partners incl. unresolved differences in aims/ research practice
  - **Skills:** knowledge gaps in research team, e.g. in how to tailor research projects for seamless progression to later stages of development
  - **Infrastructure:** lack of underpinning infrastructure, e.g. GMP facilities; data capabilities
  - **Institutional support:** insufficient support, e.g. for regulatory process, IP and contracts, quality assurance, ethics; requirements of academic institution not conducive to industry collaboration
  - **Incentives and culture:** e.g. translational research outputs and team-work not aligned with academic career progression; research translation not valued in by academic researcher / academic institutions
- **Between research and clinical practice, e.g.** lack of professional awareness of the state of the art of biomedical sciences; lack of infrastructure (e.g. IT) or professionals' skills; resistance to change in the health system; barriers to market access, e.g. entry of innovations into the health system is difficult to achieve and roll-out is slow
- **Between implementation and improved health,** e.g. expenses related to the use of a therapy/reimbursement processes limit use by the health system; lower efficiency of health intervention in real world conditions as compared to R&D findings

2.3 Enabling research

Funding was also channelled through a range of initiatives (see Annex A for the specific initiatives) aimed to support projects in specific areas of discovery science identified as being able to facilitate or support translation research. These activities focus on supporting projects to generate new and deeper understanding in the area of life sciences and human health. This section describes their intended outputs, outcomes and impacts.

The grants focused on the development of discovery science involve the following **activities and outputs:**

- **Delivery of discovery science projects:** Activities to develop new and deeper understanding of a scientific area, including the following:
  - **Data collection and analysis:** We expect projects to involve the collection of a broad range of scientific data (e.g. the collection of disease specific blood samples; biobanks), drawing on existing evidence and research in a subject area, datasets or phenomenon. Discovery science projects may also involve the undertaking of data analysis with the aim of identifying potential correlations or patterns in the data that may inform the development of hypotheses.
  - **Developing new and refining existing methodologies:** We expect that some projects will involve the development of new approaches and methodologies for scientific research, including data analysis (e.g. new animal models, bioassays and biomarkers) and biomedical research.
- **Achievement of project milestones:** Projects may be expected to achieve key milestones set out in their application. This will provide an indication of whether projects have progressed.
- **Hypothesis formation:** A key output from some enabling research projects (e.g. within the 'Other' portfolio) are likely to be the formation of new hypotheses about a phenomenon. This will be shaped by the research findings of a project (i.e. the identification of a panel of plasma biomarkers for Alzheimer's disease) and may lead to further confirmation or clarification research to determine effectiveness.
- **Research tools and methods:** A direct output, occasionally stated in the planning and application phase, for projects of discovery science nature will be new research tools and methods. These may or not be shared with others more widely (where they are, the impact will be felt), and could cover a range of new tools and techniques including statistical modelling to new approaches to collating and storing information, for example the production

of research or clinical databases. These tools and techniques, if shared and used, have the potential to assist others in fundamental research and intervention (and may also lead to licensing deals).

- **Support of early interactions and knowledge exchange:** It is likely that some activities (e.g. proximity to discovery) will support collaborations between academics and industry, as well as collaborations with clinical settings, and may lead to the exchange of skills and knowledge. As people from different sectors work together on projects, this will facilitate the environment for exchanging information about working practices, methods as well as the improving knowledge in the subject matter itself. These early interactions and exchange of knowledge may also occur between academics and policymakers/regulators, influencing the health agendas and future commissioning.

The initiatives focused on the progression of discovery science can be expected to produce a list of the outputs described above, and in turn, these outputs are expected to lead onto the following **direct outcomes and impacts**:

- **New scientific knowledge:** Successful projects are likely to lead to the discovery of new scientific knowledge (e.g. the discovery of disease patterns), forming important research materials for potential future projects and translational progression. For example, addressing significant gaps in understanding (e.g. in the causes and progression of human diseases), may support wider research through providing evidence to support the funding of a new drug. They may also open new research fields, recycle old ideas into new discovery science, result in the development of new mechanisms or methodological approaches for conducting research and the creation of new hypotheses (for testing at a later progression stage). Unsuccessful or closed projects may also generate new knowledge, such as the demonstration of negative outcomes (e.g. a compound is not efficacious) based on robust.
- **Academic publications:** As stated above, for medical products and health-influence interventions, academic projects have the potential to lead to scientific publications in academic journals. The knowledge harnessed in researching in the area of discovery science has the potential to influence the research agenda, if picked up by others, and create new ideas and areas of focus moving forward.
- **Engagement:** As a result of a project, those involved could be invited to give talks or presentations at events and conferences. Those involved may also be identified to participate in workshops, meetings, and other similar activities, and information related to the project could be picked up by local media for example. The distribution of knowledge in this way has the potential to have wider impact, for example within the academic and industry communities, but also more widely across the NHS, government and even the public domain.

As inferred by some of the outcomes from enabling research projects, a set of **wider impacts** are likely to be observed.

- **Collaborative effects:** Projects which form collaboration between academia, industry and clinicians in terms of delivery may bring about direct outcomes and impacts related to partnership working (e.g. multi-disciplinary research involving academics, clinicians and industry; mobility of individuals across different sectors; sustainable culture change; fostering international strategy across a specific field), sharing of information, resources and ideas, and the creation of further hypotheses. This may well stimulate content for talks, seminars and workshops and lectures, for example.
- **Support for further funding applications:** Drawing on evidence from the production of publications or presentations given at conferences, as an example, often projects will provide the evidence needed for others to go on to secure further funding to progress the original hypothesis, or even to investigate further research questions produced as a result of a project.
- **Policy influence:** As mentioned above, as a result of a project, those involved (either directly or indirectly) could end up participating in activities which have much wider impact, for example being invited to be part of an advisory committee, or a national consultation. As well, knowledge produced as a result of the original project could make its way into training or course material for students, practitioners or researchers thus the impact could be much wider in reach.

It is important to note that these wider impacts will be the most difficult to trace – as (1) the translational research programme is not delivered as an integrated strategy focused on particular challenges, so it is a matter of chance whether those receiving grants for translational research absorb or build on the knowledge produced by these projects; (2) cross-references between documentary outputs may not always provide the desired links (e.g. written clinical trial protocols may not reference MRC research even if it has been influenced by it); and, (3) these emerge much slower than direct impacts.

2.3.1 Indirect effects

In turn, a further set of **indirect effects** (i.e. effects on other individuals beyond those that were directly funded through the grant) can be anticipated at a variety of levels (other academics, academic institutions, clinical settings, and in the private sector):

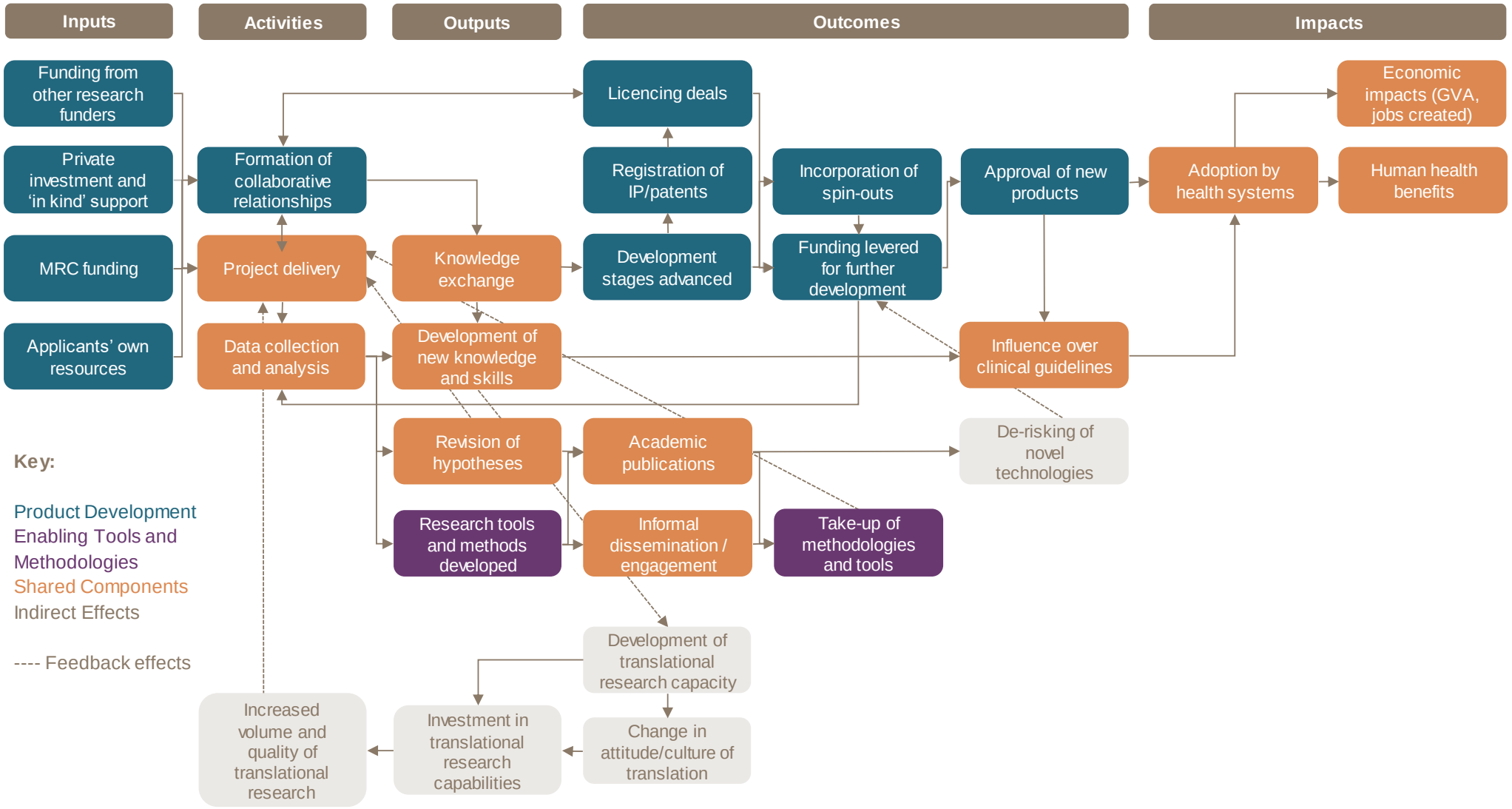
- **Culture change:** The widely anticipated effect of MRC funding was that it would produce a form cultural change in which translational research was more widely perceived as legitimate scientific endeavour (driven partly by the availability of targeted funding in this area, but also by wider efforts by the MRC to support interaction between academia, clinicians and industry). Stakeholders were more reluctant to define specific markers that would signal this form of cultural change, but at a basic level these cultural effects could be expected to lead to greater levels of translational research being completed in academia, and more appetite for interaction with industry (and vice-versa). Other markers of change could include the degree to which universities have made investments in complementary capabilities to support translational researchers – such as the establishment of Translation Research Offices.
- **Agglomeration effects:** MRC funding for translational research may have a cumulative effect on the capabilities of individuals and – by extension – institutions to engage in translational research. As researchers build their technical skills and non-technical skills (e.g. understanding of industrial or health system needs, project management skills, regulatory requirements) – and universities build complementary capabilities – this may create external economies of scale for other actors in the innovation system to locate in proximity to those institutions to take advantage of potentially profitable interactions with academic institutions. This would result in a form of clustering effect in which new spin-outs, venture capitalists, established pharmaceutical or biotechnology firms, as well as skilled labour – display a tendency to locate in the same areas, producing efficiency gains throughout the system and attracting inward investment. Traces of these types of effect can be seen in the location decisions being made by spin-outs (e.g. MeiraGTx, which is developing a set of gene therapies in ophthalmology which originated in research taken forward by UCL, have taken a location in Hoxton, presumably to take advantage of the benefits of proximity to Moorfields Eye Hospital where much of the relevant clinical trial activity being taken forward). The causal nature of these effects can potentially be established through quantitative analysis and plans for exploring these types of effect will be produced as part of the next stage of the study.
- **Knowledge spill-over effects:** As with all investments in R&D, there is a possibility of spill-over effects by which the knowledge developed through projects can be adapted, repurposed or built on others engaged in parallel research programmes. These types of effect could arise in both fundamental and translational research and be taken forward by industry or within academia. There are wide variety of formal and informal mechanisms through which spill-overs might arise – while the publication of results (or presentation of findings at seminars or conferences) provide a formal conduit through which others can familiarise themselves with findings, spill-overs are often mediated by direct interactions between researchers. Spill-over effects are particularly difficult to capture as it is often challenging to identify the specific firms or individuals that have benefited from a spill-over – though the citations included in patents and academic publications often provide a signal that a spill-over may have occurred. As such, spill-overs may be more straightforward to establish through quantitative analysis than through interviews with researchers (who may or may not be aware of that such a spill-over may have occurred).
- **De-risking:** MRC's funding may also have a de-risking effect (from the point of view of the investor) on the development of novel technologies products by proving that development of a product is promising or viable (also termed a 'demonstration effect'). These types of effect are most likely where novel therapies carry particularly high-degrees of risk and there is limited (or no) evidence that the underlying technology can be safely administered, that it can outperform other available technologies or clinical practices, and that health systems are willing to pay. A risk averse private sector will be reluctant to invest large sums of resources into these technologies without some assurance or proof of concept around these parameters. Where MRC funding has helped clarify some of these parameters – this may contribute to greater appetite amongst investors to invest in parallel technologies using similar techniques (a crowding in effect). One example of this highlighted in the stakeholder consultations was the role of MRC funding in de-risking gene therapies – where after initial enthusiasm amongst investors, some high-profile failures in the first gene therapy trials in humans caused disinvestment within the private sector and a slowdown in activity. On-going research by funded by the MRC was thought to have helped both demonstrate the safety and efficacy of some types of gene therapy, triggering greater levels of investment. These types of effect cannot be explored adequately through interviews with researchers receiving funding, though can be explored through interviews with opinion leaders (while causal effects can

potentially be established through statistical analysis, and proposed methods for doing so will be developed as part of the next stage of the study).

2.4 Overarching logic model

The overarching logic model for the evaluation of the MRC's translational research portfolio is presented in Figure 1.2 below.

Figure 1.2 Translational research programme logic model



3 – Translational Research initiatives

Table 1.1: Mapping of Directed Translational research initiatives to intended outcome

Initiative	Activity	End output	Number of awards	Approximate spend	Duration of award
Biomedical Catalyst (BMC)/Developmental Pathway Funding Scheme (DPFS)/Developmental Clinical Studies (DCS)	Funds pre-clinical development/early testing of novel therapeutics, devices and diagnostics to accelerate the process of identifying and validating new targets or interventions which have potential for making significant health benefits: goal-oriented rather than hypothesis-led and may involve high-risk / high-payoff studies.	**Medical products and health-influence interventions**	169	£112m	2008-
AZ Mechanisms of human disease	Provides access for UK academic researchers to AZ's high-quality compound library, supporting two main types of projects: pre-clinical studies to enable and inform further clinical insight into disease or clinical research studies using compounds in new disease areas to build on evidence.	**Enabling research** (Mechanistic knowledge)	15	£5.6m	2013 - 2018
The MRC-AZ Centre for Lead Discovery pilot	The MRC/AstraZeneca Centre for Lead Discovery (CLD) aims to support academic researchers in discovering potential starting points for small molecule therapeutic approaches with a clear line-of-sight to therapeutic use.	**Enabling research** (Target validation and the identification of early clinical matter)	Post 17/18	Post 17/18[2]	2018-

[2] Initiatives launched recently will not have any awards included in this analysis, as no projects will have completed

	Initially announced in 2014, and following a successful pilot in 2015/16, the scheme opened to applicants in August 2017 with awards funding beginning in 2018/19".				
The MRC-UCB Antibody Initiative	The MRC/UCB Antibody Discovery Initiative aims to support academic researchers seeking to develop antibody-based therapeutics. It is intended to accelerate the transition from discovery research to translational development projects by enabling generation of novel antibodies suitable for testing in models of disease.	**Enabling research** (Development of antibody-based therapeutics)	Post-17/18-	Post 17/18-	2018-
Stem cell and regenerative medicine **(includes TSCRC , RMP and RMRC)**	Funds both projects to enhance scientific knowledge and understanding, as well as the development of new tools and technologies for regenerative therapies and disease-focused stem cell research with underpinning support from RMP Hubs.	**Medical products and Enabling research** (Hubs, Platforms and methods)	77	£74.6m	2008-
Experimental Medicine	Funds the development novel therapeutics, devices and diagnostics, faster identification of pathways of disease, and/or demonstrate proof-of-concept evidence of the validity and importance of new discoveries or treatments.	**Enabling research** (Understanding basic biology)	32	£11.5m	2008 - 2015

Confidence in Concept scheme	Devolved funding intended to accelerate the transition from discovery research to translational development projects by supporting preliminary work or feasibility studies to establish the viability of an approach.	**Enabling research** (Early translational knowledge generation)	75	£39m	2012-
Proximity to discovery: Industry Engagement Fund	Facilitates collaborations between academia and industry.	**Enabling research** (Early engagement supporting product development)	32	£6.1m	2015-
Experimental Medicine Challenge Grants[3]	Funds research into disease pathophysiology conducted in humans. It aims to fund studies which address the biggest gaps in our understanding of the causes and progression of human disease and which produce major new mechanistic insights. Projects also aims to produce major improvements in the understanding of human disease mechanisms.	**Enabling research** (Understanding human disease mechanisms)	(21)	(estimated £42.4m)	2013-2021
Stratified Medicine (including MRC/ABPI Inflammation and Immunity Initiative[4]**)**	Funds projects on identifying subgroups of patients with distinct mechanisms of disease, or particular responses to treatment. To improve our understanding of how to tailor treatments and interventions to the individual needs of people living with a wide range of diseases and conditions: support for single-	**Enabling research** (Understanding of clinically important disease subtypes)	6	£10.4m	2011-

[3] None of the experimental challenge grants have yet finished and so none of these awards were included in the evaluation.
[4] All six stratified medicine consortia included in the evaluation were awarded under the first wave of grants in the MRC-ABPI inflammation and immunity initiative)

	condition focused research consortia studying the disease aetiology within patient groups.				
MRC/NIHR Methodology Research Programme	Aims to inform research, practice, policy and healthcare and support research that has generalisable research methods development as its primary purpose.	**Enabling research** (Generation of knowledge concerning how best to design, conduct, analyse and evaluate medical and health research)	105	£38.7m	2008-
Molecular Pathology Nodes Calls[5]	Funds proposals to establish high-quality molecular pathology nodes. Each node will be a multidisciplinary centre of innovative molecular diagnostic test discovery and development bringing together the research base, pathology/genetic services and industry.	**Enabling research** (Provision of tools and technique to assist translation)	(7)	(£25m)	2015-2019
Joint Patient Research Cohort Initiative (JPRCI)	The initiative aims to create small, extensively defined groups of patients to help detect, treat or prevent disease in areas of high unmet need or where there are bottlenecks in turning research into therapies.	**Enabling research** (Infrastructure support for data, materials and biobanks)	14	£6.8m	2008 - 2015

[5] Not included in this evaluation as all awards ran until 2019

Models of Human disease	Aims to develop models for evaluation and validation of human disease: in vivo, in vitro or in silico. Primary activity areas in the funded-projects include biological and endogenous factors in the areas of detection or therapeutics.	**Enabling research** (Infrastructure, including tools, to support the discovery and development of animal models for human disease)	21	£10.3m	2008 - 2013
MRC-GSK Experimental Medicine Initiative to Explore New Therapies (EMINENT)[6]	It is hoped that combining the disease biology expertise of these academic scientists with GSK's drug development expertise and resources will ultimately lead to breakthroughs in understanding that could accelerate the development of innovative treatments for patients.	**Enabling research** (Generation of knowledge concerning the fundamental biological mechanisms responsible for a range of inflammatory diseases)	(9)	(£0.9m)	2017-
Biomarkers	Funding towards the development of potential biomarkers for their predictive and prognostic capability for the diagnosis of disease, disease heterogeneity and underlying mechanisms, susceptibility, exposure or response to interventions.	**Enabling research** (Infrastructure supporting the development of products or tools)	41	£17.4m	2007 - 2013
Industry Asset Sharing Initiative[7]	The aim is for this to be a long-standing initiative with a 'virtual library' of assets held on the MRC website that applicants can use in their experimental medicine research studies.	**Enabling research** (Provision of access to deprioritised compounds)	(7)	(£0.2m)	2017-

[6] Not included, no projects have yet completed.
[7] Not included, no projects have yet completed.

Table 1.2: Outline of MRC research board funding activity

Board	Funding Activity	Number of awards	Total spend
Infections and Immunity Board (IIB)	Responsible for funding research into infectious human disease and disorders of the human immune system, including areas such as human pathogens and the development and functioning of the human immune system. The Board's strategy includes extending its global health activities, addressing the challenge of antimicrobial resistance, strengthening pandemic preparedness, investigating immunity and infection through the life course, and supporting data integrative and systems approaches.	447	£248m
Molecular and Cellular Medicine Board (MCMB)	Regenerative medicine funding sits under MCMB as well as research under three key areas; understanding dynamic biological systems, exposures biological mechanisms and disease and radiation, oncology and biology.	559	£309m
Neurosciences & mental health (NMHB)	Responsible for funding research into the human nervous system and the disorders which can affect it. The Board's strategy includes addressing the challenges of mental illness and neurodegenerative diseases as well as exploring what we can learn from the direct study of human brain tissue to gain insight into the human brain.	587	£356m
Populations and systems medicine (PSMB)	Funds research which utilises systems approaches from multiple internal and external factors to understand control pathways and mechanisms, their interactions with major organs and how this manifests in health and disease. PSMB explores the relationship between human health and disease by using 'Big data', promoting integrated/systems approaches, utilising cohorts and cohort-derived data, developing methodology and resources and developing partnerships for improved impact.	550	£296m