

MRC Translational Research 2008-2018

Evaluation Report: Literature Review (Annex A2.3)





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Annex A2.3: Literature review

1.1 The translational research ecosystem

1.1.1 History of translational research

Historically a stark divide existed between fundamental scientific investigation and applied research. Where the former was conducted by academics, the latter was perceived as the responsibility of industry. replaced with a simple statement about wanting to put research into practice. As biomedical science developed over the course of the 20th century and especially following World War II, which catalysed research within hospitals and the clinic, the line between basic and applied biomedical research became less relevant and began to fade (Flier and Loscalzo, 2017). In his 1945 report 'Science, The Endless Frontier' to the American President Franklin D. Roosevelt, Dr Vannevar Bush poignantly summed up the need to put research into practice:

"Progress in the war against disease depends upon a flow of new scientific knowledge. New products, new industries, and more jobs require continuous additions to knowledge of the laws of nature, and the application of that knowledge to practical purposes." (Bush, 1945).

The term 'translational research' began to appear in biomedical journals in the first half of the 1990s publications, mostly in the area of cancer research. This was predominantly attributable to the Specialised Programs of Research Excellence (SPOREs), established by the U.S. National Cancer Institute (NCI) in 1992. The initiative was implemented to promote collaborative and interdisciplinary research in order to progress basic research relevant to cancer therapies from the laboratory to applied settings (van der Laan and Boenink, 2015). The NCI also originally linked the term translational research to the phrase 'from bench to bedside', as displayed by the following definition of translational research by the NCI Director Broder and his colleague:

"Translational research moves knowledge about cancer in either direction, between findings at the laboratory bench and clinical observations at the bedside. Both preclinical and clinical research are translational if the specific goal is to move the fruits of basic knowledge closer to clinical application" (Broder and Cushing, 1993).

Over the following decade, the term translational research started to be used more frequently, still mostly in biomedical articles relating to cancer research, e.g. in the area of biomarker discovery and validation, as this was thought to have significant potential for accelerating and reducing the costs of developing cancer prevention strategies (Mulshine *et al.*, 1993). Towards the late 1990s the term translational research appeared in the name of cancer research centres in Canada and North America for the first time. These centres facilitated translational research by creating collaborations between researchers involved in different stages of cancer research, as well as alliances between researchers and private partners (van der Laan and Boenink, 2015). Towards the end of the 1990s and at the turn of the 21st century the term translational research slowly lost its unique association with cancer and was taken up by all areas of biomedical research and increasingly outside of Canada and the USA.

In 2003, an important turning point in the history of translational research occurred when the US National Institutes of Health published the Roadmap for Medical Research. This document aimed to address the gaps in the translational pathway that fundamentally blocked the transformation of scientific discoveries into improvements in health (Zerhouni, 2003). It stimulated a subsequent number of similar initiatives in other countries which increased the appearance of translational research on the policy agenda for biomedical research (van der Laan and Boenink, 2015). Specifically, within the EU, the European Advanced Translational Research Infrastructure in Medicine (EATRIS) was established to provide a platform for fast and efficient translation of research discoveries into new products aimed at preventing, diagnosing or treating disease.

The distinction of research by 'basic' and 'applied' or 'translational' categories has more and more been called into question (Narayanamurti and Odumosu, 2016; Flier and Loscalzo, 2017). Since Vannevar's 1945 report, scientific enquiry has largely been classified as either 'basic' or 'applied', with 'basic'

research perceived as purely curiosity-driven to develop general knowledge without any application or use in view, while 'applied' research is performed with a specific practical aim or objective. This model permeates how funding organisations allocate money and is perpetuated in research classification systems, such as the OECD's Frascati Manual (OECD 2015, p.44). The distinction has also impacted on how the public perceives science, presuming the creativity of basic science will somehow be lost if constrained by thoughts of practicality1. However, this distinction between basic science as a pure ideal on the one hand and applied science as a practical (and inherently less prestigious) activity on the other, is criticised as 'anachronistic' (Flier and Loscalzo, 2017). The creation of new knowledge and understanding is essential for enabling innovations to be developed (e.g. see section 0); a full understanding of how research 'happens' underscores that discovery and invention are often two sides of the same coin that moves innovation forward.

Disease can be identified through diagnostic tools and addressed through a range of interventions, including drugs (e.g. small molecule or biologics), cellular and gene therapies, medical devices and physical or behavioural therapies. Health improvements can also be achieved through preventative interventions (e.g. vaccines, nutritional guidelines) and disease management tools - including the relatively new area of patient-facing mobile apps. Many strands of translational research feed into this vast health innovation landscape. However, much of the attention in the published literature centres on drug development, with the central position of the private sector in this area. The following sections mirror this focus, with most information relating to the pharma and biotechnology industry (biopharma). This is not to say that other areas of innovation play less important roles in improving health; the emphasis merely reflects the 'bias' in the literature.

1.1.2 The global translational research landscape

R&D investment

The global spent on biomedical R&D was approx. USD 268 billion in 2012, a 2.4% increase over the 2007 level when adjusting for inflation (Chakma, Sun and Steinberg, 2014). This encompasses increased expenditure in Asia-Oceania, as well as decreases in spent in the USA, Europe, and Canada. As a result, the share of the United States' biomedical R&D expenditure fell from 51.2% in 2007 to 45.4% in 2012; Europe's share stayed relatively unchanged at approx. 29%, and Asia-Oceania's share increased from 18.1% to 23.8%.

Over the same period, public sector expenditure (adjusted for inflation) increased in all regions, particularly in Asia-Oceania which increased its share of public sector spent from 16.6% to 19.1%, primarily driven by a USD 2.2 billion increase in Japan and a USD 1.4 billion increase in China. Private sector R&D expenditure was hence the main driver for decreased US expenditure, with a USD 12.9 billion reduction between 2007 and 2012 (representing a drop from a 50.4% share of global industry R&D expenditures to 42.3%) (Chakma, Sun and Steinberg, 2014). The balance between public sector and industry expenditures changed little over the 2007 to 2012, with just over one third from the public sector (35.6% in 2007; 37.1% in 2012) and two thirds from industry (64.4% in 2007; 62.9% in 2012).

From 2006 to 2016, R&D expenditure by pharma and biotech companies increased from USD 108 billion to USD 157 billion, growing at an average of 4% per year2. More than half of the pharmaceutical company R&D investment was into the US (53%), followed by Japan (17%), the UK (7.7%), Germany (6.9%) and Switzerland (6%)3. In terms of government expenditure on health R&D, the US leads by far at USD 33.4 billion (2015), followed by the UK with approximately one-tenth the US expenditure at USD 3.4 billion, and Germany, Spain and France at USD 1.3-1.8 billion4. The total investment in R&D for

¹ <u>http://blogs.nature.com/thescepticalchymist/2013/06/speaking-frankly-the-allure-of-pasteurs-quadrant.html</u> (2013) Accessed December 2018

² <u>https://www.abpi.org.uk/what-we-do/developing-researching-medicines/investing-in-innovation/worldwide-pharmaceutical-company-rd-</u> expenditure/ Accessed December 2018

³ https://www.abpi.org.uk/what-we-do/developing-researching-medicines/investing-in-innovation/worldwide-pharmaceutical-company-rdexpenditure-by-country/ Accessed December 2018 ⁴ https://www.abpi.org.uk/what-we-do/developing-researching-medicines/investing-in-innovation/global-public-funding-of-health-rd/

Accessed December 2018

2015 amounted to approx. USD 200 billion, with around 75% invested by biopharma companies (USD 148 billion) and 25% by government (USD 54 billion).

Over the 2006-2016 period, global company R&D expenditure as a share of sales (R&D intensity) remained around 20%, placing the pharmaceutical industry among the sectors with the highest R&D intensity5. Among the top 10 pharmaceutical companies, the R&D intensity ranges between 15% to 26%6. Roche, the top pharmaceutical company in terms of absolute R&D spend, had an R&D intensity of 21.9%. Other pharmaceutical companies' R&D intensity were: Merck & Co. (25.4%), Novartis (19.4%), Johnson & Johnson (12.7%), Pfizer (14.9%), AstraZeneca (25.6%), and Sanofi (14.9%).

In 2016, investors moved USD 3.6 billion into 291 seed and Series A <u>biotech venture</u> rounds in the US and Europe, slightly below 2015 figures but much higher than figures for the 2008 – 2014 period (at 150-180 deals; USD 1–1.8 billion) (EY, 2017b). Most of the early-stage financing went to US companies (180, or 62%), and US companies captured the bulk of the total capital (USD 2.8 billion, or 78%). In Europe, the UK took the lead in venture capital raised (see section on R&D investment).

The drug pipeline and approvals

The number of New Active Substances (NAS)7 launched has increased over the past decade (PharmaIntelligence, 2018). Following a decrease from 43 NASs launched in 2000 to 23 NASs launched in 2004, numbers started to increase and reached a high point of 63 NASs launched in 2014. While 2015 and 2016 saw fewer NAS launched, at 46 and 41 respectively, there was an uptick in 2017 with 54 NASs launched. Looking at broader trends, the average number of NASs launched between 2000 and 2007 was 35.7, compared to 37.8 between 2008 and 2012, and 50.4 between 20013 and 2017. The number of NASs approved varies by regulatory authorities, with many – but not all - of NASs overlapping. In 2017, the US FDA approved the highest number of NASs (50), followed by Europe's EMA and Health Canada (both 30), Switzerland's Swissmedic (29), Australia's TGA (24) and Japan's PMDA (22) (Bujar, McAuslane and Liberti, 2018). Despite variation from year to year, the overall number of NASs approved by the six agencies has increased: the number of common products approved by all six agencies increased from 12 in 2008-2012 to 51 in 2013-2017 (Bujar, McAuslane and Liberti, 2018); or from 4 NASs in 2011-2012 to 13 NASs in 2015-2016 (Bujar, McAuslane and Liberti, 2017).



Figure 1.1: Number of New Active Substances launched

Source: adapted from PharmaIntelligence - Pharma R&D Review 2018 webinar slides

⁵ <u>https://www.abpi.org.uk/what-we-do/developing-researching-medicines/investing-in-innovation/worldwide-pharmaceutical-company-rd-expenditure/</u> Accessed December 2018

⁶ https://www.dcatvci.org/4768-measuring-innovation-where-does-the-pharma-industry-stand Accessed December 2018

⁷ Generally, an NAS is a substance not previously authorised as a medicinal product

Small molecules, the 'traditional' drugs, continue to account for the majority of pharma sector revenue, at 83% (Results Healthcare, 2017). Biologics have entered the stage more recently; these are more complex, large molecular weight molecules such as proteins (e.g. monoclonal antibodies), peptides and plasmid DNAs. Biologics are forecast to grow steadily; they currently represent approx. 50% of the product and portfolio mix (Gautam and Pan, 2016) and are expected to deliver 45 of the world's top 100 selling pharmaceuticals in 2020 (EvaluatePharma, 2014).

PhRMA estimates that there are currently 7000 medicines in clinical development globally, of which 74% have the potential to be first-in-class treatments8. Cancer treatments 'lead' the pipeline, with 1120 medicines and vaccines currently in development. Approx. 200 candidates target cardiovascular disease and 500 neurological disorders (e.g. epilepsy, migraine headaches, MS, Parkinson's disease and Alzheimer's disease). Other sources put the figure of pipeline candidates higher; e.g. a recent report put the number of pipeline drugs at over 8000, with another 5500 in clinical trials (2127 in Phase I, 2360 in Phase II, and 1006 in Phase III) (PharmaIntelligence, 2018).

The biopharma industry landscape

The biopharma sector encompasses businesses that develop and/or producing their own pharmaceutical products – from multinational 'Big Pharma' ('pharma) to small, R&D-focussed biotech companies ('biotech'). The industry landscape for R&D this sector has been changing.

The 1995-2005 period was marked by intense mergers and acquisitions activity, driven by 'Big Pharma' with the aim of achieving economies of scale, diversification of portfolios and business across the healthcare spectrum to counteract the approaching 'patent cliff', and improving R&D productivity (Gautam and Pan, 2016; Schwartz and Macomber, 2017). This led to 'bloated' company operations, with multiple R&D hubs across the globe, multiple manufacturing sites, and often complex governance structures. Additional issues arose from a lack of cultural integration of the merged companies; multiple R&D hubs continued to function within self-contained silos. The 1995-2005 period was also marked by a focus on blockbuster drugs and primary care therapy areas which accounted for approx. 80% of revenues of large pharma companies.

Following this period, the sector turned to more 'lean and focussed' models (Gautam and Pan, 2016). Large companies actively divested non-core assets and focussed on areas of strengths, with large M&As predominantly aiming to build complementary capabilities rather than following the 'bigger is better' approach of the preceding years. Research hubs were consolidated and co-located with innovation clusters, such as Boston, San Francisco, Cambridge and London (Gautam and Pan, 2016; Schuhmacher, Gassmann and Hinder, 2016). This has enabled companies to draw on innovation through targeted alliances and collaborations, feeding and progressing their drug pipelines (see 0). The sector has also increasingly made use of long-term alliances with CROs and CMOs (Gautam and Pan, 2016; Buvailo, 2018). There has also been a trend of creating spin-off companies in R&D areas not considered core to the parent company's strategy. This eliminates R&D and maintenance costs if the parent company can find investors, often venture capital, to capitalise the new firm, allowing the parent to maintain earnings growth despite struggling revenue while capturing some of the potential upside by retaining partial ownership of the new firm or distributing shares to current investors9.

Overall, companies tend to focus internally more on late (phase II/III) clinical development and distribution of products, with the discovery of candidates for new therapies and subsequent pre-clinical and early (phase I/IIa) clinical evaluation have increasingly become the domain of academic parties and SMEs (de Vrueh & Crommelin 2017). This is illustrated by a shift in the share of the overall development pipeline: Smaller companies developing only 1 or 2 drugs have increased their 'pipeline share' vis-à-vis the top 25 companies over the past decade (PharmaIntelligence, 2018). This has gone hand-in-hand with an increase in the overall number of companies in the sector year on year, from just under 2000 in 2008 to more than 4100 in 2017, at least partially driven by the dramatic increase in the availability of venture-capital funding for early-stage biotech companies, from USD 4.0 billion in investments in 2007 to USD 9.8 billion in 2017 (seed to stage C)10. As these companies have matured, both the number

⁹ <u>http://www.bioworld.com/content/spinouts-popular-despite-difficulties-measuring-roi-1</u> Accessed December 2018

⁸ https://www.phrma.org/industryprofile/2018/; data from 2017 CMR Factbook; Clarivate Analytics. Accessed December 2018

¹⁰ <u>https://www.mckinsey.com/industries/pharmaceuticals-and-medical-products/our-insights/r-and-d-in-the-age-of-agile</u> Accessed December 2018

and proportion of trials initiated by companies other than the top ten pharma companies has increased (from 4,500 trial starts in 2007 (72%) to 5,900 in 2017 (85%))11.

The sector's increase in 'externalisation' of R&D is also demonstrated by a 2014 analysis of FDAapproved New Molecular Entities (NMEs) (Kinch *et al.*, 2014). The study determined that there were 115 organisations that controlled at least one NME. Nearly half of these organisations (54 of 115) controlled only one NME, 30 organisations controlled two to five NMEs, 19 controlled between six and 20 NMEs, and twelve companies controlled more than 20 NMEs each. The top five holders of NMEs accounted for more than 40% of all NMEs (Pfizer (198) and followed by Merck (106), Novartis (98), SanofiAventis (84) and GlaxoSmithKline (79)). Large, established companies invariably rose from the middle tier as a result of mergers and none grew without at least one major merger. The small 'singlet' companies were often the target of acquisitions, usually by medium-sized companies holding 2-20 NMEs. In turn, latter were occasionally acquired whereas a few merged to form larger corporations. An 'externalisation' of R&D is also evidenced by the increasing proportion of externally-sourced compounds in later-stage development: while in 2002, 38% of compounds moved through Phase III trials by the pharma industry had been externally sourced, this figure had risen to 62% by 2010 (McKinsey, 2012).

Taking this externalisation even further, a relatively new 'type' of company emerged over the past 20 years: companies with minimised internal R&D activities which focus instead on obtaining NMEs from licensing, mergers and acquisitions (Kinch *et al.*, 2014). The rise of these 'acquiring organisations' with limited internal R&D capabilities has been rapid – while in 1990, only two NMEs (0.26% of all NMEs awarded up to that date) were controlled by organisations that had not been directly awarded an NME, this number had increased to 215 NMEs (or 14.8% of all NMEs granted) by 2013. Of the 118 companies that hold at least one NME, 25 (21.1%) had not received an NME approval from the FDA.

A recent trend has been the rise of corporate venture capitalists (CVCs), where pharma companies invest their own funds in emerging start-ups. CVCs participated in nearly half of all venture rounds for biotech companies in the US and Europe in 2016 (up from 34% in 2014). This trend has also been observed in the UK, where corporate venture capital has become a key factor in the increase in capital being invested in private UK life science companies in recent years (ABPI, 2017). This type of investment can bring several strategic benefits to the investor, beyond financial rewards, such as growing their understanding of a new or emerging scientific field, developing scientific networks and accessing novel expertise and the potential to identify new assets.

Big pharma companies have shifted more and more away from development of primary care and smallmolecule medicines toward specialty medicines and biologics targeted at areas of high unmet need, e.g. addressing rare diseases (so-called orphan drugs) (Khanna, 2012; Gautam and Pan, 2016; de Vrueh and Crommelin, 2017). This trend is underpinned by a better understanding of the underlying disease biology, maturation of biologics technology, the 'coming of age' of stratified medicine and companion diagnostics, and the development of regulatory frameworks and accelerated development timelines for such medicines. Both sales figures and development pipelines of large companies confirm this trend: From 2010 to 2014, the share of speciality products and biologics sales increased by more than 10%, and biologics made up between 20 and 60% of the development portfolio of many of the big pharma companies (e.g. 58% of Lilly, 44% BMS, 39% AZ, 40% Roche, 23% Pfizer) (IMS Health data, cited in Gautam & Pan 2016). Drug approvals / positive opinions by the FDA have shown an upward trend for orphan drugs: In 2015, almost half of the approvals/positive opinions in the US were for orphan drugs, compared with one third in 2005 (de Vrueh & Crommelin 2017, and references within). A similar trend was observed for Europe.

The focus of pharma companies has also shifted from 'quantity' to 'quality'. AZ's analysis of their drug pipeline showed that funnelling a larger number of candidates through translational research did not lead to higher success rates (Cook *et al.*, 2014). The company developed a new framework - the '5R framework': right target, right tissue, right safety, right patient, right commercial - to increase scientific

¹¹ <u>https://www.mckinsey.com/industries/pharmaceuticals-and-medical-products/our-insights/r-and-d-in-the-age-of-agile</u> Accessed December 2018

rigour of its translational research; this has led to increased success rates (Figure 1.4) (Morgan *et al.*, 2018). AZ is also using partnerships to improve the quality of the pipeline.



Figure 1.2: AstraZeneca translational research pipeline - success rates (as %)

Source: (Morgan et al., 2018)

The high cost of development

The average cost of developing a successful medicine has been estimated at approx. USD 2.6 billion (2013 dollars, includes cost of abandoned compounds), rising to USD 2.9 billion if post-approval R&D costs are taken into account (DiMasi, Grabowskib and Hansenc, 2016). Previous research by the same authors had estimated the average R&D costs in the early 2000s at USD 1.2 billion (2000 dollars), indicating increases at an annual rate of 8.5% above general price inflation. Others estimated the cost to be somewhat lower (2011 prices), at USD 1.9 billion (Paul *et al.*, 2010) and USD 1.5 billion (Mestre-Ferrandiz, Sussex and Towse, 2012).

Table 1.1. sets out a break-down of R&D expenditure by phase of development, with Phase III clinical trials representing the largest share – more than one third – of the cost (industry survey PhRMA 2018; see also 12).



Table 1.1: Company-financed R&D by phase

Source: adapted from Pharmaceutical Research and Manufacturers of America, PhRMA Annual Membership Survey, 2018; *This figure includes USD 13.4 billion R&D spend reported by PhRMA members but not categorised to any of the 6 R&D stages.

¹² A second analysis of expenditure per R&D phase, with broadly similar trends (in places, R&D stages are differently defined): <u>https://www.abpi.org.uk/what-we-do/developing-researching-medicines/investing-in-innovation/global-pharmaceutical-rd-expenditure-along-the-development-cycle/</u> Accessed December 2018

The low success rate of biopharma R&D

One issue is the high cost and relatively low success rate in bringing pharmaceutical R&D products to market. The overall success rate for drug R&D from the 'start of the journey' has been estimated at 4-10%13 (Paul et al., 2010; Thomas et al., 2016). At a more granular level, success rates for NMEs progressing to market were determined to be 5% from first toxicity dose, 7% from first human dose, 16% for first patient dose, 60% for first pivotal dose (generally Phase III trials), and 91% when submitted - indicating that the risk of failure drops significantly once a product is at the first pivotal dose stage, with a progression rate of only 26% from first patient dose to first pivotal dose 14. Similarly, other studies found that the success rate for progression from Phase II to Phase III was 30.7% (Thomas et al., 2016), and that progression through all clinical development phases was only 12.8% (Paul et al. 2010). Hence, Phase II emerges as a crucial point in the translational pathway, with the lowest success rate of all phases. Not only is this generally the first time where proof-of-concept is deliberately tested in human subjects, with the risk of low efficiency compared to non-human models; it is also the point at which industry must decide whether to pursue expensive Phase III studies or terminating development due to commercial viability. A 2012 study of FDA approvals found that the most probable reasons for failure in Phase II and III trials were lack of efficacy (56%) and safety issues (28%) (Schuhmacher et al. 2016 and references within). Similarly, an analysis of 142 drug R&D projects found that preclinical and Phase I projects most commonly failed for safety reasons while Phase II and III projects failed due to lack of efficiency. R&D products in disease areas with the highest likelihood of approval from Phase I trials were haematology (26.1%), infectious disease (19.1%) and ophthalmology (17.1%); those with the lowest success rate were oncology (5.1%), psychiatry (6.1%), and cardiovascular (6.6%) (Thomas et al., 2016).

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. An analysis of the 68 cancer indications approved by the EMA between 2009 and 2013, the majority entered the market based on a surrogate endpoint, i.e. without clear evidence that they improved survival or quality of life for patients (57%; 39)15. After a median of 5 years on the market, only 8 of these 39 drug indications had shown survival or quality of life gains. Thus, out of the 68 approved indications, only 35 (51%) showed improved survival or quality of life over existing treatments. For the remaining 33 (49%), uncertainty remains over whether the drugs extend survival or improve quality of life.

Reasons for these high attrition rates include lack of reliability of published data, biopharmaceutical issues including suboptimal pharmacokinetics, poorly predictive preclinical models in discovery research and preclinical testing, the complex process of target validation, the complexity of clinical trials, and the lack of know-how of smaller organisations resulting in a lower success rate from Phase I to submission than for large organisations (Schuhmacher et al. 2016 and references within). More detailed evidence is provided in Section 0.

The MedTech and digital health sectors

The MedTech sector includes all businesses whose primary business falls under developing and producing their own Med Tech products, such as single-use consumables and complex hospital equipment and implanted medical devices; the sector also includes digital health products.

The global MedTech industry generated USD 364 billion in revenue in 2016 (EY, 2017a). In aggregate, MedTech companies in the US and Europe expanded their top line 5% in 2016 and grew their total bottom line 17%. In Europe, the Medical Device Directive provides the basis for regulation (and is implemented by the notified bodies of the member states); it sets out four classes depending on the risk of the device: Class I, e.g. simple bandages or wound care products; Class II, e.g. syringes for pump infusion; Class IIb, e.g. anaesthesia machines; and Class III, e.g. pacemakers (MedTech Europe,

¹³ https://www.abpi.org.uk/what-we-do/developing-researching-medicines/investing-in-innovation/probability-of-medicine-s-success-tomarket/ Accessed December 2018

¹⁴ https://www.abpi.org.uk/what-we-do/developing-researching-medicines/investing-in-innovation/probability-of-medicine-s-success-to-

market/ Accessed December 2018 ¹⁵ https://www.bmj.com/company/newsroom/no-clear-evidence-that-most-new-cancer-drugs-extend-or-improve-life/ Accessed December 2018

2018). While low risk devices have relatively simple requirements for getting to the market, 'implantable devices', which, in general, belong to Class III have to go through stringent regulatory approval processes. In 2016, the FDA approved 39 new class III medical devices via its pre-market approval (PMA) pathway, the number of approved devices over the preceding 10 years fluctuated between approx. 20 and 40 per year, with no clear trends across this time period (EY, 2017a). The industry landscape is characterised by a large number of SMEs; of the approx. 27,000 medical technology companies in Europe, almost 95% are SMEs with the majority employing less than 50 people (MedTech Europe, 2018). Going forward, many potential benefits are associated with connecting medical devices to the internet, hospital networks, mobile products, and other devices or hospital systems. Achieving these benefits will require innovators to effectively address a new area of risk related to cyber and patient safety, and associated uncertainty regarding regulatory requirements (Deloitte, 2018).

Digital health is a relatively 'new' arrival in the health market. The digital health sector was estimated to be worth £70 billion in 2016 and is expected to increase to £150 billion by 2020 (Office for Life Sciences, 2018). Products comprise a range of consumer-centric and patient/provider-centric technologies, including mobile health applications and devices (which are expected to show the fastest growth within the digital health sector) and health analytics - software solutions and analytical capabilities needed to assimilate 'big' health data and extracting insights, either to shape national policy, manage local organisations or inform the care of an individual (such as AI-aided diagnosis).

1.1.3 Challenges in translational research

The past decades have seen huge advances in many of the scientific, technological and managerial factors. Yet, when focussing on the number of new drugs approved per billion US dollars spent on R&D, R&D efficiency has halved roughly every 9 years since 1950 (Scannell *et al.*, 2012). This low efficiency has been attributed to a variety of factors, including rapid scientific and technical advances, alongside increasing regulatory burdens, increased complexity of clinical trials, and hurdles to reimbursement. Here, we set out some of the key challenges in taking R&D through to real-world health impact; in section 0, we will then describe the role of early translational research / discovery science in addressing some of these issues.

Scientific and technical advances

With recent scientific and technical advances, researchers are using new approaches for R&D, often at the molecular and genetic levels. This is reflected in the growing complexity of treatments being developed, such as Advanced Therapy Medicinal Products (ATMPs); new drug delivery technologies such as lipid nanoparticles and devices to improve delivery of vaccinations; and 3D printing of personalised polypills (MHRA, 2017; The Royal Society, 2018). Products based on cell and gene therapies now make up 12% of the global clinical pipeline (an 11% compound annual growth rate from 2007 to 2017)16. Companies such as AstraZeneca have expanded from 'traditional' small molecule drugs and well-established biologics such as monoclonal antibodies to new drug modalities, including antisense oligonucleotides, modified RNA, bicyclic peptides, and proteolysis targeting chimeras (PROTACs) (The Royal Society, 2018). This much wider array of technologies provides broader options for making key targets 'druggable'. However, this new territory in translational research brings with its new regulatory aspects (see below).

Advances in genetics and precision medicine have allowed much more tailored approaches to disease treatment. Taking advantage of these developments, biopharma companies including AZ, Roche, Novartis and Sanofi, are progressing as much as 60-80% of their clinical portfolios with companion diagnostics (IMS Health data, cited in Gautam & Pan 2016). However, while there have been some successes, notably in the field of oncology, precision medicine products are not currently in use for most diseases. Additional costs arise as researchers need to collect patient data and implement databases for storage. In the UK, the required 'data capability' may move precision out of the reach of the NHS for some time, with many hospitals struggling to implement electronic health records (The Royal Society, 2018).

¹⁶ <u>https://www.mckinsey.com/industries/pharmaceuticals-and-medical-products/our-insights/r-and-d-in-the-age-of-agile</u> Accessed December 2018

Rapid scientific and technical advances, alongside increasing regulatory burdens are resulting in more complex clinical trials. A recent study found that while Phase I protocols remain the most complex and demanding to execute, Phase III protocols have seen the most substantial growth in protocol complexity (Getz & Campo 2017, 17). Compared to trials conducted between 2001-2005, Phase III trials conducted between 2011 and 2015 saw the total number of endpoints within a typical trial grow from 7 to 13, the number of procedures (such as routine exams, blood work and x-rays) from 110 to 187, and the number of investigative sites from 40 to 65. The number of data points collected jumped by 88%, from just under 500,000 to over 900,000. In addition, the clinical development timeline has expanded substantially. While the average clinical development time for drugs approved between 2005 and 2009 was 6.4 years, this increased to 9.1 years for the 2008 to 2012 period. The largest increases in duration were seen for Phase I (+58%) and the preclinical development phase (+17%) (Schuhmacher, Gassmann and Hinder, 2016).

At the same time, technical advances can lead to increased R&D productivity (EY 2017b). For example, genetic information helps target early translational research to the most promising candidates. A retrospective analysis of approved and experimental drugs in different indications found that drugs developed against targets that were linked to an indication by human genetic evidence were twice as likely to succeed as those without such supporting genetic evidence (Nelson *et al.*, 2015). Artificial Intelligence technologies are also employed to support and accelerate the drug discovery process (EY, 2017b). Personalised medicine approaches, supported by advances in genome sequencing, diagnostics and biomarker identification, are used to reduce failure rates in the drug development process and improve timelines, e.g. by identifying patients most likely to respond to a drug which allows trials to be smaller, potentially reaching significance faster. Data suggests that drugs developed with predictive biomarkers, which help select likely responders, are three times more likely to achieve approval than those without (EY, 2017b).

Regulatory uncertainty and issues with trial design

Regulatory processes used for existing therapy types are not always suitable for use for novel modalities and delivery mechanisms; the need to adapt or develop new regulatory approaches represents uncertainty and additional risk for the private sector. A recent literature review on barriers to personalised medicine found that regulatory uncertainty was the most discussed challenge for PM R&D and implementation (Knowles, Luth and Bubela, 2017). The key issue highlighted was that existing regulations were described as inapplicable to personalised medicine and suffering from a lack of harmonisation, and thus interfered with PM development. The 'fast follower' corporate strategy has also been described where a company purposely avoids being first with a novel product, waiting for another organisation to map out a successful path to approval with the intent of following behind rapidly – with the result that slowing down innovation (Freedman and Mullane, 2017).

In addition, the gold standard of clinical research, randomised controlled trials (RCTs), have presented several drawbacks, including low external validity as the efficacy of a treatment is measured in a tightly controlled group of patients which cannot be directly translated to treatment effectiveness in "real-world" patient populations (Eichler and Sweeney, 2018). The gap between efficacy in clinical trials and effectiveness in daily practice may be due to several reasons, including poor patient adherence and persistence, and heterogeneity in patient characteristics. Latter is a key challenge in the development of cancer therapies, where heterogeneity exists not only among patients with any given tumour type, but also among tumours within an individual (through molecular evolution of the tumour through time and space, e.g. primary tumour to metastasis) (Renfro and Sargent, 2017). In some instances, this gap has led to removal of approved drugs from the market, even though they had a favourable benefit–risk assessment at the time of licensing (Eichler and Sweeney, 2018).

In addition, RCTs are very resource-intensive. Novel trial designs, such as adaptive trials and basket trials, can address some of these issues. These trial designs has provided a methodology with potential for decreased time to study completion, reduced resource requirements and number of patients exposed to inferior treatments, and overall improved likelihood of trial success (Thorlund *et al.*, 2018). In contrast to traditional trials with a fixed design throughout, adaptive designs allow trials to be adapted

¹⁷ https://chartpack.phrma.org/biopharmaceuticals-in-perspective-2017/research-and-development/the-complexity-of-clinical-trials-hasincreased Accessed December 2018

during the study (e.g. removing or adding treatment arms, changing the balance of randomisation or altering statistical methodologies), enabling continual learning as the data accumulate. However, their use is still problematic; for example, while adaptive trials have expanded in the scientific literature since the mid-1990s, a recent review encountered numerous cases in which regulatory officials found methodological deficiencies or data collection problems specific to the adaptive designs, resulting in lengthy correspondence with trial sponsors and complications in the review process (Bothwell *et al.*, 2018).

Advances in genomics take account of variation between patients by defining clinical trial populations on an even more granular level, resulting in the need to stratify clinical trials into more and smaller subgroups of treatment-eligible patients (Eichler and Sweeney, 2018). However, as our understanding of the complexities underlying patient heterogeneity continues to grow, even the large trials will no longer be able to accommodate all known subpopulations. This issue is exacerbated in clinical trials that evaluate stratified combination treatments.

Regulatory agencies are working to address developments in technology and trial design. For example, the MHRA set up an Innovation Office in 2013 as a single point of access to free and expert regulatory information, advice and guidance to help organisations developing innovative medicines, medical devices or novel manufacturing processes18. By October 2017, the Office had received approx. 500 queries and held over 100 meetings with enquirers, with 60% of enquiries coming from SMEs (33%) and academics (27%) (MHRA, 2017). In round figures 75% of the queries have related to medicines and 25% to medical devices.

Reimbursement

In order to be implementable and taken up into standard of care to reach patients, medical products need to be affordable and cost-effective compared to existing approaches, i.e. requiring proof of value of the innovation, and hence approved for reimbursement by the responsible authority. While the mechanisms and payers' decision criteria and processes differ, the same broad pressures apply: decreasing funds available to payers and increasing prices of innovative medicines (Ranson, 2018). In turn, payers' responses are similar: limitations on prices, restrictions on availability and requiring proof of value of the innovative medicine before agreeing to pay for it at any level. In England, the National Institute for Health and Care Excellence (NICE) was set up in 1999 to reduce variation in the availability and quality of NHS treatments and care across England19. NICE prepares evidence-based guidance and advice intended to resolve uncertainty about which medicines, treatments, procedures and devices represent the best quality care and which offer the best value for money for the NHS.

The high cost of developing and manufacturing novel medical technologies, such as cell and gene therapies, is a challenge to achieving patient impact, as it can prevent their uptake into the health system. For example, guidance from NICE had initially rejected a cell therapy (CAR-T therapy) from Gilead Science, Yescarta, which it had assessed as too expensive at £300,000 per patient20. A commercial agreement with NHS England subsequently enabled NICE to approve the lymphoma treatment's entry into NHS England's Cancer Drugs Fund in October 201821. The NHS also announced that Novartis' Kymriah, another CAR-T therapy carrying a list price of £282,000 for a single course, would be made available to children with a type of leukaemia22 but not to adults23. In August 2018, NICE also rejected a treatment for spinal muscular atrophy (SMA), Spinraza, a novel antisense oligonucleotide product by Biogen, due to its high cost of £450,000 per patient for the first year and £225,000 for subsequent years24. However, other European countries, such as Germany and Belgium, cover the treatment. The uncertainty around uptake, and hence commercial success, represents a

¹⁸ <u>https://www.gov.uk/government/groups/mhra-innovation-office</u> Accessed December 2018

¹⁹ https://www.nice.org.uk/about/what-we-do Accessed December 2018

²⁰ <u>http://www.pharmatimes.com/news/nice_says_no_to_gileadss_yescarta_in_draft_guidelines_1250351</u> (Aug 2018) Accessed December 2018

²¹ <u>http://www.pharmatimes.com/news/gilead_strikes_deal_with_nhs_england_on_yescarta_access_1254812</u> (Oct 2018) Accessed December 2018

https://pharmaphorum.com/news/nhs-to-fund-novartis-car-t-therapy-kymriah/ (Sep 2018) Accessed December 2018
 http://www.pharmatimes.com/news/nice_rejects_novartis_car-t_kymriah_for_adult_lymphoma_1252794 (Sep 2018) Accessed

December 2018

²⁴ https://pharmaphorum.com/news/nice-in-talks-with-biogen-after-rejecting-sma-drug/ (Aug 2018) Accessed December 2018

significant risk for the private sector, who consequently may shy away from investing into the development of novel advanced therapies.

1.1.4 Collaboration platforms and industry partnership models

Large pharmaceutical companies may acquire external technology vendors or innovative units involved in promising R&D projects, license the required technologies, outsource operations to external vendors such as Contract Research Organisations (CROs), or partner with companies or academic research centres through a variety of models (Buvailo, 2018). There are several drivers behind these activities:

- Sourcing innovation and feeding the pipeline: Getting ideas and expertise from external sources is a well-established practice in the pharmaceutical industry. Illustrating this point, about one-third of all drugs in the pipelines of the top ten pharmaceutical companies in 2012 had initially developed elsewhere (Rockoff, 2014). And while in 2002, 38% of compounds moved through Phase III trials by the pharma industry had been externally sourced, this figure had risen to 62% by 2010 (McKinsey, 2012).
- Increasing success rates of drug discovery programmes and decreasing R&D costs: In most cases, it is cheaper and more efficient for companies to outsource research that can accelerate the early drug discovery process than it is to create in-house infrastructure and hire the necessary research staff. This can improve *in vitro*, *in vivo*, and *in silico* methods and models, which in turn can better support target identification and validation or reach through all the way to a well-characterised preclinical drug candidate.
- Accessing specialised knowledge and technologies: Biopharmaceutical companies may not have the required expertise and infrastructure in-house to make full use of new technologies, such as genomics, artificial intelligence (AI), combinatorial chemistry, and high-throughput screening, and therefore outsource these research components to specialised CROs or academic centres.
- Increased flexibility: Given the high failure rate of drug candidates and rapidly advancing research and technology, the development of specialised in-house infrastructure and expanded staff with specific expertise represents a significant risk to companies. Especially at the earliest stages of the drug discovery process, when uncertainty is highest, companies may prefer to maintain only the most important core functions and competencies, while outsourcing research-intensive early stage research to specialised CROs or academic labs.

R&D partnerships can be placed into two broad categories, asset-based partnerships and non-asset-based partnerships (Deloitte, 2017).

Asset-based partnerships

Asset-based partnerships include acquisitions and licensing of compounds, products, or technology. Traditional asset-based partnerships typically involve two parties (e.g. companies) and are focussed on a particular asset (i.e., a drug candidate), and use a structure (a "sponsor" and "partner" model) to assign control, risks, and rewards. A common objective is to progress a single asset through the R&D process, obtain approval, and launch (Deloitte, 2017).

Mergers & Acquisitions (M&As): Following a dip in the level of investment in M&A from USD \$235 billion in 2008 to USD 105 billion in 2012, life sciences M&A transactions have risen again to around USD 250 billion per year for the 2015-2017 period (Figure 1.5) (Clarivate Analytics, 2018). However, the number of transactions has been increasing steadily over the entire 10-year period, from 260 transactions in 2008, reaching a peak in 2016 of 547, and to 449 in 2017. (see also section on biopharma industry landscape)



Figure 1.3: Mergers and acquisitions in the life sciences

Source: Clarivate Analytics (2018) Trends in Dealmaking, Fundraising, and Partnerships: The Changing Landscape

 Licensing transactions: The last decade has seen a strong increase in the number of licensing transactions (Clarivate Analytics, 2018). From approx. 800 transactions in 2008, this figure rose to more than 1700 transactions in 2016. This upwards trend persisted through the period following the economic crisis; however, the average and median deal sizes were depressed over the 2011-2013 period.





Source: Clarivate Analytics (2018) Trends in Dealmaking, Fundraising, and Partnerships: The Changing Landscape. Dollars are adjusted for inflation; the chart includes all announced License, Joint Venture, and Research-Only collaborations.

Non-asset-based partnerships

Non-asset-based partnerships include Joint Ventures (JVs), consortia, and other collaborations, e.g. focussed on education and awareness (Deloitte, 2017). Non-asset-based partnerships, such as consortia, often aim to expand knowledge and understanding. Collaborative alliances may include three or more parties and are often comprised of a mix of stakeholders including companies, academia, non-profit organisations, and government representatives. These partnerships share control and decision-making, thus spreading both the potential risks and rewards.

An analysis of the types and number of biopharmaceutical partnerships created between 1995 and 2014, identifying the following key trends (Deloitte, 2017):

- A rise in the number of biopharmaceutical R&D partnerships: Approx. 9000 new biopharmaceutical R&D partnerships were formed between 2005 and 2014 This is more than double the number formed from 1995 to 2004 (approx. 4000).
- A rise in the number of new R&D consortia: Between 2005 and 2014, 334 new R&D consortia were formed, approx. nine times the number formed during the prior decade. (see PPP section below)
- Partnerships are increasingly formed in earlier stages of the R&D process prior to entry into clinical trials - with the average number of new early-stage partnerships more than doubling between 2005 (256) and 2014 (578).

These increases in JV, consortia, and other non-asset-based partnerships highlight the growing role and importance of more open, collaborative approaches to R&D innovation.

The benefits and limitations of different approaches to translation and commercialisation of discoveries employed by a research institute (the Gladstone Institute in San Francisco, USA) were described in a recent publication (see Table 1.4).

Table 1.2: Models for translation and commercialisation of medical discoveries (Gladstone Institute, San Francisco)

Translation & commercialization strategies	Opportunities & benefits	Limitations
Sponsored research agreements	Straightforward Clear demarcation of scope Activities funded	Limited upside potential for success Not transformational
Thematic programs Projects grouped around a specific theme offer 'more shots on goal' Opportunity to compare different approaches Competitive Return of opportunities not taken up		Most advanced program can garner most support Early-stage collaborations
Strategic partnerships/ Addition of skill sets not available internally (e.g., medicinal joint ventures Opportunity to advance programs to higher value inflection Partial de-risking increases attractiveness		Pre-agree future ownership to avoid concerns over value of contributions
Academic translational center	Benefits of scale, scope and skill sets Harness synergies across programs and approaches Can adjust resources to match success Develop programs to higher value inflection points	Tendency to be inward looking regarding ideas and skill sets
Creation of for-profit entity	Enables pursuit of some commercial goals without compromising 501(c)(3) tax exemption status Independent governance Institute intellectual property taken into entity	Time and complexity of creation
Venture philanthropy	Shared vision and joint planning Relatively early-stage programs Extended time frame Potential access to other resources (e.g., legal, financial, business through connections of philanthropy group)	Access to right people with shared vision and commitment
VC-backed NewCo Build optimal team formation Focus & commitment Clear vision and plan		Loss of control Financial returns low until late-stage success

Source: (Freedman and Mullane, 2017)

Public-private partnerships

In the last decade, alongside bilateral 'one-to-one' interactions between academic and industry researchers, PPPs involving multiple stakeholders have increasingly emerged (Khanna, 2012; Yildirim *et al.*, 2016; de Vrueh and Crommelin, 2017). These R&D networks facilitate pre-competitive collaborations – described as the sharing of knowledge, expertise and resources with collaborative partners without the burden of commercial sensitivities or interests are a tool for enhancing preclinical research and experimental medicine (AMS/ABPI, 2018). Collaborations include not only 'traditional' academia and industry stakeholders but also charities, patient organisations, and/or national competent authorities ('regulators'). These collaborations are especially suited to basic research on biological

mechanisms that lead to better understanding of disease, pharmacology and target discovery. Results, data and resources are shared across scientific collaborators with the understanding that improving the fundamental knowledge base can benefit the entire research community.

In the biomedical sector, there are essentially two categories of PPPs (de Vrueh and Crommelin, 2017):

- Product Development PPPs, termed PDPs, formed to develop pharmaceutical solutions for lowand middle-income countries along the entire innovation pathway
- Precompetitive PPPs, which aim to generate novel scientific concepts (e.g. disease targets and research models) and infrastructures (e.g. databases) through multi-stakeholder collaboration based on mutual trust, pooling of complementary expertise and knowledge, and sharing of rewards. Activities are limited to the precompetitive space to avoid potential disputes, e.g. over IP.

The average number of multi-stakeholder PPPs launched per year has grown substantially, including some high-profile PPPs such as the European Innovative Medicines Initiative (IMI), the Dutch Top Institute Pharma, and the US Foundation for National Institutes of Health. An analysis of 369 consortia showed that between 2006 and 2013, the number of new consortia per year increased from 18 to 46, with a peak of 63 in 2012 (Lim, 2014). The largest rise was apparent in Europe between 2007 and 2013; this can be attributed to support for new consortia from the European Seventh Framework Programme (FP7, incl. IMI) during this time, which accounted for 111 of 183 consortia launched during this period. While government-funding was responsible for initiating the majority of consortia, industry started playing an increasingly important role from 2009, with two-thirds of industry-initiated consortia launched between 2007 and 2013 supported by IMI (Lim, 2014). Interestingly, the aim of approx. 20% of the 369 consortia analysed included to advance regulatory science through the participation of a regulatory official in the consortium's research or on an oversight committee. Most consortia (45%) intended to improve drug development, and of these, most were initiated by government (31%) and then industry (27%). Most consortia, irrespective of the initiating sector, aimed to create tools for use by the entire research community, such as procedures for biospecimen handling, methods for clinical trials, predictive methods for designing safer drugs, and collective research resources (libraries, repositories).

1.1.5 The role of academia in translational research

Academic research contributes several crucial components of the translational research ecosystem.

Underpinning knowledge for medical innovation

Traditionally, academic research contributes to translation by providing an enhanced understanding of underlying biological processes. Much of this knowledge developed in academic laboratories underpins today's discovery efforts, leading to fundamental changes in the way new therapeutics are conceived and applied. These range from *fundamental therapeutic approaches and modalities*, such as vaccines, monoclonal antibodies, antisense oligonucleotides and RNAi, and chimeric antigen receptor T cell therapy (CAR-T) to *R&D and diagnostics tools*, such as high-content imaging and screening, patient-derived pluripotent stem cells, genome-wide analyses, the '-omic disciplines' and gene-editing tools (e.g. CRISPR), as well as the *application of big data* linking patient symptoms and treatments to their genetic and -omic profiles (Freedman and Mullane, 2017).

The importance of public funding for biomedical research, and the understanding that underpins progress towards health impacts is illustrated in a recent analysis of the contribution of public-sector funding to the emergence of new drugs (Galkina Cleary *et al.*, 2018). The authors identified more than 2 million publications related to the 210 new molecular entities (NMEs) approved by the FDA from 2010–2016, or their 151 known biological targets. Of these publications, more than 600,000 (29%) were associated with NIH-funded projects in the NIH's online reporting tool, RePORTER (accounting for project costs of more than USD 100 billion over the 2010-2016 period, approx. 20% of the NIH budget over this period). NIH funding contributed to all the 210 NMEs approved and was *focussed primarily on the drug targets rather than on the NMEs themselves*. Funding related to targets preceded funding related to the NMEs. This is consistent with the expectation that basic research provides validated targets for targeted screening.

Technologies classically mature through a technology growth cycle, which can be quantitatively modelled as an 'S-curve', with exponential growth between a statistically defined 'technology initiation

point' and an 'established technology point' (McNamee and Ledley, 2017). Novel technologies arise from precursor studies through scientific insights or inventions, which initiate a period of exponential technical growth; as a new technology advances and becomes established, technological progress slows and approaches a limit. Early stage technologies commonly fail to generate products that can meet the performance or market standards set by more mature, established technologies; only after new technologies achieve a certain level of technological maturity, they consistently produce products that can meet, or redefine, these standards. This 'S-curve' of innovation is mirrored in the rate of accumulation of scientific publications. An analysis of publications to determine timelines of translational research for 138 drugs and biologicals approved by the FDA from 2010-2014 further demonstrated the important role of underpinning academic research in drug discovery came from (McNamee and Ledley, 2017). The study found that research on targets for 102 products exhibited the characteristic S-curve maturation pattern. Most products (72 of 102) only entered clinical trials after the technology 'established point' was reached, and development timelines were significantly longer when clinical trials began before this point, at 11.5 years compared to 8.5 years. None of the NMEs approved 2010-2014 were approved before this point. Technological maturation hence significantly impacts the efficiency of drug development.

• De-risking through early stage Translational Research

Academic research also plays a clear role in providing evidence needed for technology maturation, derisking technologies to a point where either a company can either be formed or will license the technology for further development (Fuentes *et al.*, 2016; Schwartz and Macomber, 2017). While industry-led drug discovery is guided largely by Return on Investment (ROI)-driven business decisions, academic research remains unencumbered by ROI-driven decisions, and is in a position to fill the gap unaddressed by the private sector (Roy, 2018). Given substantial technical and regulatory challenges of first-in-class technologies, academic research can be a driving force, such as in the field of ATMPs (Volk *et al.*, 2015; Abou-EI-Enein, Volk and Reinke, 2017). However, academia can rarely 'go it alone' to achieve impact, with few institutions able to access the financial, commercial and operational resources required for market entry. It generally relies on industry to recognise the IP and translate to market (Driscoll *et al.*, 2017).

Publicly-funded research can also help to address high-risk areas, e.g. those with a poor track record of translational success, such as central nervous system (CNS) disorders or many cardiovascular indications (which require large clinical trials) (see section on biopharma industry landscape; (Freedman and Mullane, 2017). These growing areas of unmet medical need are well-suited for academic-industry collaborations as they do not compete with large internal industry R&D programmes. Illustrating this trend, the second largest number of partnerships, collaborations and licensing deals in 2017 was the CNS field, behind oncology25. Academic researchers, together with clinical staff, can also provide the necessary expertise in biological pathways and physiology to provide early evidence and inform decisions on whether to progress a candidate into clinical trials (AMS/ABPI, 2018). This process is not linear; findings from later stage research in turn can inform and open new avenues for investigation for academic research (see section scientific failure).

In support of a model of a complementary relationship between public biomedical and health research expenditure and private pharmaceutical R&D expenditure, it was found that a 1 % increase in UK public sector expenditure is associated with a 0.81 % increase in private sector expenditure (Sussex *et al.*, 2016).

• Addressing health needs and innovation of limited interest to the private sector

As described above, industry-led R&D is guided largely by Return on Investment (ROI)-driven business decisions, and hence companies are not incentivised to engage in endeavours without a clear pathway to economic benefit for their shareholders. However, many health improvements stem from interventions that do not involve the purchase of a therapy or device. These include behavioural and physical therapies and approaches for disease prevention, new surgical techniques, and ways to guide

²⁵ <u>http://www.evaluate.com/vantage/articles/data-insights/other-data/oncology-continues-reign-licensing-world-0</u> (Sep 2018) Accessed December 2018

treatment decisions and predict patient outcomes, which feed into clinical guidelines and public health policies.

• Independent expert advice

Publicly-funded research also provides an independent pool of expertise to keep company-R&D in check. Many scientists, policy makers, and the public are sceptical that industry-funded research can be trusted. A poignant example is the distortion of the scientific process by the tobacco industry for commercial ends during the second half of the 20th century (Brandt, 2012); more recently, a study argued that studies funded by industry has compromised the research on sugar-sweetened beverage consumption and weight gain (Bes-Rastrollo *et al.*, 2013).

Translational science centres

The significant challenges associated with the translational process, and the varied expertise required to overcome these, created an opportunity for publicly-funded organisations to establish translational science centres, to develop (and hence de-risk) research to the point where it becomes attractive for commercial organisations. Between 2000 and 2011, governments, not-for-profit organisations and academic researchers in the EU, Canada, Australia and the USA recognised the value of improving national translational capacity and capability. In the UK MRC Technology (now LifeArc) was created to expedite the translational process and catalyse therapeutic innovation. Similarly, the European Infrastructure for Translational Medicine (EATRIS), The Centre for Drug Research and Development (CDRD) in Canada, Therapeutic Innovation Australia (TIA), and the National Centre for Advancing Translational Sciences (NCATS) in the US were established during this period (Fuentes *et al.*, 2016). However, some of these efforts also attracted criticism; for example, NCATS, seeking to cover the entire process from basic research to clinical development and implementation to promoting public health was questioned on its thinking that publicly funded academics could perform drug discovery better and faster than industry professionals (Freedman and Mullane, 2017).

Translational research centres can also combine teams from academia and industry. An example of this is the AK project, a partnership between Kyoto University and Astellas Pharma (for an extended case study, see 0). The partnership was established in 2007 as part of a programme of the Japanese Ministry of Education, Culture, Sports, Science and Technology (MEXT) with the aim of overcoming the 'valley of death' through integrated industry-academia collaboration26. With approx. USD 100 million in matched public-private funding over 10 years, the AK project sought to develop 'next-generation immunoregulatory medicines' by combining Astellas Pharma's drug discovery technologies with basic and clinical research at the Kyoto University Graduate School of Medicine and Kyoto University Hospital. The 'Fusion laboratory' on the Kyoto University campus was set up, co-locating fifteen principal investigator groups (scientists and clinicians) from the Graduate School of Medicine of Kyoto University with three research teams from Astellas Pharma; the University Hospital provided access clinical and pathological samples. The AK project resulted in the identification of 35 drug targets, fifteen of which were transferred to Astellas' R&D programme, and seven have been taken forward for further development in Astellas' drug development programme. The model has been applied to develop partnerships with five other Japanese companies, and the partnership with Astellas extended (now funded from private sources only).

Public funders have recognised that moving health-related knowledge to achieve real world impact, e.g. knowing how to access it, assess it, adapt it to the local context, apply it in the practical world and know when it is not suitable for practical application – is a challenge beyond the immediate reach of the research community. A programme of interviews with representatives of 26 medical research funding organisations indicated that knowledge transfer, i.e. the synthesis, dissemination, exchange, and application of knowledge to improve health, is an increasingly important global objective and that funding agencies are following suit (Mclean *et al.*, 2018). This is supported by the fact that 20 (77%) of the funding organisations had included the concept of knowledge transfer directly in their agency mandate. However, the perception of increased importance of knowledge transfer was not clearly reflected in other proxy measures of the 'KT role', the level of staff and budget. And while 23 of the 26 funding agencies had a defined and planned KT strategy to some extent, only 7 agencies had evaluated

²⁶ <u>https://www.jst.go.jp/shincho/sentanyugo/downloads/2014sentan-en_low_Wpage.pdf</u> (2014) Accessed December 2018

KT efforts and only one (Alberta Innovates) could demonstrate that evaluation results had been used to guide KT programmes or practice.

1.2 Translational research in the UK

1.2.1 UK government policy for health research

The 2006 *Review of UK health research funding* (Cooksey Report) was pivotal in proposing a structure for funding arrangements across the whole spectrum of health research within the UK. The report highlighted that the "UK Health Research System has many strengths", including a long tradition of undertaking "excellent basic science" as evidenced by the 27 Nobel prize winners funded by the MRC since its establishment in 1913. It also noted the unique strength of the UK's health research base in combination with the NHS, which exists as a major attraction for R&D investment from the pharmaceutical and biotechnology industries (Cooksey, 2006). However, the report also concluded that "the UK is at risk of failing to reap the full economic, health and social benefits that the UK's public investment in health research should generate" and noted the lack of an overarching UK health research strategy to ensure UK health priorities are considered and investigated via all types of research. In order to improve the coherence and comprehensiveness of funding arrangements for supporting translation of ideas from conception, the responsibilities of the MRC and the National Institute for Health Research (NIHR), within the translational research space, were to be more explicitly delineated27.

The Cooksey report led to the establishment of the Office for Strategic Coordination of Health Research, an organisation tasked with overseeing the budgetary and research strategies of the MRC and NIHR. Specifically, the MRC were to provide project funding for the early part of the translational pathway (from basic research to early clinical trials), and the NIHR to cover the later stages (late clinical trials and Health Technology Assessment (HTA)) and to provide the necessary clinical infrastructure.

In 2011, the Coalition Government published a *Strategy for UK Life Sciences* (Office for Life Sciences, 2011), which was designed to sit alongside the NHS Chief Executive's Review *Innovation Health and Wealth: Accelerating Adoption and Diffusion in the NHS* (Department of Health, 2011)28. The strategy was designed around 3 key principles: to build a life science ecosystem in the UK; to attract, develop and reward the greatest talent; and to overcome barriers and establish incentives to promote health care innovation. The report stated the importance of creating an environment conducive to translational research, by encouraging innovation through the translational funding gap, and decreasing regulatory hurdles to provide a more direct route to early adoption and diffusion in the NHS. It set out a few actions including a £75 million investment into expanding the European Bioinformatics Institute in Cambridge to provide a new facility for biological data storage. This was in response to several UK-funded research breakthroughs which led to an exponential increase in commercially available high-throughput gene sequencing technology, which created challenges relating to the storage and analysis of such vast quantities of data.

The report also set out the importance of preserving Academic Health Science Centres (AHSCs)29 and building on them to create Academic Health Science Networks (AHSNs)³⁰ to facilitate NHS-industry

²⁷ See Cooksey Report (Cooksey, 2006), Box 5.2

²⁸ The NHS Chief Executive's Review *Innovation Health and Wealth: Accelerating Adoption and Diffusion in the NHS* set out the NHS's strategy for innovation and how best the NHS could adopt these innovations to deliver greater health benefit; support the growth of the life sciences industry; and provide new business opportunities abroad for UK companies.

²⁹ AHSCs have a tripartite mission to integrate research, teaching, and clinical care in order to drive synergy between these areas, with the ultimate goal of improving the health of the population. Although fundamental research is likely to be undertaken by a clinical research unit, the AHSC can facilitate the scale up and spread of research findings to larger patient populations with an eventual positive impact on public health.

³⁰ AHSNs connect the NHS, academic organisations, local authorities, the third sector and industry. They act as a gateway for NHS organisations requiring support with innovation and provide industry with clear points of access to the NHS. The overarching aim of the AHSNs is to improve health and generate economic growth within the region. They are positioned to spread health innovation at pace and scale and drive adoption across significant patient populations.

collaborations. In addition, it noted the importance of empowering patients to participate in research as a key enabler of translational research. In order to support patient participation in clinical research, the NIHR re-launched an enhanced web-based UK Clinical Trials Gateway in 2012. This site provided patients and the public with accessible information about clinical trials in the UK. In addition, as a means of maximising opportunities for utilising patient data to support research, the report also stated the launch of a cross-funder call for Centres in e-health31, which committed £15 million to centres aimed at building a sustainable health informatics research capability in the UK.

In 2014 the Government commissioned the Accelerated Access Review (Department of Health and The Wellcome Trust, 2016), which considered ways in which patients access to innovative drugs, devices, diagnostics and digital products could be expedited. The report recommended a new accelerated access partnership to speed up and simplify the process for getting new treatments and diagnostics safely from pre-clinical development to patients. As a result of this partnership innovators would be able to access joined-up help for clinical development, regulation, and assessment of cost effectiveness. The intention was to create a "win-win" scenario, where innovators would benefit from earlier access to the NHS market and in return the NHS would be able to provide a better value to their patients.

Most recently, in 2017 Sir John Bell led the report *Life Sciences Industrial Strategy – A report to the Government from the life sciences sector* (Bell, 2017), which set out recommendations to government regarding the long term success of the life sciences sector. In the translational science space, the strategic goal was to support a 50% increase in the number of clinical trials over the following five years, especially 'change of practice' trials and trials with novel methodologies. In order to achieve this goal, the report recommended:

- Documentation of the number of novel trial designs used as well as the quantity of 'change of practice' trials in the UK compared to elsewhere.
- Collaboration with industry and regulators to establish a working group to evaluate the use of digital health care data and health systems; and to evaluate the safety and efficacy of new interventions.
- Government focus on improving the UK's clinical trial capabilities in order that we can compete globally in our support for industry-academic research at all phases.
- Design of a translational fund to support the development of clinically-useable molecules and devices, which can then be progressed to preclinical and early clinical studies.
- Better use of Government and charitable funding to attract world-class scientists to the UK over the next 10 years.

The resulting UK Life Science Sector Deal (HM Government, 2017) committed to help raise the intensity of R&D in the UK, strengthen the environment for clinical trials by investing in NIHR and NHS infrastructure, and speed up clinical trial approvals by the Health Research Authority. In addition, the report outlined the implementation of the Accelerated Access Review to streamline the pathway to product commercialisation and an £86 million investment focussed on supporting innovators and the NHS. The creation of a digital health catalyst to support SMEs partnering with the NHS to develop technologies was also actioned along with strategies to support the development and improvement of the UK's health data infrastructure.

1.2.2 UK health R&D funding

Private sector

Private sector expenditure accounts for the largest proportion of all R&D in the UK. In 2016, businesses invested more than the public (government and research councils), non-profit, and higher education

³¹ MRC in partnership with Arthritis Research UK, the British Heart Foundation, Cancer Research UK, the Economic and Social Research Council, the EPSRC, the NIHR, the National Institute for Social Care and Health Research (Welsh Assembly Government), the Chief Scientist Office (Scottish Government Health Directorates) and the Wellcome Trust

sectors combined, at 67% versus 33% respectively32. This equated to £22.2 billion of the overall UK R&D expenditure of £33.1 billion.

Within the private sector, the pharmaceutical industry expends a considerable amount on R&D33. Following steady growth from 2007 to 2011, from £3.9 billion to £4.9 billion, expenditure dropped between 2011 and 2014 to £3.9 billion and rose again for 2015 and 2016, to £4.1 billion. As a share of total business expenditure on R&D across sectors in the UK, the pharmaceuticals sector reached its peak in 2010 at 29%, dropping to 19% in 2016. Compared to other countries, the UK's pharmaceutical sector is relatively R&D-intensive, with an intensity (i.e. UK R&D expenditure as a share of UK sales) of 33% in 2016. This compares to an R&D intensity range of 15% to 26% among the top 10 pharmaceutical companies34.

The UK took the lead in venture capital raised in 2016, with the largest number of financings of any European market (but behind the US market) (see section on R&D investment). Total venture financing amounted to USD 590 million, or 30% of all European venture capital, with total innovation capital financing was estimated at USD 1.3 billion, or 25% of the total. (EY, 2017b).

Public sector

A wide range of translational funding programmes have existed within the UK over the past 10 years, offered by both the public and charitable sectors. The main funding bodies supporting health-related research are the Medical Research Council, Innovate UK (both of which are now part of UK Research & Innovation (UKRI)), and the National Institute for Health Research. In addition, charitable organisations such as The Wellcome Trust and Cancer Research UK (see section on biopharma industry landscape) offer funding via dedicated translational research grant schemes or via more general research calls.

Between 2000 and 2015, government expenditure on health R&D in the UK rose from USD 1.4 billion (approx. £892 million based on historical exchange rate) to USD 3.4 billion (approx. £2.25 billion based on 2015 exchange rate)35. Suggesting a strategic reprioritisation of funder activities to accelerate translation from 'bench to bedside', the proportion of investment towards translational research across public and charity organisations36 increased by 9.3% between 2004 and 2014 (UK Clinical Research Collaboration, 2015).

The Medical Research Council

The UK Medical Research Council (MRC) funds scientific discovery to improve human health, investing in research at universities and hospitals on behalf of the UK taxpayer37. The MRC's gross expenditure on research (as funded by its BEIS allocation and contributions from other bodies) was £814.1 million for 2017/2018 and increase from £755.5 million in the previous year38. Of this, £380.2 million went to grants for researchers in universities, medical schools and research organisations, and £150 million to programmes within the MRC's own units and institutes. In its 2016-2020 Delivery Plan, the MRC set out to allocate a total of 15% of its resource expenditure to academic industry relationships and clinical and population health translation (Medical Research Council, 2016b).

Other research councils are also supporting health research in specific areas. Research relevant to the engineering elements of translational research is supported by the Engineering and Physical Sciences Research Council (EPSRC), while the Biotechnology and Biological Sciences Research Council (BBSRC) funds research into the underpinning bioscience (e.g. greater systems-based understanding of biology to enable improved bioprocessing).

³² <u>https://www.abpi.org.uk/facts-and-figures/science-and-innovation/uk-health-research-expenditure/</u> Accessed November 2018

³³ <u>https://www.abpi.org.uk/what-we-do/developing-researching-medicines/investing-in-innovation/uk-rd-intensity-by-industry/</u> Accessed November 2018

³⁴ <u>https://www.dcatvci.org/4768-measuring-innovation-where-does-the-pharma-industry-stand</u> Accessed November 2018

³⁵ <u>https://www.abpi.org.uk/facts-and-figures/science-and-innovation/global-public-funding-of-health-rd/</u> Accessed November 2018

³⁶ The UK Health Research Analysis includes the Department of Health and devolved administration Health Departments, six research councils (AHRC, BBSRC, EPSRC, ESRC, NERC and NC3Rs), the MRC, Innovate UK, and 52 charities (in coordination with the AMRC)

³⁷ <u>https://mrc.ukri.org/about/what-we-do/</u> Accessed November 2018

³⁸ https://mrc.ukri.org/about/what-we-do/spending-accountability/facts/ Accessed November 2018

Innovate UK

Innovate UK is the UK's innovation agency, providing support for innovative businesses to accelerate sustainable economic growth39. The Health and Life Sciences sector is one of the agency's four focus (Innovate UK, 2018b), supported through a range of sector-focussed as well as open call mechanisms, with a net grant expenditure of approx. £75.5 million on health and life sciences grants in 2017-2018 (Innovate UK, 2018a). These include:

- the Biomedical Catalyst providing grants for businesses to test and develop innovative health and care projects, in partnership with the MRC (£34 million in 2017/18)
- the Digital Health Technology Catalyst, for feasibility studies and research and development projects aimed at improving patient outcomes and transforming healthcare through digital innovation (£8 million in 2017/18)
- the UK Small Business Research Initiative (SBRI) which acts as a bridge for the seed funding gap experienced by many early stage companies wishing to progress their products to market. Although not specifically aimed at medical research, the initiative has run health-related calls focussed on challenges relevant to the NHS (£313,000 in 2017/18)
- the Industrial Strategy Challenge Fund, which will provide a total of £197 million for infrastructure and as research grants to develop technologies for the manufacture of medicines (£15 million in 2017/18)

Innovate UK also supports commercialisation of research discoveries through its Catapults - the Cell and Gene Therapy and Medicines Discovery Catapults and the Cell and Gene Therapy Manufacturing Centre - which provide infrastructure and teams of experts to translate early stage research into commercially viable and investable therapies (£26 million from Innovate UK in 2017/18).

The National Institute for Health Research

The National Institute for Health Research (NIHR) were established by the Department of Health in 2006, with the aim to improve the health and wealth of the nation (see section 0). To achieve this aim, the NIHR funds high quality research to improve health, trains and supports health researchers, provides research facilities working with the life sciences industry and charities, and places emphasis on patient involvement. Its annual research expenditure is approx. £1 billion. Most of this budget supports the NIHR's research infrastructure, such as the Clinical Research Network and Biomedical Research Centres (£633 million in 2016/17, see section 0) (NIHR, 2017). A further £242.0 million were spent across the NIHR research programme, which includes Health Technology Assessment (HTA and grants for applied research, and approx. £100 million went towards training schemes.

The NIHR provides funding to support translational research via several mechanisms. The Invention for Innovation (i4i) scheme funds collaborative R&D projects within medical technology SMEs, universities and the NHS, with the aim of de-risking projects that have demonstrated proof-of-principle and have a clear pathway towards adoption and commercialisation, making them attractive to follow-on funders and investors. The expected i4i output is an advanced or clinically validated prototype medical device, technology or intervention. The i4i Connect scheme provides an additional funding stream aimed at SMEs who require a 'funding boost' in order to reach the next stage in the development pathway and to be able to apply for further funding40. These schemes received £12.8 million in funding in 2017-2018 (NIHR, 2017).

The Efficacy and Mechanism Evaluation (EME) programme is delivered in partnership with the MRC. It focusses on supporting clinical trials and other studies that investigate the efficacy of interventions. It aims to attract studies with novel designs that are intended to deliver results more efficiently, in order to reduce the overall study timeline, and expedite the route to knowledge gained. Novel study designs involving stratification and the use of routinely collected digital data are strongly encouraged.

³⁹ <u>https://www.gov.uk/government/organisations/innovate-uk/about</u> Accessed November 2018

⁴⁰ <u>https://www.nihr.ac.uk/funding-and-support/funding-for-research-studies/funding-programmes/invention-for-innovation/</u> Accessed November 2018

Charitable sector

The charitable sector is a strong contributor to UK health R&D funding. The Association of Medical Research Charities (AMRC), whose membership includes 140 charities in the UK, estimate a total investment of £1.6 billion in research from charities during 2017; 92% of this research takes place in universities and hospitals in the UK41. The £1.6 billion invested by the charitable sector represents a considerable proportion of research expenditure in the UK, compared to the approx. £1 billion research expenditure of the NIHR (NIHR, 2017) and approx. £0.8 billion of the MRC (Medical Research Council, 2016a). Several UK charities, including the Wellcome Trust, Cancer Research UK (CRUK), the British Heart Foundation (BHF), and Arthritis Research UK (ARUK) have funding streams relating directly to translational research or covering some aspect of the translational pathway within their calls for proposals.

1.2.3 The UK translational research infrastructure

The 2006 report by the Department of Health and Social Care, *Best Research for Best Health* (BRfBH), outlined the government's strategy for the proceeding five years. Its aim was to create a health research system in which the NHS supported leading research with a focus on the key needs of patients and the public (DHSC, NIHR, & UKCRC, 2006). The strategy was developed in order to establish the NHS as a centre of research excellence that focussed on transparency, quality and value for money while responding to the challenges within the applied health research system at the time. A central goal was to develop R&D infrastructure in order to sustain research capacity in priority areas and drive the uptake of innovation within the NHS. In order to facilitate the passage of innovation toward patient impact it was recognised that NHS input in the research process was key.

The increased focus on research infrastructure within the UK and the increased understanding of the importance of fostering a collaborative environment led to the establishment of various research centres and networks within the UK. Two initiatives of the BRfBH were the creation of Biomedical Research Centres (BRCs)42 and Biomedical Research Units (BRUs)43. Eleven BRCs were announced in 2007, followed by the creation of fifteen BRUs between 2008 and 2009. Building on this considerable investment into the clinical translational research infrastructure, the DHSC went on to establish five Academic Health Science Centres (AHSCs) in 2009 and a further five in 2013 (there are currently six established AHSCs in England). A further 15 Academic Health Science Networks (AHSNs) were established in 2013 to strengthen NHS-industry connections.

Around the same time the NIHR Collaborations for Leadership in Applied Health Research and Care (CLAHRCs)44 were piloted for a five-year period. As a result of this pilot and the subsequent portfolio of applied health research that it created, a further £144.8 million of investment was allocated to 13 new collaborations from 2014-201945. The NIHR in partnership with other major UK funders (under the umbrella of the UK Clinical Research Collaboration) also set up 19 Clinical Research Facilities (CRFs) 46 within the NHS between 2012 and 2017. More recently, a further £112.3 million of funding for CRFs has been awarded to 23 NHS organisations (to be provided from 1 April 2017 to 31 March 2022).

⁴¹ <u>https://www.amrc.org.uk/2018-infographic</u> Accessed November 2018

⁴² Biomedical research centres (BRCs) are partnerships between an NHS trust and a university to undertake translational research in areas of clinical need and high disease burden. They were created to provide the means by which to produce a coherent, patient-focussed research strategy, and a more streamlined pipeline from research to the clinic by allowing researchers access to the required resources (Department of Health, 2008).

 ⁴³ BRUs are smaller and more specialised in comparison with BRCs, and aim to assist the development of NHS-university partnerships in order to achieve critical mass and allow the BRU to submit a credible bid for BRC status in the future.
 ⁴⁴ CLARHCs are collaborations between local providers of NHS services, NHS commissioners, universities and the relevant AHSN and are hosted by a single representative NHS organisation. The aims is to develop and conduct applied health research relevant at the local and national level, and to create a link between those who conduct research and those who use it in practice. The major focus of the activity within the CLARHCs is applied health research at the second translational gap to improve patient outcomes across the wider NHS (NIHR, 2012).

⁴⁵ <u>https://www.nihr.ac.uk/about-us/how-we-are-managed/our-structure/infrastructure/collaborations-for-leadership-in-applied-health-research-and-care.htm</u> Accessed November 2018

research-and-care.htm Accessed November 2010 ⁴⁶ CRFs exist as dedicated purpose-built facilities with the aim of supporting experimental medicine research than can be translated to patient benefit; providing patient access to new treatments and diagnostics; and helping the UK secure sustainable economic growth (NIHR, 2017). The facilities allow specialist clinical research and support staff from universities and NHS trusts to work collaboratively on commercial and non-commercial experimental studies.





Source: Prof Gary Ford, Oxford AHSN. Presentation: Academic Health Science Networks Supporting Diagnostic Innovation⁴⁷

Innovate UK funds infrastructure to support commercialisation of research discoveries through its Catapults programme - the Cell and Gene Therapy and Medicines Discovery Catapults and the Cell and Gene Therapy Manufacturing Centre - which provide facilities and teams of experts to translate early stage research into commercially viable and investable therapies 48 (see section on drug pipeline and approvals).

1.2.4 Adoption and diffusion within the NHS

The 2011 reports, Investing in UK Health and Life Sciences (HM Government, 2011) and Innovation Health and Wealth: Accelerating Adoption and Diffusion in the NHS (Department of Health, 2011), stated the importance of building an integrated system in order to facilitate translation from development to adoption within the NHS and provided a number of recommendations in order to facilitate this. This included the adoption of new value-based pricing (VBP) in 2014 to ensure that pricing took a broader perspective of value, reflecting society's priorities regarding innovative treatments for conditions with high unmet need. At the same time, NICE began work on a review of its Health Technology Assessment (HTA) methods and implemented the automatic adoption of all NICE Technology Appraisal recommendations into the appropriate local formularies to remove local duplication and reduce variation. In addition, the reports highlighted a continued investment in incentives such as NHS Innovation Challenge prizes and the Small Business Research Initiative to encourage translational research within the NHS.

The creation of BRCs, BRUs, AHSCs and AHSNs (see section 0 and 0) also helped to create the infrastructure necessary to drive adoption and diffusion within the NHS, ensuring that the most impactful innovations are pulled through into clinical practice. They have allowed the creation of a collaborative environment whereby academia, industry and clinicians can work together to expedite applied clinical research with the purpose of improving patient outcomes.

Several initiatives have also been developed in order to encourage translational research within the NHS. These include the NHS Innovation Accelerator49 (launched in 2015) which aims to support the

⁴⁷ Prof Gary Ford, Oxford AHSN. Presentation: Academic Health Science Networks Supporting Diagnostic Innovation. https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=6&ved=2ahUKEwj5_vqI1fbdAhWUHsAKHdp6AG8QFjAFegQIA xAC&url=https%3A%2F%2Fwww.community.healthcare.mic.nihr.ac.uk%2Ffiles%2Freports-and-resources%2Fahsn-supporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transporting-transpordiagnostic-innovation.pdf&usg=AOvVaw1IKS9XC3op3csr-eHr-j34 Accessed November 2018

https://catapult.org.uk/catapult-centres/ Accessed November 2018

⁴⁹ https://nhsaccelerator.com Accessed November 2018

delivery of the NHS's strategy, the Five Year Forward View (NHS England, 2014), by expediting the uptake of high-impact innovations within the health service. The initiative is delivered in partnership with all 15 AHSNs across England to support researchers to scale their evidence-based innovations. All selected innovations undergo a robust and competitive assessment process involving assessors from NHS England, NHS Digital, AHSNs, NICE and the Health Foundation.

The NHS Test Beds Programme (NHS England, 2017) was also created in response to the Five Year Forward View. It was recognised that innovation in healthcare could no longer be bolstered by standalone diagnostic technologies or treatments; rather, there was a significant opportunity to promote the adoption and acceleration of 'combinatorial innovations' and new ways of working to transform the delivery of care in a real-world setting. Seven test beds across the UK have been developed to serve as real world sites to test these combinatorial innovations that integrate new technologies, care models and health informatics. These sites pull together the experience and resource of multiple organisations by forming partnerships between healthcare providers, commissioners, patients and technology developers to create a collaborative ecosystem. To date, 40 innovators have worked with over 15,000 people on 51 digital products to test, evaluate and if successful commercialise their products. A second wave of the test beds programme is currently in its implementation phase with a further seven sites being supported across England.

In 2017, the government has announced a £17 million investment over five years into three NIHR Patient Safety Translational Research Centres50. The focus of these centres will be to push forward improvements in patient safety by supporting critical mass of both people and infrastructure within dedicated centres focussed on patient safety early translational research.

1.3 Translational research evaluation

1.3.1 Conceptual models of translational research

Translation is the principle of turning fundamental discoveries into improvements in human health and economic benefit51.

A number of models have been developed to provide a concise description of the translational research concept and represent the major features or characteristics from bench to health impact (reviewed in Trochim et al. 2011; Rajan et al. 2012; Fort et al. 2017). This variety of phase definitions has complicated communication about translational research and makes it difficult to draw comparisons between evaluations of translational research initiatives.

With their origin in medical research, the 'T' models are the most widely applied models by health funding bodies. Four models were summarised by Trochim et al (Trochim *et al.*, 2011), each of which offers a different rationale for dividing the translational research process into two, three, or four phases (see Figure 1.8).

⁵⁰ <u>https://www.nihr.ac.uk/news/17-million-invested-in-nihr-patient-safety-translational-research-centres/5481</u> (2017) Accessed November 2018

⁵¹ <u>https://mrc.ukri.org/funding/science-areas/translation/</u> Accessed November 2018



Figure 1.6: Comparison of four major translational research models

Source: Trochim, W et al (2011) Evaluating Translational Research: A Process Marker Model. Clin Trans Sci 4: 153-162; p. 157

The first model was developed in deliberations of the Clinical Research Roundtable convened by the US Institute of Medicine (Sung *et al.*, 2003). It identified two major obstacles, or 'translational blocks': The first block involves the transfer of new understanding of disease mechanisms from the laboratory into the development of new methods for diagnosis, therapy, and prevention and their first testing in humans. The second translational block relates to the translation of results from clinical studies into everyday clinical practice and health decision making.

The second model divides translational research into three phases (Westfall, Mold and Fagnan, 2007). The first (T1) spans from basic to human clinical research, with the latter consisting of early phase clinical trials in humans. The second and third phases of clinical research (T2 and T3) collectively span practice-based research: in T2 'Translation to Patients', knowledge from early clinical trials moves to use with patients in phase III and IV clinical trials, e.g. through guideline development, meta-analyses, and systematic reviews. T3 'Translation to Practice' encompasses dissemination and implementation research. The endpoint of the model is clinical practice, rather than improved health (as in most other models).

The third model also proposes a three-phase model (Dougherty and Conway, 2008). T1 spans from basic biomedical science to clinical efficacy knowledge (i.e. whether an intervention produces the expected result under ideal circumstances), T2 to clinical effectiveness knowledge (whether an intervention produces the expected result under 'real world' clinical settings in clinical effectiveness trials, and development of practice guidelines), and T3 to improved health quality and value and to population health. T3 activities hence address the 'how' of health care delivery so that interventions are delivered reliably to all patients in all settings and improve the health. The model points out that each translational step moves to progressively broader settings over time.

The fourth model, which was developed with a focus on translation research in genomics, is composed of four phases (Khoury *et al.*, 2007). The first two phases are similar to the 'third' model by Dougherty and Conway, separating efficacy (T1 - 'From (gene) discovery to candidate health application') and effectiveness (T2 - 'Health application to evidence-based practice guidelines') studies in clinical research. There are two phases in post-guideline translational research: T3 - 'Practice guidelines to health practice' encompasses dissemination, implementation, and diffusion research. T4 – 'Practice to population health impact' is described as "outcomes research" and defined as "research that describes, interprets and predicts the impact of various influences, especially (but not exclusively) interventions on

'final' endpoints that matter to decision makers"; latter include patients, families, individuals at risk, providers, and private and public payers.

The US Institute of Medicine defined a research classification system spanning five phases, from T0 to T4 (Surkis *et al.*, 2016):

- T0: basic biomedical research, including preclinical and animal studies
- T1: translation to humans, including proof of concept studies, Phase 1 clinical trials, and focus on new methods of diagnosis, treatment, and prevention in highly-controlled settings
- T2: translation to patients, including Phase 2 and 3 clinical trials, and controlled studies leading to clinical application and evidence-based guidelines
- T3: translation to practice, including comparative effectiveness research, post-marketing studies, clinical outcomes research, as well as health services, and dissemination & implementation research
- T4: translation to communities, including population level outcomes research, monitoring of morbidity, mortality, benefits, and risks, and impacts of policy and change.

All five models characterise translational research as a sequence from basic to clinical to post-clinical (practice-based) research, followed by implementation and use of research, which leads to health impacts. At the same time, all models acknowledge that this is not a linear process; information also flows from a later stage 'to the left', e.g. insights from clinical research can inform basic research; human biospecimens, often from clinical trials, can be used to study new phenomena or to confirm and extend prior findings. The process is hence iterative; scientific discoveries are integrated into clinical applications and, conversely, clinical observations are used to inform and generate research foci for basic science. Others have gone beyond the clinic, regarding the translational process as a "continuous data exchange within and between various research and non-research practices" (van der Laan and Boenink, 2015). A sixth model, proposed by Glasgow et al (Glasgow *et al.*, 2012) acknowledges these multi-directional effects by presenting the phases as interconnected components set in a circle; in addition, this model defines a fifth phase (T0) which centres on the identification of a problem and the 'discovery' of an opportunity or approach to tackle a health issue.

The multi-directionality poses a clear challenge to evaluation approaches trying to estimate the effects of translational interventions over time or across different parts of the continuum. In addition, the 'subject' of translation, the original direction of a research finding, can change substantially, complicating evaluations further. As Trochim et al (Trochim *et al.*, 2011) explain: "The unit that you begin evaluating may shift into a different unit as you track it over time. What begins as a study in genetics may transform into a pathway of work on molecular mechanisms, a study of a new drug, a study of a variation of that drug that emerged from refinement based on interactions with clinical practitioners, guidelines based on many studies of that drug, refinements based on implementation challenges, new policies for insurance provision, and so on. This makes it extremely challenging to trace this evolution in evaluations and determine how long it took and how that process may be made more efficient."

The point has been raised that the 'T' models for translation sit more naturally with basic and clinical sciences and have limited practical application in other research areas. Public health research does not follow the path from laboratory to the clinic, and the models do not adequately describe the processes required for wider adoption and dissemination of research evidence into systems (Ogilvie *et al.*, 2009; Milat and Li, 2017). Khoury et al addressed the issue through the addition of the T4 phase 'Practice to population health impact' in their model (Khoury *et al.*, 2007). Ogilvie et al (Ogilvie *et al.*, 2009) developed an adapated translational research model for public health, which redefines the endpoint of translational research from 'institutionalising effective interventions' to 'improving population health', and highlights the key role of evidence synthesis, the iterative nature of public health research and public health action, and the interface with policy makers and the general public, where decisions that influcence population health are made.

Other models used in translation include the RE-AIM framework (Reach, Efficacy and effectiveness, Adoption, Implementation, Maintenance), which assists in the planning, evaluation and reporting of applied research and interventions, e.g. in chronic disease management and public health52 (Milat and Li, 2017). This framework is used to estimate public health impact, compare different health policies, plan policies designed for increased likelihood of success, and identify areas for integration of policies with other health promotion strategies. RE-AIM provides information on generalisability and external validity of interventions and has been applied in real-world case studies.

1.3.2 Evaluation frameworks and indicators

The end point of translational research is ultimately in health outcomes and impacts, as in the models described in the previous section, and set out in the MRC's mission: "Encourage and support research to improve human health and wellbeing" (MRC, 2013). However, the translational research activities supported by MRC funding will generally not directly reach through to health impacts. This poses a significant challenge to evaluation — how can the many and varied translational interventions be linked to these ultimate outcomes? The interconnectedness of the translational research system adds another layer of complexity. While short-term proximate impacts are easier to attribute, benefits from complementary assets, such as the development of research infrastructure, key partnerships, or changes in attitude/culture) accumulate in the longer term but are more difficult to capture. (Greenhalgh *et al.*, 2016).

A range of evaluation frameworks and techniques have been developed to measure and encourage research translation and impact, subject to numerous reviews (Trochim et al. 2011; Searles et al. 2016; Greenhalgh et al. 2016; Grant et al. 2010; Banzi et al. 2011). In an overview of reviews (Banzi *et al.*, 2011), the Payback model, developed by Buxton and Hanney (Buxton and Hanney, 1996), and its adaptation into the Canadian framework (CAHS) emerged as the most frequently quoted. A more recent study confirmed that the Payback Framework remained the most widely used approach (Greenhalgh *et al.*, 2016). This study reviewed the strengths and limitations of six established approaches and provided examples of each (Payback, Canadian Academy of Health Sciences, Research Impact Framework, monetisation, societal impact assessment, UK Research Excellence Framework – as well as a few novel approaches, including Realist evaluation and Participatory Research Impact Model).

The following section describes three evaluation frameworks in more details; the associated indicator categories are summarised in Table 1.5.

The **Payback Framework** was designed to capture the diverse ways in which impact may arise, notably the bidirectional interactions between researchers and users at all stages in the research process, from problem identification and specification to dissemination and implementation (Greenhalgh *et al.*, 2016). It consists of two elements:

- A logic model of seven stages of research from conceptualisation to impact topic/issue identification, inputs to research, research process, primary outputs from research, secondary outputs: policy-making and product development, adoption by practitioners and the public, and final outcomes, and
- Five categories to classify the paybacks: knowledge (e.g. academic publications), benefits to future research (e.g. training new researchers), benefits to policy (e.g. information base for clinical policies), benefits to health and the health system (including cost savings and greater equity), and broader economic benefits (e.g. commercial spin-outs).

Two interfaces for interaction between researchers and potential users of research ('project specification, selection and commissioning' and 'dissemination') and various feedback loops connecting the stages are crucial. Noted limitations of the Payback approach are that applying its approach through case studies is resource-intensive; and potential limitation of the Payback Framework is that it is generally project-focussed (commencing with a particular funded study) and is therefore less able to explore the impact of the sum total of activities of a research group that attracted funding from a number of sources.

⁵² http://www.re-aim.org/about/what-is-re-aim/ Accessed November 2018

The **CAHS** framework is similar to the Payback Framework but aims for more of a 'systems approach' that takes greater account of the various non-linear influences at play in contemporary health research systems (CAHS, 2009; Greenhalgh *et al.*, 2016). CAHS is intended to be preceded by a careful assessment of context, followed by a consideration of impacts under five categories: advancing knowledge (measures of research quality, activity, outreach and structure), capacity-building (developing researchers and research infrastructure), informing decision-making (decisions about health and healthcare, including public health and social care, decisions about future research investment, and decisions by public and citizens), health impacts (including health status, determinants of health – including individual risk factors and environmental and social determinants – and health system changes), and economic and social benefits (including commercialization, cultural outcomes, socio-economic implications and public understanding of science). Each category has associated metrics and measures, a total of 66, which are to be drawn on flexibly depending on context and circumstances.

More recently, the **Translational Science Benefits Model (TSBM)** was designed to support assessment of translational research outcomes and capture the benefits of translational science beyond scientific productivity (bibliometrics) (Luke *et al.*, 2018). Drawing on 240 indicators identified in the literature, drawing on a range of existing models, the TSBM defines four areas of health and societal benefits with 30 associated indicators.

Payback	CAHS	TSBM	
 Knowledge (e.g. academic publications) Benefits to future research (e.g. training new researchers) Benefits to policy (e.g. information base for clinical 	 Advancing knowledge (measures of research quality, activity, outreach and structure) Capacity-building (developing researchers and research infrastructure) Informing decision-making (decisions 	 Clinical & medical benefits Procedures and guidelines Tools and products Community & public health 	
 policies) Benefits to health and the health system (including cost savings and greater equity) 	about health and healthcare, incl. public health and social care, decisions about future research investment, and decisions by public and citizens)	Health activities and products Health care characteristics Health promotion	
 Broader economic benefits (e.g. commercial spin-outs) Two interfaces for interaction between researchers and potential 	 Health impacts (including health status, determinants of health – including individual risk factors and environmental and social determinants, and health system changes) 	 Economic benefits Commercial products Financial savings and benefits 	
users of research:Project specification, selection and commissioningDissemination	 Economic and social benefits (including commercialization, cultural outcomes, socio- economic implications and public understanding of science) 	 Policy & legislative benefits Advisory activities Policies and legislation 	

Table	13.	Indicator	categories of	three	evaluation	frameworks -	Pavhack	CAHS	and TSBM
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Source: Technopolis Group, drawing on information from (Greenhalgh et al., 2016; Luke et al., 2018)

Funders have widely acknowledged the need for standardised metrics and reporting requirements to evaluate the outcomes and impacts of supported researchers (e.g. Frechtling et al. 2012; Wissenschaftsrat (WR) 2017). Several agencies have implemented reporting requirements, such as the US NIH (RePORTER) and the MRC (ResearchFish®).

In order to maximise the CTSA Program's impact, NCATS is developing and disseminating a set of Common Metrics (CM) tailored to TR for use by the CTSA hubs.53 Currently, four Common Metrics have been developed and disseminated as tools for collaborative strategic management, measuring aspects of the research process, career development, and scientific productivity:

⁵³ <u>https://clic-ctsa.org/common_metrics/established-common-metrics</u> Accessed November 2018

- IRB duration: The median number of calendar days from the official IRB application receipt date to the official IRB final approval date for fully reviewed protocols submitted to the institutional or "local" IRBs at the CTSA Program primary institution (hub).
- Careers in Clinical & Translational Research: The number and percent of institutional scholars and trainees who completed the Clinician (KL254) and Pre-doctoral (TL155) training programmes, respectively, who are currently engaged in clinical and translational research. Of those who are currently engaged in clinical and translational research, the number and percent of underrepresented persons and women.
- Informatics: Level of availability and completeness of the baseline types of data in a standard (CTSA- interoperable) format within a clinical data repository at the CTSA Program primary institution (hub). Interoperable clinical data availability and completeness.
- Pilot Funding & Publications: Number and percent of research projects that expended hub pilot funding that resulted <u>in at least one publication</u>.

A fifth metric, Pilot Funding & Grants, is currently optional: Number and percent of research projects that expended hub pilot funding that resulted <u>in additional funding</u>.

1.4 Analysis of existing programme evaluations

We identified and analysed existing evaluations of 21 translational research-focussed efforts to gain an overview of evaluation practices and methodologies employed, and to identify any emerging themes relating to barriers or enablers of programme success as well as recommendations made by evaluators.

The existing evaluations cover a wide range of programmes and initiatives either committed entirely to translational research or covering an aspect of translation/commercialisation within their remit (see Table 1.6).

Programme	Funder (Country)	Type of support	Evaluation title
Clinical and Translational	l NIH NCATS al (USA) rards	Funding of CTSA Programme Biomedical Research Institutions – "hubs"	Impact evaluation (Frechtling <i>et al.</i> , 2012)
Science Awards		Funding awards for collaboration initiatives and career development	Evaluation of impact on clinical trial activities (Liu <i>et al.</i> , 2013)
		Funding: USD 500 million in 2017	Evaluation of publication and citation patterns (Llewellyn <i>et al.</i> , 2018)
			Social network analysis to assess the impact on biomedical research grant collaboration (Nagarajan <i>et al.</i> , 2015)
			Social network analysis to assess the impact on biomedical research grant collaboration (Bian <i>et al.</i> , 2014)
			Social network analysis to assess the impact on collaboration (Luke <i>et al.</i> , 2015)
Specialized Programs of Research Excellence	NIH NCI (USA)	Grants for both basic and clinical/applied scientists to undertake translational research	Impact evaluation (Hautala <i>et al.</i> , 2014)
		Grants for pilot projects	Working group report (Davidson and
		Career Development Awards Funding: approx. USD 114 million in 2017	National Cancer Institute, 2014)

Table 1.4: Evaluations and reviews of translational research-relevant programmes

⁵⁴ Mentored Career Development Award, to support newly trained clinicians appointed by an institution for activities related to the development of a successful clinical and translational research career.

⁵⁵ Linked Training Award, to support research training experiences for pre-doctoral trainees who are interested in pursuing research careers in multi-disciplinary clinical and translational science.

Programme	Funder (Country)	Type of support	Evaluation title
Prevention Research Centres	Centres for Disease Control and Prevention (USA)	Funding of prevention research centres to conduct research on innovative applied public health interventions aimed at prevention.	Outline of logic model and programme indicators (US Department of Health and Human Services & CDC, 2010)
University of Florida's Clinical and Translational Science Institute	Various NIH grants including a \$26 million USD CTSA in 2009 (USA)	Training programmes via the Translational Workforce Development Programme Provision of technical support to investigators carrying out translational research Pilot project awards Pipeline to Proposal Development Grants	Economic impact evaluation (Dewey, 2013)
Centres of Excellence for Commercialisation and Research	NSERC, CIHR and SSHRC (Canada)	Funding for research centres and networks Funding: CAD 30 million /year	Process evaluation (Government of Canada, 2017)
CIHR's Commercialisation Programmes	CIHR (Canada) *To note CHRP awards are a joint initiative between CIHR, NSERC and SSHRC.	Operating grants for industry-academia collaborations focusing on commercialisation Grants for people with a health-related PhD to pursue an MBA Grants for proof of principle studies Funding: approx. CAD 14 million; 2012-2013	Impact and process evaluation (Constantinescu et al., 2015)
CIHR's Knowledge Translation Funding Programme	CIHR (Canada)	Grants to support integrated knowledge transfer (involving researchers and knowledge users) Grants to facilitate end of funding knowledge translation	Impact evaluation (McLean <i>et al</i> ., 2013)
Innovative Medicines Initiative Joint Undertaking	EC and EFPIA (Europe)	Funding for collaborative research projects between universities; pharmaceutical and other industries; SMEs, patient organisations and medicine regulators	Impact evaluation (Syrota <i>et al.</i> , 2017)
The Kristian Jebsen Foundation's Support of Translational Medicine	The Kristian Jebsen Foundation (Norway)	Funding for centres with a focus on translational medicine	Impact evaluation (Benner & Terenius, 2014)
German Centres for Health Research	BMBF and state funding (Germany)	Funding for translational research centres Funding: approx. €265 million in 2015	Process evaluation (Wissenschaftsrat, 2017)
Clinical and Health Services Research call	Catalan Agency for Health Information, Assessment and Quality (Catalonia)	Funding for non-commercial clinical and health services research	Impact evaluation (Adam <i>et al.</i> , 2012)
The Small Business Research Initiative Healthcare programme	NHS England since 2013, previously run by the Department of Health and Strategic Health Authorities from 2008 (England)	Grants for feasibility studies and product development aimed at small businesses Funding: approx. £17.5 million per year	Impact and process evaluation (RAND Europe, 2017)
NIHR Invention for Innovation programme	NIHR (England)	Funding for collaborative projects between at least 2 partners from academia, the NHS and industry.	Impact evaluation (RAND, 2015)

Programme	Funder (Country)	Type of support	Evaluation title
NIHR Research	NIHR (England)	Funding of research within all fields of medicine, health and healthcare	Impact analysis (via a 'deep mine' of impact case studies) (Kamenetzky <i>et</i> <i>al.</i> , 2016)
Biomedical Research Units	NIHR (England)	Funding for Biomedical Research Units consisting of an NHS organisation and a university, in order to undertake translational research	Impact evaluation (Marjanovic & RAND Europe, 2009)
NHS Health Technology Assessment programme	NIHR (England)	Funding for research regarding the clinical and cost-effectiveness; and broader impact of tests and treatments.	Impact evaluation (Hanney, Buxton, Green, Coulson, & Raftery, 2007)
Translational Cancer Research Centres	CINSW (Australia)	Funding for translational cancer research centres to facilitate closer collaboration between researchers and clinicians	Process evaluation (NSW Government & Cancer Institute NSW, 2015)
The National Health and Medical Research Council	NHMRC (Australia)	Funding of health and medical research	Assessment of policy and practice impacts (Cohen et al., 2015)
National Health and Medical Research Council	NHMRC (Australia)	Funding of health and medical research	Economic evaluation (Deloitte, 2011)
National Breast Cancer Foundation	NBCF (Australia)	Funding of targeted breast cancer research	Impact evaluation (Donovan <i>et al.</i> , 2014)
The Health and Health Services Research Fund	The Health and Health Services Research Fund (Hong Kong)	Funding for health and health service-related research	Impact evaluation (Kwan et al., 2007)

1.4.1 Evaluation methodologies

The evaluations employed a wide range of methodologies ranging from purely qualitative assessments to mixed method approaches including some level of quantitative analysis. The methodologies also varied depending on the focus of the evaluation (i.e. full impact versus process evaluation), with a few smaller studies focusing specifically on a key output such as publication and citation impact; or impact on clinical trial recruitment. Overall, we found that the techniques employed most frequently were portfolio analysis/document review, surveys, interviews and case studies. The depth to which the evaluations explored both primary and secondary data, to triangulate between sources was sometimes limited. This was mostly due to the lack of a mixed methods approach or a small sample size with respect to surveys and interviews. The impact evaluations of the US NIH CTSA (Frechtling *et al.*, 2012) and SPOREs (Hautala *et al.*, 2014) were more extensive and employed a comprehensive methodology. Although most of the evaluations aimed to assess the impact of the programme or initiative in some way, relatively few looked at human end-points. This is most likely attributable to the point in the translational pathway that the programmes were designed to fund, and the considerable length of time associated with translating discoveries to health benefits. Finally, a relatively small proportion of the evaluations included some level of economic analysis within their methods.

1.4.2 Common themes across evaluations

A wide range of barriers and enablers were identified across the existing evaluations. An initial assessment of these factors showed the emergence of key themes relating to programme success. A more extensive overview for each evaluation is available in 0.

Regarding **barriers**, several evaluations noted difficulties in attracting follow-on funding or industry investment which inhibited progression along the translational pathway. In addition, the short time frame

associated with many of the funding opportunities was a challenge when considering the extended timelines associated with many translational research projects. The complex and bureaucratic regulatory system also existed as a barrier to the progression of translational projects, with researchers finding it difficult to navigate this process effectively and efficiently. Finally, several of the UK evaluations highlighted a resistance to change within the NHS as a challenge to consider when designing and carrying out research projects.

Regarding **enablers** of impact, it was clear that strong in-house skills (i.e. the level and nature of expertise) within the project team facilitated successful project outcomes. Academic-industry collaborations were also noted as a key enabler of success owing to the breadth and depth of knowledge and expertise that can be drawn on, and the access to equipment and resource that either party may lack when working independently. Finally, access to clinical insight during the translational process was highlighted as a beneficial tool to allow end-user opinions on usability and ease of implementation to be leveraged.

Considering these thematic enablers and barriers, the evaluations went on to make several recommendations. First, collaboration between academia, industry and clinical partners was encouraged (particularly via the use of collaborative incentives) to make use of industry resource and to pool knowledge and expertise. The input of industry was also seen as beneficial when considering potential follow-on investment and the facilitation of progress towards commercialisation. Furthermore, clinician input was viewed as being useful throughout the research process to promote buy-in and to ensure that potential products are suitable for implementation within a healthcare setting. In addition, some of the evaluations recommended the implementation of a programme monitoring system, to more accurately capture process and outcome data; and to capture the long-term impacts of the funded projects, making future evaluations more efficient.

1.5 The translational research gap and 'why translation fails'

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.

1.5.1 Types of translational research failure

Scientific failure

<u>Scientific</u> 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 translational research 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 translational research 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 and 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. Health interventions may also show lower efficiency in real world conditions as compared to R&D findings.

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 <u>non-scientific barriers</u>, such as operational and economic obstacles (van der Laan and 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.

1.5.2 Barriers and bottlenecks in translational research

Over the past years, several analyses of barriers in the translational research pathway have been carried out.

To trace the many components required for research translation, and the main technical bottlenecks in this process, the Forum on Drug Discovery, Development, and Translation of the US National Academies of Sciences, Engineering, and Medicine recently built 'maps' of the domains and steps required for the discovery, development, and deployment of small molecules and biologics (Wagner *et al.*, 2017, 2018). Using a crowdsourcing process with participants from across the drug development spectrum, the forum defined eight 'neighbourhoods', each consisting of a complex network of steps that

interact with steps in other neighbourhoods (see Table 1.7; the full maps are available here: https://ncats.nih.gov/translation/maps)56.

The crowdsourcing process included a consultation on steps that representatives and stakeholder groups from across the drug development spectrum had found most problematic in terms of time requirement, likelihood of failure, and/or cost. More than a third of participants identified identification of therapeutic targets, biomarker qualification, clinical study recruitment and participant enrolment, and incorporation of patient perspective into NDA decisions during regulatory review as bottlenecks; and highlighted sharing of clinical trial data (including from failed trials) and patient perspectives as difficult areas.

Table 1.5: Drug Discovery, Development, and Deployment Map – Translational 'neighbourhoods' and bottlenecks

	Neighbourhood	Bottlenecks identified
1	Basic science research and target identification	Data mining
		Therapeutic targets
2	Target pharmacology and biomarker development	Biomarker development programme: Prognostic/predictive biomarkers Response biomarkers
		Biomarker qualification
3	Lead identification	
4	Lead optimisation, candidate selection, IND-enabling studies and scale-up for manufacturing	
		IRB approval Contractual & legal agreements (study sponsor/investigators & staff)
5	Clinical research and development	Collecting and using patient registries and EMRs Natural history and epidemiological studies (measurement of outcomes and severity, target population identification) Decision-making regarding therapeutic and clinical end points
		Recruitment and participant enrolment
6	Regulatory review	Incorporation of patient perspectives in NDA decision
7	Post-marketing	Pharmaco-epidemiological observational studies New indicators/repurposing
		Pragmatic safety and efficacy trials (phase IV interventional)
	Medical landscape	Incorporation into clinical practice
8		Insurance coverage and reimbursement
	"Layers" of information	Business considerations/investment perspectives
		Regulatory science FDA/regulatory review Rare disease/other accelerated pathways
		Data sharing (clinical trial, failure data) Patient perspectives

Red: at least 35% of votes; Light red: 20-35% of votes; Cyan: 10-20% of votes Source: adapted from (Wagner *et al.*, 2017, 2018)

⁵⁶ A number of aspects of these neighbourhoods were found to be missing from the conventional linear translational research model, e.g. *biomarker development*, which takes place over multiple stages of the development process; inclusion of *natural history studies, epidemiology and patient input* in the clinical research and development neighbourhood; a post-marketing neighbourhood that includes observations on safety, usage patterns and effectiveness; and a medical landscape neighbourhood covering the increasingly important issues of access and reimbursement.

In the early stages of translational research, a key challenge is to reduce the attrition of projects in later clinical development by improving target selection and validation and the ability to predict failures earlier (AMS/ABPI 2018). Identification of a novel molecular drug target candidate is thus followed by detailed molecular target assessments with the aim of increasing confidence in a drug target. This process strengthens the initial hypothesis that a molecular target is key or even causative for pathogenic or symptomatic mechanisms in a disease. Given the large costs of later stage trials (Phases IIb and III, target validation is crucial to reduce attrition. Research into new methodological approaches can help to address these barriers to translation and reduce research failure. For example, to increase the scientific relevancy and efficiency, and lower the cost of human chemical toxicity testing, researchers are steadily moving from whole animal testing toward a human cell- and organoid-based in vitro approach (Zhang et al., 2018). Computational approaches, such as improved mechanistic and predictive models, can further reduce attrition in trials and accelerate research and development. For example, computational modelling can extrapolate the toxicity in vitro findings to real-world, in vivo dose-response outcomes. By incorporating genetic and epigenetic information, this can also enable more reliable predictions for heterogeneous human population responses, opening the door to population-stratified and personalised risk assessment. Industry is also engaging in collaboration with the wider research environment to improve this step (AMS/ABPI 2018), e.g. GSK developed the Open Targets platform in collaboration with the Sanger Institute and European Bioinformatics Institute to share knowledge and expertise to genetically validate targets and increase the success rates of programmes with both patient and economic benefit.

Biomarkers are characteristics can be measured and evaluated as an indicator of disease type and progression (diagnostic/prognostic), or of patients' responses to a therapeutic intervention (including toxicity effects). Biomarkers can also serve to predict the effect of a therapy on a patient. They are often used as surrogate endpoints in phase II and phase III clinical trials, substituting for hard endpoints (such as 'death'), to provide signs of efficacy and to increase the efficiency of clinical development in terms of cost and time (Gerlach et al., 2018). This is especially helpful for translational programmes developing therapies for diseases with slow progression or long latency periods. However, this 'expediency' in clinical trial design needs to be balanced with the time and effort required to appropriately confirm and reproduce the performance of candidate biomarkers in independent multiinstitutional collaborations, as well as rigorous validation of reagents and appropriate storage of biospecimen - or trials run the risk of measuring indicators that do not sufficiently reflect the patient's response to the tested therapy, and hence increase the likelihood of failure. Biomarker development can hence require significant investment, which a single company or academic lab may struggle to justify (Gerlach et al., 2018). In recent years, a few multi-stakeholder precompetitive biomarker consortia with common interests and goals have been formed to share and pool data in order to accelerate biomarker development, such as the public-private Biomarkers Consortium in the USA which includes the NIH, FDA, and PhRMA57.

Issues during the clinical trial phases, such as high attrition rates, cost, and patient recruitment were already touched on in section on regulatory uncertainty and issues with trial design. Novel trial designs have the potential to decrease time to study completion, reduce resource requirements and number of patients exposed to inferior treatments, and increase the overall likelihood of trial success (Thorlund *et al.*, 2018).

A number of studies have investigated barriers to research translation as a result of knowledge and skills gaps, as well as other 'non-scientific' barriers (see Staff et al. 2014).

In a report published in 2007, the National Cancer Institute of the US NIH used case studies of 21 discoveries across the spectrum of drugs, biological agents, risk-assessment strategies, medical devices, and lifestyle alterations to identify bottlenecks (National Cancer Institute, 2007). The majority of the cases encountered bottlenecks; several cases required the development of new assays or screening techniques to validate the discovery and encountered bottlenecks in preclinical development (e.g. GMP manufacturing); others encountered difficulties in early-stage clinical trials because of

⁵⁷ <u>https://fnih.org/what-we-do/biomarkers-consortium</u> Accessed December 2018
regulatory approval or patient recruitment issues, in drug formulation – or in interesting academic trialists in bringing the drug into early-stage clinical trials.

Other studies investigated translation barriers from the academic investigator's perspective.

A systematic review of 416 publications identified a cohort of academic investigators who had published the results of largely positive, preclinical animal model studies in nerve regeneration, and showed that very few of these discoveries had been translated into clinical practice (Cousin *et al.*, 2016). Surveys sent to the studies' authors identified that most important causes for failure to translate were lack of a commercial partner (21%) and insufficient financial resources (21%). Other reasons provided were that the respondents considered themselves to be in "a research programme not involved in translation", and a lack of expertise in regulatory affairs.

A systematic search and narrative synthesis examined factors enabling or hindering translational research from the perspective of basic and clinician scientists (Fudge *et al.*, 2016). It found wide-spread reporting that organisational and system levels influenced scientists' ability to conduct translational research, with complex and lengthy ethical and regulatory research governance processes, difficulties with patient recruitment, and poor access to bioinformatics identified as key barriers limiting translation. Research settings with readily accessible patient populations, e.g. university-hospital collaborations, were found to facilitate patient recruitment for trials and encouraged partnerships with industry, hence enabling translational research. Other barriers highlighted were a cultural divide between 'science' and 'medicine', and reward systems of academic organisations based on individual output from publications and research grants (and thus not aligned with team working as part of a translational research team).

A survey of faculty members at the University of Kentucky, involved in cancer-related research programmes, highlighted the most frequently cited barriers that inhibited researchers' ability to commercialise: Expense (65%), time (59%), infrastructure (55%), and lack of industry partners (46%) (Vanderford, Weiss and Weiss, 2013). Respondents who had not attempted to commercialise their research cited university policies/ procedures, lack of industry partnerships, expense, and time more frequently than those who had attempted commercialisation. Not being aware how to commercialise, limited research application, and having no interest in commercialising did not to a significant level inhibit respondents from attempting to commercialise their research.

A study on barriers to research by clinical researchers in emergency care pointed to a cultural aspect inhibiting translational research. The key barriers identified were a shortage of trained (clinical) investigators, lack of role models and training opportunities, inadequate protected research time, poorly defined research-based career paths, and a culture of valuing clinical care over research (Homer-Vanniasinkam and Tsui, 2012). Other barriers cited were poor infrastructure, lack of interdisciplinary research collaborations, lack of relevant funding streams, and ethical and regulatory issues.

The main challenges identified in a symposium on engaging basic scientists in translational research included differences in culture and mindset between basic and clinical scientists, insufficient or non-supportive infrastructure (including regulatory issues), difficulties developing and sustaining collaborations, inadequate training, insufficient funding, and lack of incentives and rewards. Recommendations were made as to how to tackle these hurdles, emphasising the roles of institutions, professional societies, funding organisations, and individual scientists (Hobin *et al.*, 2012).

A case study of the Kyoto University-Astellas Pharma partnership (2007-2017, the 'AK Project') pointed to several enablers of and challenges to academia-industry partnerships (for the full case study, see 0). These included:

Enablers:

 Long-term funding, which allowed the collaboration, to explore various set-ups and make changes where necessary (e.g. establishment of the Fusion laboratory committee), to improve awareness within the academia and industry partners of the alliance, build infrastructures, and to recruit and nurture young researchers.

- Close collaboration between the academic and industry partners, including weekly teleconference calls, and monthly meetings of the (high-level) Fusion laboratory committee
- Introduction of the Astellas quality check sheet for data by the academic partner, for publications and patents. This supported data reproducibility for the academic partner.

Challenges:

- Extensive, time-consuming negotiation of the collaborative agreement, especially regarding royalties, utilisation of research results, and publications
- Lack of communication with the industry partner at the start of the AK project (which was addressed by establishment of the Fusion Laboratory committee)
- Changes in strategy of the industry partner Astellas Pharma, leading to Go/No Go decisions on components of the research programme

1.6 Key ingredients of translational research

Translational research relies on availability and use of the necessary physical infrastructure (research facilities, platforms), and on bringing together a range of skills and knowledge, both by combining expertise from a range of professionals (in collaborations, networks, and advisory functions) as well as by developing a range of skills in individuals through development of a cadre of 'translational research'. In addition, researchers must be motivated to participate in translational research projects and prioritise these over other activities (incentives). The following section explores these factors in more detail.

1.6.1 Collaboration

Collaboration enables research teams to pool knowledge, skills, and tools/infrastructure across many different disciplines and sectors. Collaboration is widely considered a key requirement for translational research, but can be inhibited by a range of factors, such as the compartmentalisation of departments within universities and hospitals; a cultural divide between researchers from academia, industry and clinicians; and academic researchers without training or experience in multidisciplinary team working (combined with a university system that rewards individual achievement rather than joint working practices) (Ameredes *et al.*, 2015; Fudge *et al.*, 2016).

• Academic collaboration

A factor driving academic collaboration is the necessity in many areas of science requiring teams and skills from different disciplines (e.g. incorporating computational approaches), institutions, and countries to work together. Indeed, the biomedical research field is experiencing an increase in collaboration, demonstrated by a rising average number of authors on papers over time, an increasing proportion of papers involving multiple disciplines and international collaborations, and a rise in the number and percentage of publications in biomedical and clinical journals in which two or more co-authors claim first authorship (The Academy of Medical Sciences, 2016). Larger projects can also be driven by a desire to increase the volume of data collected and improve the statistical power, and often require international collaborations, such as whole genome-wide association and population studies, and clinical trials. Many funding agencies encourage collaborations in order to enable complex projects such as clinical trials, translational studies, and projects addressing grand global challenges to be undertaken, and are increasingly prioritising such projects (The Academy of Medical Sciences, 2016).

Collaboration between groups and disciplines is also driven by the establishment of Translational Research centres. Illustrating this point, a network evaluation study found growth in scientific collaborations among members of the NCATS CTSA ICTS at Washington University over the 3-4 year period after the centre was launched (Luke *et al.*, 2015). ICTS members had become involved in a greater number of scientific planning collaborations (as measured by new grant submissions) and scientific dissemination collaborations (as measured by journal article co-authorships). Collaborations also became more cross-disciplinary over time. However, the study points out that they did not have a valid comparison group, as most scientists involved in clinical and translational research are ICTS members at the university.

Industry-academia collaboration

Industry- academia collaboration models have undergone changes and 'fine-tuning' over the past decades.

University institute-wide collaborations with industry were commonly established before 2000, e.g. industry partnerships with renowned research institutes with the opportunity to review any discoveries. These were subsequently criticised as "too broad, ill-defined and lacking in structure", and evidence of impact of these broad partnerships remains anecdotal (Schachter, 2012; Freedman and Mullane, 2017). While academia welcomed the injection of funding from the private sector, e.g. the Scripps Institute's 10-year agreement with Novartis for USD 200 million in 1997, followed by a 5-year agreement with Pfizer for USD 100 million in 2006, the benefit to industry has been less clear. Industry partners also missed potential 'winners', e.g. in Hoechst's USD 70 million partnership with Harvard, the firm declined the option to further develop the compound that became Enbrel (etanercept), which was later developed by another company, Immunex, now part of Amgen (Schachter, 2012). Consequently, the private sector has moved toward models where roles and outputs are more clearly demarcated, and there is mutual interest in a successful outcome.

Academia-industry collaborations have also taken a more project-based approach. Several companies have created innovation centres, such as Pfizer's Centres for Therapeutic Innovation58 and the Johnson and Johnson's Innovation Centres59. In the Pfizer model, industry experts review new opportunities from academic groups to determine whether they fit within their areas of interest and meet scientific and clinical demands. The centres then pair academic and company scientists to carry out joint research and development projects, with access to all the resources of a large company, including laboratory space. Any intellectual property jointly developed is also jointly owned. This programme includes a partnership with the NIH, coordinated by NCATS60. The goal of the NIH-Pfizer programme is to identify biologic compounds with activity in a pathway or target of interest to an NIH intramural researcher and to Pfizer and working jointly to move these compounds through laboratory testing and into clinical evaluation. However, this model is not without its problems. Key challenges identified were the alignment of timelines in academic research with those of commercial drug development, and complex contract negotiations including resolving legal issues in setting up contracts between the partners (Yildirim et al. 2016 and references within). Industry representatives have also highlighted a gap between academic researchers' view of their project's status and what industry require; however, while the discovery may have been published in a good journal, much of the preclinical validation required by companies has not been carried out (Fishburn, 2014). Concerns about collaborations between industry and academia summarised are in a recent paper by (Freedman and Mullane, 2017).

Open innovation models are used to highlight specific needs or problems to the research community in an attempt to increase the likelihood of resolution, often on a competitive basis (Freedman and Mullane, 2017). Crowd sourcing in biopharma began in 2001 when Eli Lilly created InnoCentive as a web-based platform to draw on global network of problem solvers. This was followed by similar efforts by other companies (e.g. Astra Zeneca, Pfizer, GSK, J&J, Sanofi), foundations (e.g., Epilepsy Foundation SUDEP Institute), and research organisations (e.g., Cleveland Clinic) and government agencies (e.g. US Department of Defense). This approach avoids any protracted negotiations, and benefits industry through its low cost, as small financial rewards are offered for resolution of discrete problems, and clear ownership of the resultant information.

There has also been a steady rise in the number of large public-private consortia active in the precompetitive space (Lim 2014, see also section on public-private partnerships). One example, the Critical Path Institute61 was founded in 2005, and has since grown to a global public–private partnership involving government regulatory agencies, patient advocacy organisations, academic centres and 41 major biopharmaceutical companies. Its aim is to develop "drug development tools", to accelerate the pace and reduce the costs of medical product development. This includes the creation of new data standards, measurement standards, and methods standards that aid in the scientific evaluation of the

⁵⁸ <u>https://www.pfizercti.com</u> Accessed December 2018

⁵⁹ https://www.jnjinnovation.com/ic Accessed December 2018

⁶⁰ https://ncats.nih.gov/cti/about Accessed December 2018

⁶¹ <u>https://c-path.org/about/</u> Accessed December 2018

efficacy and safety of new therapies. (C-Path is also involved in the Biomarker Consortium mention in section 0.) Other consortia are supported by the European Union's Framework Programme, including the Innovative Medicines Initiative, a PPP with a budget of €3.276 billion over the 2014-2020 time period (IMI2)62. Of 369 consortia established between 1996 and 2012, the majority (45%) intended to improve drug development, and of these, most were initiated by government (31%) and then industry (27%) (Lim, 2014). At the time, IMI managed approx. 59% of all industry-initiated consortia within the drug development category.

Table 1.6: Concerns expressed around forming collaborations between academia and industry

Mutual concerns Time required for even simple deal structure Appropriate recognition of what each brings to collaboration Inherent mistrust		
Poor reproducibility of research		
High valuation of early intellectual property (IP)	Failure to recognize value of early IP Inventions during collaboration not given value	
Milestones and royalties for early or exploratory collaborations	Reversion rights if discontinued	
Maintaining confidentiality	Freedom to publish	
Work done by junior lab member but paying for Principal Investigator (PI)	Treated as a CRO	
Lack of sense of urgency	Project duration to justify reallocation resources (lack of financial flexibility for short-term changes)	
No real commitment – perceived as ATM (automated teller machine)	Loss of project champion at company jeopardizes continuation or success Strategic change (discontinuation) regardless of scientific success	

Source: (Freedman and Mullane, 2017), p. 986

1.6.2 Skills

The translational research process requires a range of expertise, and researchers engaged in translation need to have a sound understanding of the steps involved. However, professionals specifically trained to facilitate the complex processes of the translational medicine continuum remain scarce (Petrelli *et al.*, 2016). Taking drug development as an example, this process encompasses target identification and validation, high-throughput screening, medicinal chemistry, pharmacokinetics and pharmacodynamics analyses, assessment of animal models, preclinical safety assessment and clinical trials, and regulatory approval. There is now a need for the career development of a "qualitatively different" kind of investigator comprising the future workforce.

For example, students in basic research programmes are rarely exposed to clinical cases or pathophysiology during their degrees (Hobin *et al.*, 2012; Pickering, Bast Jr and Keyomarsi, 2015). However, these are key to understanding the mechanisms of disease and the disease relevance of their work. Combined with little to no opportunity to interact with clinical researchers or patient populations, many basic scientists may neither think about their research in the context of human health and disease, nor appreciate the unmet clinical needs or the clinical context in which potential interventions would operate. Other disciplines required to engage in translational research but generally not covered in the curriculum of science students include biostatistics, pharmacology and toxicology, biomedical informatics, clinical research design, and regulatory processes. Although significant strides have been made in developing translational research training programs that teach these and other relevant skills, inadequate training remains a barrier for many basic investigators (Hobin *et al.*, 2012; Homer-Vanniasinkam and Tsui, 2012).

In addition to the 'traditional' research content of graduate education, developing deep expertise in a defined scientific field, educational programmes need to foster the development of multidimensional skills - ranging from specific competences on the translational process to communication, coaching, creative thinking, problem solving, management, and the ability to go beyond the 'silo' mentality, sharing information and knowledge with other scientists, healthcare providers and industry. Competencies

⁶² https://www.imi.europa.eu/about-imi/imi-funding-model Accessed December 2018

required for success in translational and interdisciplinary research have been defined by a number of studies and education programmes (reviewed (Begg *et al.*, 2015)), and share core themes: conducting research/cross-disciplinary training, communication, and interacting with others/translational teamwork. Five competencies defined through an analysis of the literature are presented in Table 1.9 (Rubio *et al.*, 2010).

Table 1.7: Five competencies for translational research

- Critically examine the research process
- Think "out of the box" to develop ways to impact healthcare by transferring knowledge from and to the bench, bedside, and community
- Engage in multidisciplinary collaboration
- Understand successful approaches to community engagement
- Develop appropriate techniques to manage multidisciplinary research teams in the future

Source: (Rubio et al., 2010)

Approaches to closing the knowledge gap for basic science graduates tend to fall into broad four categories:

- Courses and seminars in multiple disciplines, such as medical statistics; the economic, social and ethical aspects of translational research; and courses including case studies with lecturers from industry
- Interdisciplinary courses, e.g. providing an overview of the theory and methods for interdisciplinary research, including speakers who present on the interdisciplinary work they have engaged in
- Laboratory and field experiences, such as company internships and rotations through different clinical departments/clinical observation
- Interdisciplinary team training, e.g. as part of multidisciplinary research collaborations, or through mentorship programmes of basic science students by clinical researchers.

(Ameredes *et al.*, 2015; Begg *et al.*, 2015; Pickering, Bast Jr and Keyomarsi, 2015; Petrelli *et al.*, 2016; Gamo, 2017)

However, assessment of the impact of these training approaches is limited to date.

Collaborations and research partnerships can bring together the many areas of expertise required for driving research translation. In addition to facilitating innovation, team-based projects can also be viewed as providing training for a new generation of scientists. A survey of scholars involved in multidisciplinary translational teams (MTTs) associated with NCATS' CTSAs indicated that the development of a number of translational research competencies was associated with MTT membership (Ameredes *et al.*, 2015). Specifically, MTT membership was associated with scholars' confidence in the translational competency categories of Study Design (such as formulating a translational research question for study in *in vivo* models and proposing study designs for a research question), Research Implementation, and Statistical Approaches.

Approaches to measuring participation in, satisfaction with, and perceived impact of *interdisciplinary collaboration* include the Cross-Disciplinary Collaborative Activities Scale and the Research Collaboration Scale (Begg *et al.*, 2015). An analysis of learning outcomes and early career trajectories of graduates of the US National Science Foundation's Integrative Graduate Education and Research Training (IGERT) programmes found that dissertations of IGERT graduates were more interdisciplinary, drawing on an average of three distinct disciplines (vs. only two for non-IGERT graduates) (Carney *et al.*, 2011). IGERT graduates were somewhat more likely to be "integrating multiple disciplines" as part of their current work (84% vs. 73%), more likely to be teaching courses requiring them to integrate two or more disciplines (63% vs. 50%) and had a higher probability of working and networking with scientists or technologists in other disciplines (92% vs. 84%).

Some institutions have tested approaches beyond the traditional lectures and research training to promote students' engagement in translational research. In 2011, the University of Utah created an

interdisciplinary and experiential medical technology design competition to train medical students interested in developing innovative clinical solutions (Loftus *et al.*, 2015). As part of the competition, participating medical students partner for six months with business, law, design and engineering students to form interdisciplinary teams; teams were then provided with access to clinical and industry mentors, USD500 prototyping funds, development facilities, and non-mandatory lectures in ideation, design, intellectual property, FDA regulatory requirements, prototyping, market analysis, business plan development and capital acquisition. After four years of implementation, the programme had supported 396 participants, 144 of which were medical students, led to the development of 91 novel medical devices, and launched the formation of 24 new companies. A marked increase in student participation was seen following an adjustment of incentives, allowing competition projects to fulfil the scholarly activity requirement, as well as the establishment of milestone funding to continuing teams and pairing of students with industry mentors. Full buy-in from the leadership of the university's medical school is highlighted as key to the success of the programme. The competition, now in its eighth year, has expanded to include participation by teams of high school students63.

1.6.3 Infrastructure and institutional support

To identify the critical components of successful translationally focussed research institutions, 20 US research centres (NCI Comprehensive Cancer Network centers and CTSAs) were surveyed regarding their infrastructure, expertise and personnel (Grunseth et al., 2014). All 20 centres reported that they had small-animal facilities, at least one GMP facility, as well as intellectual property and licensing personnel on site. Most had large-animal facilities (80%) and designated regulatory affairs staff (75%). Fewer than half had non-human primate facilities. The study concluded that complete translational research institutions should be able to address three core areas: preclinical development, clinical development, and business development and licensing. Based on these components, the authors defined a 'minimum set' of capabilities an institution engaged in translational research needs to have on site (Level 1) (see Table 1.10, in bold): GMP facility; clinical trial capabilities; regulatory affairs personnel; small-animal facility; PK and/or PD expertise; IP and contracts personnel; and QA personnel. With modest additional investment, centres can improve their ability to move projects forward (Level 2), e.g. by providing project management personnel, centralised lead-optimisation facilities and gapfunding programmes. Level 3 institutions with further enhanced translational research capabilities require substantial investment - all surveyed institutions in this category had an annual research budget of more than USD 500 million and able to support large-animal and/or nonhuman primate facilities, multiple GMP facilities, and a strong business development team to support the GMP facilities.

Preclinical development	Clinical development resources	Business development and licensing
High-throughput screening capabilities	On-campus GLP and GMP facilities	IP and licensing personnel
In silico and/or bioinformatics modelling capabilities	Quality assurance and quality control expert teams	Contract negotiation team
Structure-activity relationship research group	Regulatory affairs personnel to prepare and advance IND applications	Continuity of basic researchers, clinicians, regulatory affairs personnel, and GLP and GMP facilities
In vitro validation capabilities	Hospital facilities and patient base to support clinical trials	Connections to other academic TTOs and/or academic institutions
Toxicology and early stage PK capabilities	Broad clinical expertise	Connections to big pharma, biotech, startups and incubators
Small-animal, large-animal and non- primate facilities		Access to gap funding

Table 1.8: Translational infrastructure by category

In bold: Minimum set of capabilities for translational research institutions; Source: adapted from (Grunseth et al., 2014)

The many facets of the translational research process are intimidating to both academic scientists and clinicians, involving ethics involved in human research, tissue banking and material transfer regulations,

⁶³ <u>https://uofuhealth.utah.edu/center-for-medical-innovation/bench-2-bedside/</u> Accessed December 2018

intellectual property rights, toxicology and manufacturing regulations, regulatory approval, study sponsorship and insurance, as well as trial and data monitoring (Homer-Vanniasinkam and Tsui, 2012). Regulatory hurdles have increased in recent years and are becoming even more complex with expanding work in the fields of cell and gene therapies and tissue engineering (see section 0). Requirements for asserting safety to proceed into human trials have become more rigorous and complex, meaning more time and money are required to fulfil regulatory expectations (Volk *et al.*, 2015).

Once IP is established, an investigator can pursue commercialisation either independently, by establishing a start-up company, or via a licensing agreement with an established or privately held company. A challenge is building a team combining all the different skills needed to run a new company, and when attempting to procure funding. In addition, agreements on the legal relationships among an investigator, the academic institution, and an established company can be a long-drawn-out process.

Some universities have responded to these challenges by investing in dedicated in-house support. For example, the Translational Research Office at University College London is a resource for academics to draw on when navigating the multi-faceted aspects and required activities of translational research (AMS/ABPI, 2018). It offers a team of industry experienced scientists able to catalyse the links to resources which can help the researchers in driving their project forward. Mile-stoned funding enables the TRO to support the translational pathway for projects, and to bring in necessary expertise as needed, such as appropriate regulatory and commercial advice as well as engaging with other partners such as CROs, contract manufacturing organisations and industry. At the Mayo Clinic (US), a position called "translational integrator" was established, described as staff "serving as a project manager whose responsibility is to facilitate negotiations between clinician-investigators, regulatory agencies, funding agencies, commercial sponsors, and contracting suppliers" (Staff, Runge and Windebank, 2014). This has accelerated processes that used to take months or years and now take only weeks. Other institutions support investigators during the initial steps of turning academic findings into commercial partnerships or new companies by setting up business "incubators" and "accelerators", offering space, use of core facilities, expert advice (e.g. through mentoring schemes), and links into the broader translational research ecosystem (Soetanto, 2016).

1.6.4 Incentives

Academia places a high value on novelty, with less attention on whether data are reproducible, scalable, reimbursable, or have commercial freedom to operate (Schwartz and Macomber, 2017). This contrasts with industry-based R&D, which builds in manufacturing, regulatory and commercial factors from the start. When investors, companies, or other later stage stakeholders evaluate academic research, the relative lack of attention to these factors can inhibit further interest. Academics do not actively choose to ignore these elements of translation development; the lack of focus stems from the fact that they are not built into the culture or incentive structure of the university environment.

A 2016 study explored whether UK biomedical researchers were being encouraged, supported and rewarded for participating in team-based approaches (The Academy of Medical Sciences, 2016). The study found that academia continued to be rooted in a tradition of individual and small-team scholarship where the emphasis is on leadership and independence, owing in large part to the fact that academic reward and recognition systems did not match the growth of team working. Evaluation of researchers' track records focus on their first and last author publications, and whether they have been 'lead' principal investigator (PI) on grants. Both metrics are relatively difficult for individuals to secure when working in teams, and systems that provide structured contribution information for other types of research contributions are rarely available and used.

Hence, a challenge is that career progression and promotion, and obtaining a fixed post in a university science department or in academic medicine, rely on criteria such as high impact publications, grants, and invited lectures. Researchers involved in translational research teams may not be able to produce the required evidence of their contribution, since translational projects generally take longer to complete, and they may be working outside their recognised disciplines (Homer-Vanniasinkam and Tsui, 2012).

Risks to translational research projects stemming from the misalignment of incentives of the various professionals involved can to some degree be addressed by strategic planning, making sure that the multiple actors collectively carry over new knowledge and technologies to development phases, even

when the academic principal investigators responsible for these advances are not interested in this work. This may involve project planning methods specifically tailored to the translational research process, led by a new cadre of translational research professionals, with knowledge of requirements across the entire pathway and skilled in the management and coordination of large teams (see also section 0) (Vignola-Gagné *et al.*, 2013). Latter can also be provided through coordination by funders such as charities and product development partnerships (PDPs).

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Appendix A - Case study: Kyoto University – Astellas Pharma partnership: the AK project

A.1.1 Kyoto University – Astellas Pharma partnership: The Center for Innovation in Immunoregulatory Technology and Therapeutics (AK project)

The Center for Innovation in Immunoregulatory Technology and Therapeutics, termed the 'AK project', was established in 2007 as part of the Innovation Centers for Advanced Interdisciplinary Research Areas Programme of the Japanese Ministry of Education, Culture, Sports, Science and Technology (MEXT) 64. The programme's aim was to overcome the 'valley of death' through integrated industry-academia collaboration focussing on future commercialisation, and to strengthen the capacity of researchers and engineering staff in advanced inter-disciplinary research areas. It created 12 R&D centres in areas of importance to Japan, each funded by MEXT for a ten-year period with an annual budget of approx. 500–700 million yen (GBP2.4-3.3 million at 2008 exchange rate; GBP4.2-5.8 million at 2012 rate; GBP 2.9-4.1 million at 2016 rate).

The AK project was a partnership between the Kyoto University and Astellas Pharma, aiming to:

- develop 'next-generation immunoregulatory medicines' by combining Astellas Pharma's drug discovery technologies with basic and clinical research at the Kyoto University Graduate School of Medicine and Kyoto University Hospital
- create a model of industry- academia collaboration for drug discovery in the post-genome era
- nurture scientists and other staff specialised in drug discovery, able to integrate knowledge and skills in medicine, drug discovery, intellectual property and other related fields, and experienced in working as the interface between industry and academia to promote future drug discovery.

Under the AK project, the 'Fusion laboratory' on the Kyoto University campus was established, colocating fifteen principal investigator groups (scientists and clinicians) from the Graduate School of Medicine of Kyoto University with three research teams from Astellas Pharma to carry out interdisciplinary research and establish an efficient drug discovery R&D system. The University Hospital provided access clinical and pathological samples. Information was shared in weekly research meetings with Astellas scientists at their Central Institute in Tsukuba (by teleconference). The centre activity was also supported by an on-site IP Office to manage patent applications and publications resulting from the collaboration. To facilitate the activities of the Fusion laboratory and solve issues arising, a 'fusion lab running committee' was established, composed of two members from the Medical School (the Dean and the Fusion laboratory leader) and two members from Astellas (the Director of the Astellas Central Research Institute, a corporate executive officer, and the Fusion lab sub-leader) and the IP managers. The committee met monthly to review action plans and check progress using a project management tool (the PDCA method).

Over its 10-year lifespan, the AK project's budget amounted to approx. USD 100 million65 in matched funding from MEXT and Astellas. It resulted in the identification of 35 drug targets, fifteen of which were transferred to Astellas' R&D programme, and seven have been taken forward for further development in Astellas' drug development programme. Of these, one candidate is in a Phase 2a trial (ASP5094, a mAb for treatment of rheumatoid arthritis66,67), and two are moving through the pre-clinical to clinical stage. Other Astellas programmes stemming from the collaboration target compound and antibody optimisation and use of -omics data for new targets. The Fusion lab also trained 25 principal investigators, with six subsequently promoted to full professor positions, and 10 securing tenured positions.

⁶⁵ Presentation by Prof Shuh Narumiya, Professor and Director, Medical Innovation Center, Kyoto University Graduate School of Medicine, at the Institute for Translational Medicine and Therapeutics (ITMAT) 12th Annual International Symposium, October 16-17, 2017, University of Pennsylvania

⁶⁶ www.jimmunol.org/cgi/doi/10.4049/jimmunol.1700941

⁶⁴ <u>https://www.jst.go.jp/shincho/sentanyugo/downloads/2014sentan-en_low_Wpage.pdf</u> (2014) Accessed December 2018

⁶⁷ <u>https://clinicaltrials.gov/ct2/show/NCT03257852</u> Accessed December 2018

The collaboration has been taken forward since 2017 through the Alliance Station ('A-Station'), a new platform for collaboration between Kyoto University and Astellas68 (see MIC below). The A-Station currently houses 12 researchers from Astellas working on nine joint research projects with various departments and laboratories of the university. The collaboration is managed by two scientists and an IP manager directly employed by the station and supports young investigators from Kyoto University through collaboration grants.

Key enablers:

- Long-term funding, which allowed the collaboration, to explore various set-ups and make changes where necessary (e.g. establishment of the Fusion laboratory committee), to improve awareness within the academia and industry partners of the alliance, build infrastructures, and to recruit and nurture young researchers.
- Close collaboration between the academic and industry partners, including weekly teleconference calls, and monthly meetings of the (high-level) Fusion laboratory committee.
- Introduction of the Astellas quality check sheet for data by the academic partner, for publications and patents (in 2015). This supported data reproducibility.

Key challenges:

- Extensive, time-consuming negotiation of the collaborative agreement, especially regarding royalties, utilisation of research results, and publications
- Lack of communication with the industry partner at the start of the AK project (which was addressed by establishment of the Fusion Laboratory committee)
- Changes in strategy of the industry partner Astellas Pharma, leading to Go/No Go decisions on components of the research programme

A.1.2 The Medical Innovation Center (MIC) at Kyoto University

Based on the project management model and experience of the AK project, additional one-to-one institutional collaborations were established as part of the Medical Innovation Center (MIC). The MIC was founded in 2010 and is coordinated by the Office of Promotion for Medical Innovation at the Kyoto University Medical Science and Business Liaison Organization (KUMBL)69. It has an annual budget of approx. USD 10 million, funded by the industry partners. The MIC charges 30% indirect costs on each project, providing financing of USD 1 million for each, the university, the medical school, and management of the MIC and KUMBL.

Each collaboration project is assigned a University of Kyoto faculty lead70. A Collaborative Research Steering Committee is established, composed of Graduate School of Medicine faculty members and representatives from the collaborating partner to ensure suitable management of the project, such as selection and evaluation of investigators, setting out of research policies, and approval of annual budget. The steering committee can appoint 'university core research group members' to participate in research of topics related to the project, hire research managers to mentor PIs, and bring in independent investigators with project-specific expertise as well as IP experts, as required. These academia-industry collaborations can utilise clinical samples of Kyoto University's Center for Anatomical Studies, carry out genomic analysis in collaboration with the Center for Genomic Medicine, and conduct exploratory clinical trials at the Translational Research Center of Kyoto University Hospital.

Collaborations are formed for a 10-year period, with review after 5 years. Since 2011, six collaboration projects have been initiated, with Takeda Pharmaceuticals, Dainippon Sumitomo Pharma, Mitsubishi

⁶⁸ <u>http://www.med.kyoto-u.ac.jp/en/english/news/news-prerelease/2017-6-5/</u> (June 2017) Accessed December 2018

⁶⁹ http://www.mic.med.kyoto-u.ac.jp/english/project/index.html Accessed December 2018

⁷⁰ http://www.mic.med.kyoto-u.ac.jp/english/project/members.html Accessed December 2018

Tanabe Pharma, Shionogi, Astellas Pharma, and Ono Pharmaceuticals; five of these collaborations continue to this day.

The MIC projects have helped to introduce new research areas at partner companies. For example, the collaboration with Shionogi led the company to shift focus to psychiatric disease research after five years, from the original focus on synaptic biology. Such changes in research focus were accompanied by a change in PIs employed through the projects, with researchers continuing in successful careers following their involvement in the MIC: Of the 19 PIs employed in the first term of four MIC projects, five have become fully tenured professors.

Appendix B – Existing programme evaluations

The following section provides an overview of existing evaluations identified during the literature review process. The purpose of collating these evaluations is to identify any emerging themes relating to barriers or enablers of programme success; and the recommendations made by evaluators. The existing evaluations cover a wide range of programmes and initiatives either committed entirely to translational research or covering an aspect of translation/commercialisation within their remit.

<u>USA</u>

B.2.1 National Institutes of Health (NIH) Clinical and Translational Science Awards (CTSA)

In 2003, the US National Institute of Health (NIH) implemented a roadmap aiming to bridge the growing gap between basic and clinical research. One of the roadmaps overarching themes was "Reengineering the Clinical Research Enterprise", with a focus on facilitating the translation of basic research to clinical research.71 As part of this effort, the National Center for Advancing Translational Sciences (NCATS) was established formally in 2012, as one of the official NIH Institutes and Centers with the mission to transform the translational science process.

The Clinical and Translational Science Award (CTSA) program was established in 2006 to "accelerate the translation of research discoveries from the bench to the bedside, train a new generation of clinical and translational researchers, and engage communities in clinical research efforts". Since 2012 under the auspices of NCATS, CTSA is a national network that currently consists of 57 medical research institutions, so-called 'hubs', that work in conjunction with one another to improve the translational research process. In 2017, NCATS allocated more than USD 500 million (approx. GBP 384) to the translational research programme.

The objective of developing this infrastructure is to speed the movement of research findings from the lab towards clinical studies and eventually to therapeutic practices that improve health in the community and reduce health disparities. The programme's goals include training and cultivating the translational science workforce and engaging patients and communities in every phase of the translational process. To this end, CTSA-supported research teams include not only scientists, but also patient advocacy organisations and community members.

B.2.2 The CTSA National Evaluation Final Report (Frechtling et al., 2012)

The authors (Westat) conducted an evaluation of the first 46 CTSAs that were funded by the initiative. It was designed to provide baseline data for tracking CTSA programme accomplishments over time and to set a framework for continued evaluation as the programme continues. Methodology included surveys, case studies, secondary data analysis of extant data and benchmarking with bibliometric data. The report includes 6 stand-alone studies (not publicly available):

- 1. Analyses of publications data to provide indicators of CTSA-related scientific advancements
- 2. Analyses of Annual Progress Report data submitted in the Non-Competing Continuation Progress Reports to understand basic programme characteristics and statistics
- 3. Field visits to a selected sample of nine CTSA institutions to obtain an in-depth examination of how the programme is implemented and what it is accomplishing
- 4. Surveys of investigators to assess the use and perceived value of resources
- 5. Surveys of scholars, trainees, and mentors to assess the efficacy of the education and training component
- 6. Development of a database of a sample of potential breakthroughs to provide a starting point for examining the CTSA's scientific contributions to the field.

The evaluation noted the key accomplishments of the CTSA programme which included:

 Success in providing research resources that improve research, support innovation, and improve process efficiency

⁷¹ <u>https://commonfund.nih.gov/sites/default/files/ADecadeofDiscoveryNIHRoadmapCF.pdf</u> Accessed November 2018

- Supporting changes in how the clinical and translational research process is integrated, as well as how individual investigators progress their own work in the right direction
- Effectiveness of the institutional pilot projects in creating new research synergies and supporting junior researchers
- High citation rates of CTSA-supported researchers, and an increase in cross-site publications
- Supporting meaningful collaborations across institutions, disciplines, and areas of medical research
- Expanded efforts to engage the community to address local health issues
- Expanded education and training support to provide researchers with an education in clinical and translational research to create new career trajectories. A key success of this aspect is the strong mentoring component and the creation of protected research time

Key challenges included:

- Awareness that the programme is not as far-reaching as it ought to be, there remains a considerable population lacking in information relating to the CTSAs and what they can offer at both an institutional and national level
- Although cross-institutional collaboration was improved, it was felt these connections were often fragile and lacked incentives. Furthermore, it was noted that although stronger, the clinical and translational ecosystem were still a distance from becoming self-sustainable
- The education and training programmes need to continue to improve ethnic diversity, expand attention to technology transfer, and communicate with the public and policy makers
- Improving the organisational structure of the consortium and moving away from the emphasis placed on process.

The evaluation also noted a key barrier whereby traditional academic reward structures were not conducive to clinical and translational research careers as tenure and promotion were more linked to the career path taken by basic researchers. This often disincentivized academics to engage with clinical research.

The evaluation offered several recommendations for NCATS and the NIH based on its findings. The first being to encourage institutional pilot programmes in order to expand this component of the programme. In addition, it was recommended to implement plans to increase researchers' awareness of the CTSA programme and its resources as this was found to be uneven. Expanding the education and training programmes was also a key recommendation as this component was found to be particularly successful. Streamlining the functions of the CTSA consortium was recommended in order to create a stronger management and more interconnected network of regional CTSAs. Finally, increased incentives for collaboration and partnerships were recommended considering the identified barriers to clinical and translational career paths.

B.2.3 Assessing the impact of the NIH CTSA program on institutionally sponsored clinical trials (Liu *et al.*, 2013)

The authors (Penn State College of Medicine) evaluated the trend in patient enrolment to clinical trials sponsored/collaborated by the CTSA consortium institutions during the years before and after the CTSA award dates. The evaluation was funded by a grant from the National Centre for Advancing Translational Sciences (NCATS). They used patient enrolment as a surrogate indicator to indirectly assess the potential impact of the CTSA on clinical trial activities and clinical/translational research more generally. Data was obtained from ClinicalTrials.gov for projects up to TRL 8 (clinical trials).

Compared to matched non-CTSA institutions CTSA consortium sites received an increase in patient enrolment following the CTSA awards, suggesting that the funding programme had a positive impact on patient enrolment.

B.2.4 Charting the Publication and Citation Impact of the NIH Clinical and Translational Science Awards (CTSA) Program From 2006 Through 2016 (Llewellyn *et al.*, 2018) From abstract as unable to obtain full text.

The authors (Georgia Clinical & Translational Science Alliance) evaluated publication and citation patterns for articles supported by CTSA hub investment over the first 10 years of the programme with the aim of obtaining a better understanding of the translational process. They aimed to do this by providing an overview of how time, hub maturity, and hub attributes related to productivity and influenced the academic literature. They used bibliometric data citing CTSA hub grants from inception to 2016 in order to examine the publication and citation rates and relative citation impact per funding year cohort.

From 2006-2016 CTSA hub publication rates accelerated as the hubs matured with multi-institutional hubs and those awarded higher grants showing much higher publication and citation rates. This suggested that multi-institutional collaborations and improved financial resource were associated with higher bibliometric activity.

B.2.5 Social network analysis to assess the impact of the CTSA on biomedical research grant collaboration (Nagarajan *et al.*, 2015)

The authors assessed the impact of the CTSA on biomedical research grant collaboration at a single institution, the University of Kentucky, pre- and post-CTSA funding. The evaluation was supported by a grant from NCATS/NIH. They analysed grant management systems data to construct collaboration networks among CTSA-affiliated investigators pre- and post-CTSA funding to assess the extent to which these networks deviated from randomness. The evaluation included projects from T stages 1 to 4. The deviation from randomness was especially marked following CTSA funding as was the level of intercommunity crosstalk, suggesting an increased number of collaborations and team-science efforts potentially as a result of CTSA funding.

B.2.6 Social Network Analysis of Biomedical Research Collaboration Networks in a CTSA Institution (Bian *et al.*, 2014)

Similar to the study described in 0, a network analysis of a university grants database was conducted to explore collaborations pre- and post-CTSA funding at the University of Arkansas for Medical Sciences.

The findings suggest that the CTSA program had a positive effect in promoting research collaboration across disciplines inside the institution.

B.2.7 Breaking Down Silos: Mapping Growth of Cross-Disciplinary Collaboration in a Translational Science Initiative (Luke *et al.*, 2015)

A network evaluation study of the NCATS CTSA ICTS at Washington University, drawing on grants data as well as publication data, also found growth in scientific collaborations among members over the three to four-year period after the centre was launched.

The analysis found that ICTS members had become involved in a greater number of scientific planning collaborations (as measured by new grant submissions) and scientific dissemination collaborations (as measured by journal article co-authorships). Collaborations also became more cross-disciplinary over time. However, the study points out that they did not have a valid comparison group, as most scientists involved in clinical and translational research are ICTS members at the university.

B.2.8 Specialized Programs of Research Excellence (SPORE)

The Specialized Programs of Research Excellence (SPOREs) were established in 1992 by the National Cancer Institute (NCI) of the NIH and sit within the Translational Research Program. Each SPORE focusses on a specific organ site or on a group of highly related cancers and functions to enable rapid progression of scientific findings into the clinical setting. Total SPORE funding for the year 2017 was valued at approx. USD 114 million (GBP 87 million), with applications for SPORE grants during the period 2018-2020 set at a maximum of \$1,400,000 (approx. GBP 1 million) direct costs per year.

SPORE grants involve both basic and clinical/applied scientists and support a range of projects that aim to result in novel approaches to the prevention, early detection, diagnosis and treatment of human cancers. All SPORE grants include at least 4 translational research projects that should be designed to

include a clinical trial, an observational study or experiments using human specimens for discovery, or development of biomarkers.

The grants also support Developmental Research Awards (funding for pilot projects) and Career Development Awards (funding to support junior and established investigators to expand their careers into translational research).

B.2.9 Evaluation of the National Cancer Institute (NCI) Specialized Programs of Research Excellence (SPORE) (Hautala *et al.*, 2014)

The authors (the IDA Science and Technology Policy Institute) were commissioned by the NCI to conduct an evaluation of the SPORE programme. The evaluation focussed on the overarching question of how well the SPOREs have been meeting the translational research goal of reaching human endpoint within the five-year funding period. In addition, the report drew conclusions concerning the role of the SPORE programme in advancing cancer-related translational research.

The analysis focussed on the 55 SPORE awards that were active at some point subsequent to 2004 and had completed at least one 5-year award cycle by 2011. Methodology included analysis of funding application documents for the selected 5-year period for each award, including the competitive application, the Type 5 progress reports, and the final report/subsequent competitive application. In addition, a series of individual interviews with SPORE principal investigators (51 of the 55 SPORE PIs, in one to two-hour discussions) were completed.

The evaluation was guided by 11 study questions which were developed by the NCI. Question 1 exists as the overarching evaluation question while the following 10 focus on specific aspects of the SPORE programme:

- 1. "What specific concepts or scientific findings that arose from SPORE research have an impact on the practice of oncology?"
- 2. "How well have the SPOREs been meeting the translational research goal of reaching a human endpoint within the five-year funding period?"
- 3. "How well have basic and applied scientists worked together on the design and implementation of individual research projects?"
- 4. "How well have SPOREs collaborated with other SPOREs in their own organ site or across organ sites; with NCI networks, such as Cancer Centers and Cooperative Groups; with other government and non-government biomedical research mechanisms; or with industry to move important findings along the translational research pathway with the ultimate goal of having an impact on medical practice?"
- 5. "How well have SPOREs used the flexibility option to change research direction to have an immediate impact on improving cancer prevention, detection, diagnosis, and/or treatment?"
- 6. "How well have SPOREs fostered translational research careers?"
- 7. "How well have the SPOREs used the Developmental Research Program for pilot studies?"
- 8. "How well have the Specialized Resource Cores supported the research projects?"
- 9. "Did the Biospecimen Core provide materials for investigators outside the SPORE?"
- 10. "How many clinical trials/studies were initiated and completed within the SPOREs?"
- 11. "What are the significant publications from the SPOREs since 2004?"

A further two additional analyses were recommended during the project. These included the role of the SPORE programme in advancing cancer-related translational research and an analysis of the SPORE research projects regarding their ultimate translational objective and the translational activities that they propose.

The evaluation lists several key findings including 3 categories of major advances: (1) advances accepted into clinical practice; (2) advances in late-phase human testing; and (3) advances with broad clinical potential. In order to corroborate the advances as entirely SPORE-derived or largely related to SPORE-conducted research, STPI researchers conducted an independent analysis of each advance

(as described by SPORE PIs during individual interviews) to verify the information provided by the PIs. This included a review of National Comprehensive Cancer Network (NCCN) Guidelines, searches on clinicaltrials.gov, analysis of publications from MEDLINE searches, and desk research of industry, government, and not-for-profit organization websites.

- A total of 67 major advances were identified, including 24 advances accepted into clinical practice, 29 in late-phase human testing, 11 with broad clinical potential and 3 landmark population studies.
- 94% of SPORE awardees designed and/or led a clinical trial (for a total of 221 trials). This varied across disease areas with haematological SPOREs having the largest number (8 per award) and gastrointestinal and ovarian the lowest (2.5 per award). Of the 221 trials, 43% were phase I, 41% phase II with 11% being phase I/II and randomised phase II.
- 89% of SPOREs involved observational studies in some way, with 28% carrying out an observational study directly.
- 1,022 external collaborations were associated with 311 SPORE projects, 45% of these collaborations involved active participation in SPORE research with 41% involving the exchange of materials or data from collaborators. Four key categories of external collaboration were deemed to be particularly associated with SPORE success: collaboration between SPORE PIs within the same disease area; collaboration with industry; collaborations with NCI-funded Cooperative Groups; and collaboration with disease-specific phase I/II clinical trial consortia72.
- Data from NIH RePORTER showed 5,655 publications acknowledging one or more of the 55 SPOREs since 2004, with an average of 105 publications per SPORE.

The evaluation notes five major conclusions, based on its findings, regarding the role of the SPORE programme in advancing cancer-related translational research:

- SPORE projects exist in practice rather than being theory focussed, with 96% of SPORE awards having a defined intervention or biomarker test development objective, and with 80% of the intervention focussed projects proposing late stage development activities (either early phase clinical trials or the development of an intervention in anticipation of clinical testing).
- The SPORE programme is associated with award-related constraints, relating to the ability of a
 project to meet its translational goals. This is most often financial as SPORE awards are typically
 valued at between \$200k to \$400k per year which is insufficient to complete a small phase I or II
 trial. This dictates that SPORE investigators obtain further non-SPORE funding if planning further
 activities. The 5-year award period can also be inhibitory due to this being a short amount of time
 to move from discovery to human testing. In this way the awards can favour projects that are already
 well advanced and restrict the pursuit of innovation.
- Despite this, the funded projects have been successful in reaching a "human endpoint" (clinical trial, observational study or use of human specimens). From the clinical trial analysis, 93% of the funded projects reached this endpoint during the 5-year funding cycle. This analysis also elucidated that for almost 50% of the projects that did not reach endpoint, this was due to the use of the flexibility option to terminate the trial early.
- Based on the SPORE PI interviews it was felt that the programme occupied 3 distinct niches within translational research:
 - the ability of SPOREs to successfully pursue translational research objectives that are perceived by industry as too high risk/complex to warrant investment.
 - The ability of the SPORE programme to facilitate the engagement of basic and applied scientists in a team environment encourages blue sky thinking and the pursuit of innovative

⁷² Examples include the Translational Breast Cancer Research Consortium, the Prostate Cancer Clinical Trials Consortium, the NCI Adult Brain Tumour Consortium and the Melanoma Research Foundation Breakthrough Consortium.

ideas. The Career Development and Developmental Research Programmes also facilitate the integration of investigators into translational research networks within distinct disease areas.

- the pursuit of industry collaboration was a key niche occupied by the SPORE programme, whereby an industry drug is progressed by a SPORE for an initial or new indication, often in combination with other approved or unapproved drugs. SPOREs can provide investigator expertise, research capabilities, access to biospecimens and patients while industry brings the necessary supplemental funding and access to drug development capabilities.
- SPOREs have a substantial impact on early translational research capacity building within a specific disease area. Within the host institution, the award provides a core infrastructure including specialised tissue repositories, laboratory equipment and technical expertise. The award can also serve to raise the profile and legitimacy of translational research within an institution. Interinstitutional collaborations (SPORE funded) within a disease area also functions to create a national community of translational researchers which can be advantageous for epidemiological studies, biospecimen sharing, recruitment of patients and clinical trial design.

B.2.10 Report of the Specialized Programs of Research Excellence (SPORE) Program Evaluation Working Group of the National Cancer Institute Clinical Trials and Translational Research Advisory Committee Working Group (Davidson and National Cancer Institute, 2014)

The report documents the outcomes of a 1 day working group meeting which convened an 11-member expert group. The group were asked to provide expert input on the value of the SPORE programme to the NCI and overall cancer research enterprise; and to make a statement on the future direction of the SPORE programme and how it might be enhanced.

The working group developed 3 recommendations for NCI to improve the effectiveness of the SPORE programme:

- Explore approaches to facilitate the efficient movement of SPORE project outputs into clinical trials via the NCI Experimental Therapeutics programme (NExT), Cancer Centres, the N01/U01 earlyphase clinical trials programmes, the national Clinical Trials Network Groups and other intramural and extramural clinical trial programmes.
- Explore approaches to develop or expand links to The Cancer Genome Atlas, the Physical Science Oncology Centres and other intramural and extramural initiatives with the aim of generating discoveries, in order that SPOREs might be able to advance these into translation.
- Explore approaches to promote industry or foundation joint funding for SPORE projects and awards.

B.2.11 Prevention Research Centres Programme Evaluation Results: Program Indicators (US Department of Health and Human Services and CDC, 2010), 73

Prevention Research Centres is a network of 26 academic research centres in the USA, investigating preventative interventions that can be employed to avoid or counter the risks for chronic illnesses, such as heart disease, obesity and cancer. The first 3 centres were funded in 1986 at the University of North Carolina, the University of Washington and the University of Texas. The programme website includes the PRC's indicator data for each year of a five-year funding cycle. The indicators include bibliometrics (books, chapters, articles, conference presentations); extra funding leveraged; and number of policy, systems and environmental changes. The below link includes an extensive list of the programme monitoring indicators. However, this data is not available via their website.

The link also contains a logic model and lists potential outcomes including: (1) translation of research to practice and policy, (2) widespread use of evidence-based programmes and policies, (3) enhanced community capacity for health promotion and disease prevention, (4) skilled public health professionals and community members, (5) expanded resources and (6) increased recognition of and support for prevention research centres and prevention research.

⁷³ <u>https://www.cdc.gov/prc/about-prc-program/program-evaluation/pdf/eswinter2010-appendices.pdf</u> Accessed December 2018

B.2.12 The Economic Impact of the University of Florida's (UF) Clinical and Translational Science Institute (CTSI) (Dewey, 2013)

The Clinical and Translational Science Institute (CTSI) was established in 2008 to strengthen the university's ability to carry out translational research and to expedite the translation of scientific discoveries. It aims to achieve this by functioning as a "catalytic hub" to connect resources, people and ideas. It offers multidisciplinary training programmes (via the CTSI Translational Workforce Development Programme), transformational initiatives (via the CTSI Pilot Project Awards and Pipeline to Proposal Development Grants) and the provision of support to facilitate health research and advance knowledge across the translational continuum. The CTSI is supported by multiple NIH grants, including a USD 26 million (approx. GBP 20 million) CTSA which was awarded by the NIH in 2009.

An evaluation of the CTSI was conducted by the Economic Analysis Programme of the Bureau of Economic and Business Research at the University of Florida. The methods included an assessment of productivity impact (before and after CTSI funding on patents and publications) and regional economic impact (earnings, value added, gross output, employment).

The report found that status as a CTSI investigator led to a 310% increase in external funding, patent applications increased by 38% and publications in top 100 journals by 41% following association with the CTSI. In addition, the regional economic impact assessment found that on average, every \$1 of the CTSI's operating expenditure supported \$11 in additional external funding. Furthermore, on average \$1 million of CTSI funding supported 122 jobs in Alachua County and 203 in Florida. The CTSI operations also supported 13,363 person years of employment in Florida (including Alachua county) from 2008-2012 and approx. USD 1,1 million in economic activity in Florida during the same time period.

<u>Canada</u>

B.2.13 Evaluation of Commercialization of Research – Centres of Excellence for Commercialisation and Research (Government of Canada, 2017)

Centres of Excellence for Commercialisation and Research (CECR) is a tri-agency programme funded in part by the Natural Sciences and Engineering Research Council (NSERC), the Canadian Institutes of Health Research (CIHR), and the Social Sciences and Humanities Research Council (SSHRC). The programme creates centres of excellence in commercialisation to deliver economic, social, health and environmental benefits to Canadians. In order to achieve this the programme functions to match clusters of academic research expertise with the needs of business, health practitioners and other end users in order to build on R&D capacity and capability. The programme was established in 2007 and invests CAD 30 million (approx. GBP 18 million) per year in innovation. It funds/has funded 15 centres and networks in the health and life science sector. The centres adopt various models in order to best serve the commercialisation needs within the sector. This can include acting as incubators, investors or service providers, with each CECR being mandated to become self-sustaining.

The authors (Goss Gilroy Inc and the Evaluation Division at SSHRC and NSERC) conducted an evaluation of the programmes' relevance, effectiveness, efficiency and delivery. The methodology included a review of documents and key literature; a financial data review; interviews with key informants; a web-based survey of centre partners and organizations served; case studies; and an econometric analysis.

The report mentions several barriers and enablers to self-sustainability including the strength and maturity of the centre's revenue model, the organisational culture in terms of a strong growth strategy and strong IP strategy, and the organisational capacity (including in-house skills and a strong and efficient management team). Challenges associated with self-sustainability included the short time frame required for achievement, issues associated with funding or attracting investment, and challenges generating enough revenues.

Findings include that the CECR is generally believed to be well delivered. However, centres need more time to become self-sustainable (particularly health centres due to the associated costs and more demanding regulatory requirements). The report makes 3 general recommendations which include:

1. "Continue to deliver the CECR programme and allow a flexibility in the centre delivery models"

- 2. "Allow more time for centres to achieve self-sustainability and clarify how the CECR programme defines self-sustainability"
- 3. "Consider the appropriateness and feasibility of the following potential areas for improvement"

B.2.14 Evaluation of CIHR's Commercialisation Programmes (Constantinescu et al., 2015)

The Canadian Institutes of Health Research (CIHR) developed a Commercialisation and Innovation Strategy in 2005, it provided a framework for the translation of health-related research into actions aimed at improving quality of life and stimulating economic growth. The strategy was implemented via several initiatives which focussed on one or more of the strategic components of the programme. These included: Industry-Partnered Collaborative Research Operating Grants (IPCR), Collaborative Health Research Projects (CHRP), Science to Business (S2B) and Proof of Principle Phase I and II (POP-I and POP-II). The total budget allocated to spending on commercialisation programmes was approx. CAD 13.8 million (approx. GBP 8 million) between 2012 and 2013.

- IPCR operating grants focus on funding research projects involving collaborations between academia and industry that have the potential for commercialisation. They were created in 2005 as a merger of CIHR's SME and R&D Collaborative Research Programmes. Funding of up to CAD 250k (approx. GBP 147k) per year for a maximum of 5 years is available.
- CHRP is a joint initiative between CIHR, NSERC and SSHRC. The grants support collaborative and interdisciplinary research projects in the fields of natural science, engineering and health science. They should have a focus on innovation and knowledge translation. The CIHR joined the initiative in 2003.
- Since 2010, the S2B programme has aimed to encourage people with a health-related PhD to
 pursue an MBA, with the idea that these individuals will go on to pursue careers that support
 commercialisation and innovation in Canada (i.e. technology transfer, finance, regulatory affairs).
 The maximum award value is CAD 30k (approx. GBP 18k) per year for up to 2 years.
- The POP I&II programmes funds proof of principle studies for up to 12 months, with a view to attract further investment and new science-based businesses. The total funding value of the programme was CAD 2.24 million (approx. GBP 1.32 million). POP I began in 2001 and POP II in 2003.

The evaluation was completed by an Evaluation Working Group at the CIHR and was undertaken to assess the relevance and performance of the commercialisation programmes to inform future programming and to comply with the requirements of the Financial Administration Act and the Treasury Board of Canada's Policy on Evaluation (2009). The evaluation covers projects that took place from the point of creation of each programme until the end of fiscal year 2012-2013. Methodology included an initial review of literature and documentation associated with the programmes, key informant interviews and a survey of funding beneficiaries.

Key findings were grouped into 4 main categories and include but are not limited to:

- Knowledge Translation and Commercialisation
 - A few key commercialisation outcomes were generated by the programme including: provisional patents (74% of funding beneficiaries), presentations to industry or other relevant partners (79%), invention disclosures (61%), patents granted (41%).
 - No less than 41 spin-off companies were created as a result of POP I and POP II programme funding since 2001.
 - 79% of funding beneficiaries published a minimum of one journal article per grant, with 45% of IPCR and 30% of POP I beneficiaries publishing a joint article with public sector partners.
- Collaboration and Partnerships
 - 65% of POP I beneficiaries involved partners within their funded projects, despite this not being a requirement of the programme.
 - 70% and 69% of IPCR and POP I beneficiaries respectively, stated that the funding they received incentivised them to work with partners. However, a similar percentage in either group

noted that they would have chosen to work with a partner regardless of CIHR funding. The main reason for this was the added benefit of the partners expertise.

- Several barriers were also identified by the industry partners: the cultural differences between industry and academia, the timing of CIHR competitions which often did not align with industry needs, a lack of industry control over project funding with the risk of researchers diverting from original plans, and difficulties in monitoring project performance.
- Capacity Development
 - 76% of S2B beneficiaries stated that the programme exceeded or met their expectations in terms of the contribution it made to the development of their commercialisation skills and knowledge. However, it should be noted that the S2B programme represents a small investment compared to the overall CIHR funding budget.
 - 30% of funding beneficiaries noted a lack of skills relating to commercialisation as a key barrier to progression of their discovery along the commercialisation pathway.
- Design and Delivery
 - POP I was considered the most highly sought-after grant to support early stage research.
 - POP II was seen to provide funding for validation studies of early discoveries that are perceived to be more high risk by industry and struggle to obtain industry investment.
 - IPCR was seen to facilitate robust industry-academia partnerships and facilitated a better understanding of the needs of each.
 - CHRP was not well known out with the research community (3 out of 10 TTOs were involved with the CHRP programme).
 - S2B was well received by funding beneficiaries regarding the contribution it made to the development of their entrepreneurial and commercialisation skills.
- Programme Relevance
 - 92% of funding beneficiaries agreed that there was a need for federal government input to facilitate the commercialisation of health research in Canada.
 - 62% identified a "lack of funding for health research commercialisation" as their most common challenge.
 - Approximately 50% of survey respondents obtained other relevant funding related to commercialisation during or within two years of the CIHR grant end date.

The report went on to make 4 key recommendations based on the evidence collected during the evaluation process:

- 1. The definition of innovation adopted by the CIHR should aim to capture the broader social, economic and health benefits arising from the use of health research to develop or improve goods, services, processes, organizations and system.
- 2. CIHR should endeavour to continue funding early stage commercialisation of research, continuing to realise the importance of this key phase in the commercialisation process to test and validate the potential of discoveries that provide a solution for unmet need among researchers and TTOs.
- 3. CIHR should act as a broker within the areas of innovation and commercialisation, in order to facilitate communication between researchers and potential users of research data to increase exposure, awareness and uptake; to foster partnerships with other commercialisation programmes in order to leverage investment across the innovation pathway.
- 4. Regarding programme design and delivery, the CIHR should focus on involving more industry experts in the peer review process; expediting the flow of funding to researchers based on their needs; offering grants with longer duration or providing flexibility to alter duration; and implementing clear milestones and tracking and monitoring systems in order to better capture the commercialisation impact.

B.2.15 Evaluation of CIHR's Knowledge Translation Funding Programme (McLean et al., 2013)

The CIHR Knowledge Translation (KT) Funding Programme consists of standalone funding opportunities which include: Partnerships for Health Systems Improvement (PHSI), Knowledge to Action (K2A), Knowledge Synthesis (Synthesis), Dissemination Events (DE), the KT Supplement (KTS) and KT Science. These programmes fundamentally function to facilitate the translation of health research into improved health. The CIHR aims to supports knowledge transfer via both investigator-initiated research and priority-driven research.

The evaluation was undertaken by an Evaluation Working Group at the CIHR. Its objectives were twofold: First to assess the performance of the KT programme and identify impacts and areas for improvement. Second to fulfil the CIHR's responsibility to the Treasury Board of Canada under the 2009 *Policy on Evaluation*. Methodology included review of relevant literature, documents and electronic information systems; an international landscape scan; surveys; in-depth interviews and case studies.

The key findings of the evaluation included:

- When compared with the CIHR's existing measures of success, all of CIHR's KT funding opportunities performed well. Specific outputs included 6 student/post-doc engagements per grant, 4 journal articles/books etc generated per grant and 17 websites/ decision aids per grant.
- The creation of useful partnerships between researchers and knowledge users was also noted as a result of KT funding.
- Evaluation data also indicated that KT funded researchers contribute more often to outcomes which
 improve the health of Canadians, strengthen the healthcare system, and create new services or
 products.
- Funded researchers noted public engagement, policy development and commercial ventures as examples of post grant activities that continued well beyond grant expiration.

The evaluation also noted key enablers and barriers to success within KT funding opportunities:

- Enablers
 - Engaging and communicating with knowledge users (KUs) throughout the research process
 - Ensuring that researchers and KUs have the correct expertise in order to be able to use the funding effectively
 - Ensuring results are disseminated to audiences in the most appropriate way
 - Engaging both researchers and KUs during the review of applications for integrated knowledge transfer
- Barriers/challenges
 - The significant effort associated with integrated knowledge transfer research, for example engaging KUs in a relevant and meaningful manner
 - Scheduling research efforts to coincide with the needs of KUs
 - Submitting non-academic curriculum vitae (associated with KUs) to the CIHR

Based on these key findings the evaluation made 3 overarching recommendations:

- 1. CIHR should continue to invest the necessary resource required to maintain its role in enabling knowledge transfer.
- 2. CIHR should develop performance metrics which accurately monitor and assess the integration of the KT Funding Programme into the open research schemes to ensure continued success and the balance of funding across all research fields. Data from this evaluation should be used as a baseline for future studies of CIHR success in knowledge transfer under the newly proposed Project and Foundation Schemes of Research.
- 3. Regarding university-based researchers who undertake integrated knowledge transfer research and then go on to conduct knowledge transfer of the results, this process is not well

aligned with the performance metrics employed by universities to measure the success of a project. CIHR should work towards reducing this tension by engaging in communication with the academic research community.

European Union

B.2.16 The Final Evaluation of the Innovative Medicines Initiative Joint Undertaking (2008-2016) operating under the 7th Framework Programme (Syrota *et al.*, 2017)

The Innovative Medicines Initiative Joint Undertaking (IMI) is a Public Private Partnership between the EU (represented by the European Commission) and the European Federation of Pharmaceutical Industries and Associations (EFPIA). The rationale for setting up the IMI originated as a result of the political and socio-economic situation in the early 2000s when Europe witnessed its private R&D expenditure drop from 73% to 59%. The IMI was established to address the barriers to drug development and to improve the competitiveness of the European pharmaceutical industry to make Europe more attractive for investments in biopharmaceutical R&D. Another key objective was to remove bottlenecks within the system to improve the quality and efficiency of the drug development process, with the future aim of expediting the safe and effective production of medicines within Europe.

The evaluation was undertaken by the Directorate-General for Research and Innovation Health to inform the European Parliament and Council, national authorities, the research community and all other stakeholders of the outcome of the IMI. The evaluation was also used to improve the implementation of IMI2 and will serve as a reference point for ex-ante impact assessments of the future JUs. The evaluation covered the period from 2008 (implementation of the IMI) to 2016 and focussed on effectiveness, efficiency, research quality and openness and transparency.

The evaluation methodology included document review of extensive data sets compiled by the IMI Executive Office, interviews with a broad range of IMI stakeholders, a survey of beneficiaries and a public consultation.

The key findings of the evaluation included successes and challenges:

Successes:

- The main achievement of IMI was the facilitation of collaborations between competing global companies, SME's and academia. The collaborations allowed new partnerships to be formed between different areas of expertise including regulatory bodies and patient representative groups.
- From the 21 projects who had reached the end of their IMI funding cycle, 16 spin-offs had been created, and 9 patents and 1071 publications reported. In addition, 2768 full-time positions were created by the end of 2016, employing highly-skilled individuals associated with IMI projects.
- There were no examples of direct health impacts at the time of publication of the evaluation, making
 it difficult to demonstrate the value of IMI for patients or society in general. However, IMI funded
 projects were found to have established infrastructure and new tools for research. The research
 topics contributed to medicines safety and a reduction in the use of animal models in research.

Challenges:

- A reliance on pre-existing networks which may have led to missed opportunities to draw new partners together which may have included better infrastructures, biobanks or researchers.
- One of the major risks associated with successful completion of a project was the premature
 withdrawal of a pharmaceutical company (it was noted this did not happen frequently), leading to
 significant implications for both the content and budget of the project. This was compounded by the
 lack of any regulations to enforce industry commitment detailed at the beginning of a project, and
 a resulting lack of penalisation for companies who did not fulfil their commitments.
- Criticism was given regarding the lack of transparency on the in-kind calculations of the EFPIA companies.

- Findings suggested that the methods used to communicate the results and outcomes of IMI projects fell short, with most results from funded projects being inaccessible to stakeholders outside the consortia who generated the results. It was felt that further efforts were required to improve awareness of the initiative and the value it can add.
- IP negotiations were difficult due to the exclusivity rights relating to the results of IMI projects and were felt to hamper the participation of SMEs and some academics. This was even more pronounced in projects involving large consortia or when the project was close to the interests of big pharma companies. This created a barrier for non-IP professionals.
- It was recognised that opportunities were missed to include sectors such as imaging, diagnostics, medical device developers and technology providers (IT, electronics, data management). These sectors were key in the development of new medicines and this issue has been addressed in IMI2.
- The authors noted that it was difficult to assess the extent to which the IMI had supported the competitiveness of the European pharmaceutical industry, due to the lack of a system to measure performance. The introduction of SMART Key Performance Indicators to measure scientific outputs and socio-economic impacts was recommended.

<u>Norway</u>

B.2.17 Evaluation of The Kristian Gerhard Jebsen Foundation's Support of Translational Medicine (Benner and Terenius, 2014)

The K.G. Jebsen Foundation supports centres with a focus on translational medical research in Norway. The authors evaluated the impact of the K.G. Jebsen Foundation and commented on the visibility; additionality; impact on host organisations; scientific impact; time frame of support; leadership; management of IP rights and the foundations procedures. The report does not mention methodology used.

The findings of the evaluation include the creation of a new form of interaction between research groups in Norway and a raised profile of translational approaches. The report also noted that collaboration between different research areas (i.e. medicine and engineering) could have been incentivised more effectively. The Foundation's programme also appeared to have triggered new and improved interactions between universities and health care providers. There was little evidence that the support stimulated any sort of organisational change within institutions, with the funding having a more short-term impact in this way.

Recommendations included but were not limited to:

- Emphasis should be placed on the international outlook, by encouraging temporary visits from scientists.
- Research programmes should be goal-orientated with milestones clearly defined from inception.
- Performance indicators should be measurable (i.e. patents, implementation of novel biomarkers, contacts with commercial partners)
- Contact with basic scientists and engineers should be encouraged, especially within the context of IT (i.e. modelling and simulation) to build capacity either internally or via collaboration.
- IP rights should be guarded to generate return for the university and to enable commercial partners to translate innovations to clinical use.

<u>Germany</u>

B.2.18 Empfehlungen zur Weiterentwicklung der Deutschen Zentren der Gesundheitsforschung (Recommendations for further development of the German Centres for Health Research)

The German Centres for Health Research' aim is to accelerate translation of medical research into application in the health system. Between 2009 and 2012, six centres were established, each targeting a different disease area: diabetes, neurodegenerative diseases, cardiovascular disease, cancer, lung disease, and infections. The centres network geographically close institutions (hub and spoke model), and include the entire spectrum, from basic to clinical, implementation and public health research. In

2015, the centres' budget was approx. EUR 265 million, financed to 90% by the German Health Ministry, and to 10% through funding from the federal states involved.

Each of the six centres was reviewed individually by expert review panels (evaluation reports are confidential, but the review described here mentions that 'research concepts' of all centres were assessed to be 'very good'). The programme's scientific advisory board then reviewed the six individual evaluation reports to arrive at an overall assessment of the support model. This review sets out conclusions on the structure and organisation of the DZGs, the training they provide, research conducted and where the DZGs sit in the broader translational research ecosystem.

Recommendations included:

- Focus on ambitious 'flagship' projects, rather than funding of many individual investigations
- An increase in interactions with industry, patient associations, and regulatory authorities
- Establishment of long-term positions, and increased recruitment of clinician scientists; setting up of
 opportunities targeted at early career researchers
- Standardisation of protocols and data formats across all centres, and leadership for the entire research community
- Implementation of a monitoring framework and evaluation practices, relating to both the outputs of
 research (e.g. publications, IP, follow-on funding, spin-outs) and the research process (progress of
 research along TR stages, establishment of supporting infrastructure, networking and collaboration
 within and between centres and with external organisations)

Catalonia

B.2.19 Assessment of the impact of a clinical and health services research call in Catalonia (Adam *et al.*, 2012)

The authors (Catalan Agency for Health Information, Assessment and Quality) conducted an ex-post assessment of its biannual call to conduct non-commercial clinical and health services research. The aim of the call is to address local research knowledge gaps and assess the implementation of innovation.

They used the Canadian Academy of Health Sciences framework and conducted bibliometric analysis, surveys of researchers and decision-makers, and a more in-depth case study of translational pathways. They also conducted an international benchmark with other health services research calls.

The assessment concluded that local agencies can have a significant impact in improving local knowledge gaps. Furthermore, the full assessment of the research cycle provides opportunities for improving the entire research process from calls for proposals to subsequent impacts. The results also highlight the need to promote awareness of the importance of translation within the research community.

<u>UK</u>

B.2.20 The Small Business Research Initiative (SBRI) Healthcare programme – An evaluation of programme activities, outcomes and impacts (RAND Europe, 2017)

The SBRI Healthcare is an NHS funded programme that provides funding to innovative companies to solve healthcare problems. The team works with front line NHS staff to identify critical issues and key challenges within the NHS, focussing on specific areas that have been identified by NHS England and the 15 Academic Health Science Networks.

The initiative typically runs two themed competitions per year, focussed on the needs identified by NHS staff and other stakeholders. Phase I awards are worth up to £100,000 Over 6 months and support feasibility studies. If successful companies can bid for phase II awards worth up to £1 million over 12 months supporting the development of prototypes. A smaller number of phase III awards have been made to advance innovations further (also valued at £1 million). From 2013-2016 the SBRI Healthcare programme awarded an average of GBP 17.5 million per year to support small businesses in the UK.

The authors (RAND Europe) conducted an evaluation of the SBRI Healthcare programmes which was commissioned by the UK Department of Health Policy Research Programme. The aim of the evaluation was to draw practical insights on how the SBRI programme contributed to the innovation process and how it could best be supported moving forward. Their methodology included telephone interviews with 16 stakeholders; a survey of unsuccessful applicants; a survey of successful applicants and telephone interviews with 5 funding recipients.

The key messages of the evaluation included:

- The main motivations for applicants were the offer of full project funding and the fit of their projects with the theme of the calls. However, applicants noted that they would appreciate more support in helping their product be implemented by the NHS, which the SBRI noted was more within the remit of the AHSNs.
- The SBRI is seen to run well in terms of the effectiveness of its processes for identifying healthcare needs. However, several unsuccessful applicants raised concerns regarding the technical expertise of the review panel and the quality of the feedback they received.
- Awardees expressed that the kudos associated with the award was valuable in addition to the health
 economic analysis that it provides. Although it was too early to identify patient and NHS impacts, a
 range of expected impacts were reported, including significant potential cost savings to the NHS.

The evaluation also noted that SBRI Healthcare awardees face barriers to the uptake of their products including a general resistance to innovation within the NHS, limited resource to progress development and secure regulatory approval, and complex and bureaucratic procurement systems. To promote uptake, it was noted that involving clinicians in the development process and piloting the innovations locally could be beneficial.

B.2.21 The NIHR Invention for Innovation (i4i) programme – A review of progress and contributions to innovation in healthcare technologies (RAND, 2015)

The i4i programme supports the development of innovative medical technologies for patient benefit and involves collaborative projects between at least two partners from academia, the NHS and industry. The aim of the programme is to provide funding to de-risk projects, making them more attractive to follow-on funders and investors. All projects are expected to have an advanced or clinically validated prototype medical device, technology or intervention by the end of the project. The programme includes three funding streams: Product Development Awards, Challenge Awards and i4i Connect 2.

The authors (RAND Europe) reviewed the progress and contributions of the programme to innovation in healthcare technologies. The review was commissioned by the UK Department of Health Policy Research Programme. Their methodology included key informant interviews, surveys and case studies. Indicators included: milestones achieved by collaborators and co-applicants (proof of concept achieved, prototype developed, testing or PCT) and reported downstream commercialisation. The funding and business advice provided by i4i support the development of early-stage innovations, generally at proof of concept and prototype stages.

The key findings of the review included:

- The programme is helping to reduce the impact of the 'valley of death' in early stage innovation and supports projects at a range of starting points from pre-proof of concept to completed prototypes.
- It positions innovators to pursue further product development following project completion, including clinical trials, commercialisation and in a small number of cases uptake by the NHS.
- Key project enablers include the level of expertise and skills of the project team, the technical and scientific nature of the project, access to clinical insight regarding usability and the adaptability of the grant.
- Key challenges included technical and scientific issues within the project and regulatory constraints. Moving forward barriers were expected to be inertia and resistance to change, procurement channels into the NHS and financial issues regarding the implementation of pivotal clinical trials.

• The programme is viewed as unique due to its willingness to support projects from diverse themes and disease areas. It is also viewed as less bureaucratic funding source compared to other investors in the space.

Key recommendations included:

- Introduction of a responsive review mechanism for projects with the funding amount phased and determined reactively based on the progress of the project.
- Design funding application forms to encourage applicants to consider adoption, product design and health economic analysis at application and selection stages.
- Consider the proportions of academic, industry and clinical led projects within the portfolio. Academic led projects may benefit from external support to help identify routes to commercialisation and uptake in the NHS.
- Reflect on the scope and scale of business support provided. Specifically relating to the facilitation
 of networks between industry and clinicians, raised awareness of the programme, and the provision
 of business training and entrepreneurship skills.
- Provide more feedback to both successful and unsuccessful applicants to improve the quality of future bids.
- Consider how best to track the long-term impacts of funded projects.
- Improve information management databases and record keeping processes within the programme.

B.2.22 An analysis of the impact of research supported by the UK National Institute of Health Research (Kamenetzky *et al.*, 2016)

The authors (RAND, PRISM and the Policy Institute at King's) conducted a 'deep mine' of impact case studies collected through the Research Excellence Framework exercise (a comprehensive peer-reviewed exercise where the majority of UK universities submitted data in order to determine the annual allocation of approx. GBP 1.6 billion of public funding across the UK's higher educational sector). From this data the authors derived narrative statements relating to research impact relevant to NIHR. They assessed the nature, scale and impact of NIHR support.

The analysis found that the nature of NIHR support most frequently referred to was the Health Technology Assessment stream, with the next two most frequently referenced funding streams being the NIHR's Programme Grants for Applied Research and Research for Patient Benefit schemes. The scale of NIHR support spanned all 21 HRCS health categories with 'general health' and 'public health' being tagged most frequently. NIHR support was also associated with a significant amount of cooperative funding involving public and charitable research funding agencies. When considering the impact of NIHR support most case studies described routes to societal benefit. Many also provided evidence of NIHR funded research contributing to changes in international practice, through changes in healthcare procedures, service delivery or training. A high proportion also noted instances where direct patient impacts were achieved and evidenced this via the inclusion of patient outcomes within their research.

B.2.23 Changing the translational research landscape; a review of the impacts of Biomedical Research Units in England (Marjanovic and RAND Europe, 2009)

The Department of Health's Best Research for Best Health strategy (BRfBH) set out to create a health research system in which the NHS supports world class research focussed on the needs of patients and the public. Two of the flagship initiatives of BRfBH were the establishment of Biomedical Research Centres (BRCs) and Biomedical Research Units (BRUs). These are both partnerships between an NHS trust and a university. They share a common goal to undertake translational research in priority areas of high disease burden and clinical need. The goal of BRUs was to develop new relationships, greater capacities and improved targeting, and an enhanced responsiveness in health research.

The authors (RAND) were commissioned by the Department of Health and Social Care (DHSC) to conduct a perceptions audit of senior executives involved in the BRU scheme to explore the impact they felt it was having on the translational research landscape. They also investigated whether and how

institutional relationships between NHS and academic partners, industry and other health research system players were changing because of the scheme; how the scheme was helping build critical mass in specific priority disease areas; and the effects of any changes on efforts to deliver the broader goals set out in Best Research for Best Health. In order to achieve this, they completed 38 interviews with senior executives.

The report notes a few enablers:

- The NHS-academia relationships facilitated by the BRUs act as an enabler of translational research and innovation. They achieve this by bringing both parties closer together allowing them to build joint research strategies and highlight the growing status of research in the NHS. The BRCs have also facilitated improved cooperation and collaboration between academia, the NHS and industry. Highlighting the value that industry can bring, especially regarding delivering innovations to the market.
- It was felt that BRCs acted as the driving force for applications for AHSC status, setting a blueprint for clinical-academic partnerships.
- BRCs also functioned to raise the awareness of translational research amongst the general public and endeavoured to involve patient groups when developing research priorities.
- In a few BRCs a more interdisciplinary translational research agenda was beginning to form, with relationships being forged outside of the traditional medical faculties in departments such as physics, engineering and chemistry.
- The BRCs also enabled the development of physical infrastructure for clinical-academic partners which was felt to accelerate research translation. In some instances, BRC funding was used to leverage further funding from sources such as the MRC and Wellcome Trust.
- The attainment of new capabilities for translational research was also noted, in terms of improved recruitment, retention and development of staff members.

B.2.24 An assessment of the impact of the NHS Health Technology Assessment Programme (Hanney *et al.*, 2007)

The NHS Health Technology Assessment (HTA) programme (now part of the NIHR) produces information on the cost-effectiveness and impact of health technologies for those who use, manage and provide care in the NHS. The findings from the HTA programme directly influence decision-making bodies such as NICE to improve the quality of clinical practice in the NHS.

The authors (Wessex Institute of Health R&D, University of Southampton), commissioned by the National Coordinating Centre for Health Technology Assessment (NCHTA), conducted a study to assess the impact of the first 10 years of the NHS HTA programme from its inception. Methodology included analysis of NCCHTA documentation, a survey of lead researchers and 16 detailed case studies. Prior to this the group also completed a literature review to identify useful approaches to assess the impact of health research programmes. Impacts included knowledge production (HTA reports, publications), research benefits (capacity building, research targeting), informing policy (nature of the policy, degree of impact) and behaviour change (level and degree of impact).

The initial literature review confirmed the 'payback' model as the most appropriate and widely used method to evaluate programmes such as the HTA. The review also suggested that it was easier to quantify the impact of a programme on knowledge generation compared to policy, behaviour or health gain. The survey showed that the HTA programme had made significant impact via publications, dissemination, policy and behaviour. The Technology Assessment Reports (TARs) for NICE had the clearest route to policy impact with the formulation of NICE guidance. The case studies highlighted the importance of a 'receptor' body, such as NICE, the National Screening Committee, or the DHSC in terms of achieving policy impact.

<u>Australia</u>

B.2.25 What works best when establishing a translational cancer research centre (NSW Government and Cancer Institute NSW, 2015)

The Cancer Institute NSW (CINSW) is a state-wide government cancer control agency in New South Wales, Australia, established under the Cancer Institute (NSW) Act 2003 to lessen the impact of cancer. The Translational Cancer Research Centre (TCRC) programme was introduced by the CINSW in 2010-2011; it aims to facilitate more efficient and effective incorporation of research, clinical training, education and service delivery within a formal framework that links leading research centres with leading clinical centres. The key objective is to facilitate closer collaboration between researchers and clinicians to enhance research and achieve improved patient outcomes.

Grants were available for a maximum AUS 1.3 million per annum (approx. GBP 720k) to fund each TCRC for five years, including a minimum AUS 100,000 per annum (GBP 56,000) towards a collaborative biobanking fund. TCRUs were funded to a maximum of AUS 500,000 per annum (GBP 280k) for three years.

The programme funded four new Translational Cancer Research Centres (TCRCs) and three new Translational Cancer Research Units (TCRUs), with latter converting to TCRCs in 2014.

The programme was reviewed in 2013-14 to examine local adaptations of the TCRC model, gather perspectives of the characteristics, mechanisms, processes and contexts which have facilitated a TCRC's success, and to identify the key characteristics and enablers of success for TCRCs. The methodology included a mixed methods approach consisting of a review of the literature and internal documents, interviews with key CINSW informants, and workshops and interviews with key stakeholders in each TCRC. A draft model was developed, grouping the possible factors influencing the success of the TCRCs into five domains: leadership, governance, research strategy, collaboration and capacity building for sustainability.

From the evidence collected the authors outlined 'what works best when establishing a TCRC':

- Leadership teams ought to include a range of disciplines and sectors across the network sites and be motivated to facilitate and champion the benefits of translational research to institutional partners.
- Governance structure and approach should be flexible to allow for shifts in research focus over time and agile in order to respond to opportunities as and when they arise. Regular evaluation and documentation of the effectiveness of TCRC facilitated interventions should occur in order to develop an audit trail. The governance structure should also include people affected by cancer to inform research priorities in a more holistic manner. Fundamentally the approach and structure should build a culture of innovation and support open transparent and continuous communication.
- Research strategy should work backwards from defined patient outcomes, rather than forwards
 from the requirements of the institution. The research workforce should have access to education
 and training in translational research skills to maximise impact. This could be facilitated by
 communication with other TCRCs to coordinate access to training programmes offered across the
 network and to reduce duplication of effort. TCRCs should also aim to support projects that focus
 on local needs within a local context.
- Collaborative efforts should focus on understanding the workplace culture within the member organisations to acknowledge diversity and develop metrics accordingly. Policy incentives should promote a non-competitive culture that focusses on collaboration and encourages trans-disciplinary collaborations. TCRCs should aim to develop methods for information exchange that attract researchers to the TCRC network.
- Capacity-building for sustainability should prioritise the funding of programmes that are already embedded in established institutions such as universities and hospitals. Investment in education programmes from undergraduate to post-doctoral studies should be prioritised across a range of disciplines relevant to translational research. TCRCs should endeavour to find diverse partners and donors, including businesses and IT specialists.

B.2.26 Does health intervention research have real world policy and practice impacts: testing a new impact assessment tool (Cohen *et al.*, 2015)

The authors (the School of Public Health, University of Sydney) proposed an expanded 'impact assessment' framework to measure demonstrable public benefit and real-world policy and practice impacts of health intervention research studies that have already been completed.

They combined and adapted the Payback and Canadian frameworks to produce a conceptual model. They grouped outcomes into four levels of impact that might arise from intervention research: i) scholarly outputs (publications, citations, new research funding, hypothesis, capacity building, journal impact factor; ii) translational outputs (plain language summaries, media engagement, formal knowledge exchange processes, lobbying, intervention ready for implementation); iii) policy or practice impacts (changes to practice, services, policy, commercialisation); iv) long-term population outputs (behaviour change, health outcomes, social outcomes, economic outcomes). To note the current study only assessed policy and practice impacts.

The final sample of included studies were those that had completed two surveys and an interview. The data collected from these studies was then triangulated with additional information collected from document analysis to develop case studies. The case studies were scored by an expert panel across four impact dimensions: corroboration; attribution; reach; and importance.

The authors found that 38% of the cases included within the final sample had policy and practice impacts. They found that although the tool facilitated a robust criterion-based assessment of impacts, it was not always possible to corroborate the impacts evidenced by document review with the impacts reported by chief investigators.

B.2.27 Returns on NHMRC funded Research and Development – Australian Society for Medical Research (Deloitte, 2011)

The National Health and Medical Research Council (NHMRC) is Australia's body for supporting health and medical research, with responsibility for developing health advice for the public, health professionals and governments.

The authors Deloitte Access Economics were commissioned by the Australian Society for Medical Research to conduct an economic evaluation of the benefits to Australian society as a result of NHMRC's contribution to health and medical research. They achieved this by estimating wellbeing gains for a group of diseases which comprise 40% of the total burden of disease in Australia. These diseases included cardiovascular disease (CVD), cancer, sudden infant death syndrome (SIDS), asthma and muscular dystrophy (MD). To note the NHMRC funds a broad range of health and medical research, not limited to translational research.

The study specifically estimates the impacts of NHMRC funded R&D for this group of diseases between 2000 and 2010, on projected gains in health system expenditures, productivity gains and commercial returns for each of the diseases in the years 2040-2050.

The outcomes measured were:

- "the net benefit (in \$ million) the sum of the discounted benefits minus the cost of the NHMRC expenditure streams;
- "the benefit/cost (B/C) ration benefits divided by costs; and
- "the ROI the B/C ratio minus one, expressed as a percentage.

From their calculations the authors estimated the following economic outcomes:

Gains in wellbeing

R&D funded by the NHMRC between 2000 and 2010 was estimated to return a benefit between the years 2040 and 2050 of approx. AUD \$4 billion for CVD, \$2 billion for cancer, \$2 million for SIDS, \$60 million for asthma, -\$0.3 million for muscular dystrophy (MD). (With regard to MD, this was not
interpreted as a lack of effectiveness in R&D but as a lack of investment to reduce the growth in burden of disease for this specific condition.)

Gains to the health system

The total value of discounted health system costs averted between 2040 and 2050 was calculated as approx. AUD \$530 million for CVD, \$162 million for cancer, \$872 for SIDS, \$6 million for asthma, and - \$24,525 for MD. (Again, regarding muscular dystrophy, the negative value was not interpreted as R&D leading to increasing costs, but rather a lack of enough investment to avert growing health care costs.)

Productivity gains

Estimates of the indirect costs avoided as a result of improved wellbeing owed to NHMRC funded R&D were calculated from previous Deloitte Access Economics cost of illness studies. The total projected value of discounted indirect costs averted by NHMRC R&D between 2040 and 2050 were calculated as approx. AUS \$402 million for CVD, \$236 million for cancer, \$0.1 million for SIDS, \$42 million for asthma, and -\$0.7 million for MD. The predominant source of averted indirect costs was in productivity gains via the avoidance of premature mortality, in addition to the increase in number of people employed and reduced levels of absenteeism associated with the avoidance of morbidity.

Commercial returns

The estimated commercialisation value for NHRMC funded R&D between 2000 and 2010 was approx. AUS \$622 million for CVD, \$831 million for cancer, \$4 million for SIDS, \$113 million for asthma, and \$20 million for MD.

The **total net benefit** derived from NHMRC funded R&D over the period 2000 to 2010 was estimated as approx. \$4.39 billion for CVD; \$1.96 billion for cancer; \$0.7 million for SIDS; and \$35.4 million for MD. A net loss of \$8.45 million was estimated for MD.

Based on these approximations the authors concluded that NHMRC funded R&D in the areas specified were estimated to avert a substantial proportion of the projected increases in Australia's health related expenses between 2040 and 2050. However, MD showed a net loss, with future burden of disease and associated health costs exceeding the investment into MD R&D. The implication of this was not that R&D was ineffective but rather that the level of R&D to date had not been of enough magnitude to reduce the projected increases in disability associated with the disease.

B.2.28 Evaluation of the impact of National Breast Cancer Foundation-funded research (Donovan *et al.*, 2014)

Australia's National Breast Cancer Foundation (NBCF) is a charity which offers a range of innovative programmes for women facing breast cancer, including a National Mammography programme and Breast Health Awareness education programme. In addition, the foundation provides funding for targeted breast cancer research.

The authors (Health Economics Research Group, Brunel University UK) conducted an evaluation of the returns from research funded by NBCF. The primary purpose of the evaluation was to independently and objectively measure the benefit of NBCF investments in research, in order that these findings could be reported back to supporters. In addition, the evaluation had the aim of guiding future investments strategies based on lessons learnt.

The evaluation covered all NBCF funded research programmes since its establishment in 1994. The main outcomes measured were the impact of NBCF funded research on knowledge production, the research system, to what extent it informed policy, product development and the broader health and economic benefits.

The methods employed a Payback Framework approach and included a review of the existing documentation available from NBCF, a survey of Chief Investigators from selected project grants and fellowships and 16 mini-case studies of showing high impact research.

The main findings of the evaluation were as follows:

- 46% of survey respondents reported career progression, including the obtainment of 121 PhDs.
- 66% of grants produced tools that built capacity across the research system.
- Research teams leveraged an additional \$1.40 for every dollar invested.
- Of all grants awarded, 15 applied and 1 basic grant impacted on policy.
- 10 basic and 4 applied grants led to the development of drugs, prognostic tools or diagnostic technologies.
- 20 applied and 2 basic grants led to changes in practice and behaviour of health care staff, consumers and the public.

The evaluation authors concluded that the NBCF's strategy to invest in a varied portfolio of research areas encouraged a broad range of impacts. Regarding basic research, the impacts tended to focus on knowledge production and drug development; while applied research generated greater impacts within the other Payback categories. It was also concluded that the funding of shared infrastructure stimulated impact across the research system.

Hong Kong

B.2.29 A systematic evaluation of payback of publicly funded health and health services research in Hong Kong (Kwan *et al.*, 2007)

The Health and Health Services Research Fund (HHSRF) functions to support research relating to health and health services in Hong Kong. The aim of the evaluation was to explore factors relating to the translation of research findings to changes in health policy. The authors conducted a survey of principal investigators who had completed HHSRF funded projects. They based their survey questionnaire on the 'payback' evaluation framework questionnaire developed by the Health Economics Research Group at Brunel University which covers six outcome areas: i) knowledge production, ii) use of research in the research system, iii) use of research project findings in health system policy/decision making, iv) application of the research findings through changed behaviour, v) factors influencing the utilisation of research, and vi) health/health service/economic benefits.

Principal investigators (PIs) reported publications in 86.5% of projects, career advancement in 34.3%, and use of results in policy making in 35.4%. The use in policy making was mainly through clinical guidance, treatment protocols and Cochrane reviews. However, a number led to PI involvement in advisory committees related to health policy. In addition, there was evidence of health service benefit in 42.1% of projects which included cost reduction via the implementation of cost-effective treatment pathways and increased revenue through sales of IP. The authors also conducted a multivariable analysis to conclude that PI participation in policy committees and interaction with potential end users were independently and significantly associated with reported health and health service benefit (ORparticipation = 2.86, 95% CI 1.28-6.40; ORinteraction = 2.03, 95% CI 1.05-3.91).