

# Bridging the preclinical-clinical boundary

**Summary report of a joint workshop  
held on 9 March 2018 by the Academy  
of Medical Sciences and the Association  
of the British Pharmaceutical Industry**

### **The Academy of Medical Sciences**

The Academy of Medical Sciences is the independent body in the UK representing the diversity of medical science. Our mission is to promote medical science and its translation into benefits for society. The Academy's elected Fellows are the United Kingdom's leading medical scientists from hospitals, academia, industry and the public service. We work with them to promote excellence, influence policy to improve health and wealth, nurture the next generation of medical researchers, link academia, industry and the NHS, seize international opportunities and encourage dialogue about the medical sciences.

### **The Academy of Medical Sciences' FORUM**

The Academy's FORUM was established in 2003 to recognise the role of industry in medical research, and to catalyse connections across industry, academia and the NHS. Since then, a range of FORUM activities and events have brought together researchers, research funders and research users from across academia, industry, government, and the charity, healthcare and regulatory sectors. The FORUM network helps address our strategic challenge 'To harness our expertise and convening power to tackle the biggest scientific and health challenges and opportunities facing our society' as set in our Strategy 2017-21. We are grateful for the support provided by the members and are keen to encourage more organisations to take part. If you would like further information on the FORUM or becoming a member, please contact [forum@acmedsci.ac.uk](mailto:forum@acmedsci.ac.uk).

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The ABPI represents innovative research-based biopharmaceutical companies, large, medium and small, leading an exciting new era of biosciences in the UK. Our industry, a major contributor to the economy of the UK, brings life-saving and life-enhancing medicines to patients. We represent companies, which supply more than 80 per cent of all branded medicines used by the NHS, and who research and develop the majority of the current medicines pipeline, ensuring that the UK remains at the forefront of helping patients prevent and overcome diseases. Globally, our industry is researching and developing more than 7,000 new medicines. The ABPI is recognised by government as the industry body negotiating on behalf of the branded pharmaceutical industry for statutory consultation requirements including the pricing scheme for medicines in the UK.

Opinions expressed in this report do not necessarily represent the views of all participants at the event, the Academy of Medical Sciences or its Fellows or the Association of the British Pharmaceutical Industry.

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# Executive Summary

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**The UK has a world-leading research ecosystem for medicines discovery research, which is supported by a multitude of translational infrastructure and targeted funding streams for early-stage clinical research. However, in order to maintain and improve upon this excellence, we need to embrace new models that can improve the translation of research. A key point along the translational pathway is the preclinical-clinical boundary, where innovative research models are likely to have significant impact on improving the efficiency and success of medicines development programmes.**

On 9 March 2018, the Academy of Medical Sciences and the Association of the British Pharmaceutical Industry held a FORUM workshop to answer: 'How can we ensure that the UK remains at the forefront of discovering and developing medicines?' in the context of improving the environment surrounding the preclinical-clinical boundary. Participants focused on four key pillars of translational science and experimental medicine: an interdisciplinary workforce that spans across sectors; research infrastructure that supports collaboration and knowledge exchange; agile and flexible regulatory processes; and new technologies that provide opportunities to enhance preclinical and early clinical research. The key themes of discussion that emerged from the workshop were:

- **The importance of adopting a team science model of interdisciplinary, cross-sector working** to reflect the breadth of skills and disciplines needed for translational research. This may require different incentives and ways to reward 'success', as well as redefining career pathways.
- Ensuring **identification of emerging and future skills gaps** so that appropriate training can be put in place to address these issues. Emerging skill gaps discussed included bioinformatics, statistics, clinical pharmacology and pharmaceutical science.
- The need **to better understand and recognise, and in some cases overcome, cultural differences across sectors** (e.g. NHS, academia and industry) to maximise collaborative opportunities. This could be done through early engagement and outreach, as well as fostering a better appreciation of the respective cultures and differing priorities across sectors. This includes **the value of increasing permeability across sectors** to allow exposure to different sectors and development of new skills.
- **Instilling a research culture into clinical training and the NHS** by embedding research skills and awareness into early medical training and establishing appropriate incentives in the wider healthcare system.
- **Making the best use of the UK's existing research infrastructure** through maximising access to infrastructure. This includes using 'front door' organisations such as university translational research offices and cluster organisations, to help signpost research sponsors to the right expertise and promote the UK's research strengths internationally.

- The potential **value of new preclinical and experimental medicine models** for de-risking research and/or accelerating development programmes. This includes new scientific technologies such as human-based microphysiological systems and medical imaging, as well as adaptive trial designs and new sources of evidence.
- The need for new models to be underpinned by **a proportionate and flexible regulatory framework** that encourages innovation in experimental medicine and helps to retain the UK's status as a leading place to conduct clinical trials.
- The **role of open innovation and pre-competitive collaborations across sectors** for exploring fundamental science and supporting discovery by better informing target selection and validation.
- Targeting **funding to support the scale-up (and proof-of-concept) of early clinical research is needed** to encourage further funding from venture capitalists and industry.

# Introduction

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**The preclinical-clinical boundary is a key checkpoint in the translational pathway for research. It refers to the point at which preclinical evidence is considered sufficient to merit the move to first-in-human clinical studies. This represents a significant escalation in both resourcing and time, with a high risk of failure, and there is particularly high risk and attrition in Phase I and II trials primarily due to issues with efficacy and/or safety. Therefore there is a drive to ensure that the evidence base for progression into clinical studies is as robust and predictive as possible to maximise the chances of success and minimise risk of failure.**

Successful progression into clinical research can be maximised through more effective 'two way' evidence exchange across the boundary. For example, supporting translation by ensuring that robust evidence from preclinical models closely shapes the design of clinical studies such as dose selection, or by using more predictive preclinical experimental models. In reverse, this means ensuring that evidence from clinical research 'in man', such as data on populations or drug interactions, is effectively fed back into preclinical research to improve aspects such as initial target selection and validation, evidence of efficacy and identification of biomarkers. Underpinning this two-way evidence exchange is the skilled workforce and research infrastructure that supports translational research. Historically, preclinical and clinical research were often conducted in relative isolation to one another, in physically separate locations and by staff that may have had only limited interactions with their counterparts and a different skill set.<sup>1</sup> It has now been recognised that a more integrated, collaborative model of preclinical and clinical research can deliver significant value, with integration in terms of location, disciplines and sectors, scientific evidence generation and funding models.

Therefore on 9 March 2018, the Academy of Medical Sciences and the Association of the British Pharmaceutical Industry held a workshop to examine how the UK can better bridge the preclinical-clinical boundary as part of this new model of translational research, and so remain at the forefront of discovering and developing new medicines. The meeting looked to identify challenges and remaining gaps, as well as where there is opportunity for greater integration of preclinical and clinical science, and the vision for the future of translational research in the UK. Professor Geraint Rees FMedSci, Dean of Life Sciences, University College London (UCL) and Co-chair of the workshop, opened by describing the landscape for research in the UK. He highlighted the significant progress that investment from Government, charities, universities

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<sup>1</sup> Department for Business, Innovation & Skills (2011). *Strategy for UK Life Sciences*. [https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment\\_data/file/32457/11-1429-strategy-for-uk-life-sciences.pdf](https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/32457/11-1429-strategy-for-uk-life-sciences.pdf)

and industry has fuelled in developing a translational pipeline of treatments that will benefit patients. However, he also highlighted the broader challenges that threaten to stall this progress such as the uncertainty of Brexit and its implications for funding and regulatory alignment. Professor Rees noted that exploring ways for sectors to come together to collectively address and overcome some of the ongoing challenges is vital to ensuring that the UK's research base remains a world leader in producing effective treatments.

# The challenges and opportunities of translational research

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Professor Paul-Peter Tak FMedSci, Chief Immunology Officer and Senior Vice President R&D Pipeline, GlaxoSmithKline (GSK) introduced some of the key issues facing translational research at the preclinical and early clinical phases of medicines development. He noted that the UK has a powerful ecosystem for drug discovery research and so it is crucial to maintain this in the face of challenging circumstances such as Brexit.

A key challenge is the attrition of projects throughout clinical development. Given the large costs of later stage trials such as Phases IIb and III, it is vital to reduce attrition through improving target selection and validation and predicting failures earlier. Professor Tak described the recognition in industry that this cannot occur without collaboration with the wider research environment and to this end, GSK developed Open Targets in collaboration with the Sanger Institute and European Bioinformatics Institute.<sup>2</sup> This platform aims to share knowledge and expertise to better identify and prioritise promising therapeutic targets. By genetically validating targets, it looks to increase the success rates of programmes with both patient and economic benefit. Professor Tak also described the need for a strong focus on the quality of a molecule based on its physicochemical properties, and the value of identifying the right early clinical studies, especially in experimental medicine, that can better inform late stage development.

As the majority of clinical studies fail for reasons of efficacy and safety, experimental medicine can provide the early evidence to support decisions on whether to proceed with further trials. Experimental medicine studies aim to address scientific questions beyond the safety and tolerability questions that Phase I trials typically entail, such as the effects on biomarkers, fundamental biology questions and the feasibility of novel trial designs. Professor Tak emphasised that such studies require close collaboration of industry with academia and the NHS, who often hold the expertise in biological pathways and physiology.

Finally, he stressed the importance of increasing clinician and patient participation in experimental medicine. Part of the challenge of this is getting buy-in from the clinicians to recruit patients. With this in mind, transparency for both the clinician and the participant is vital, especially in the case of experimental medicine studies, where there may not be an obvious benefit to the patient of taking part in a trial, but instead a wider societal benefit can result from a greater scientific understanding.

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<sup>2</sup> [www.targetvalidation.org/](http://www.targetvalidation.org/)

# The workforce of the future

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## Team science

Research that bridges the preclinical and clinical spheres of discovery and development involves multidisciplinary teams, requiring many different skills and sector perspectives to identify and seize opportunities and overcome challenges. This 'team science' approach recognises that many scientific projects are enhanced or accelerated through interdisciplinary collaboration, as outlined in the Academy's 2016 report.<sup>3</sup> In particular, the unique teams at the translational interface were termed 'early development teams' that reach across the breadth of skills from basic scientists, project leads and regulatory experts to clinicians and statisticians. This reflects the many facets of drug development such as target selection and validation, safety, exposure, statistical significance and commercial opportunity. In addition, it was noted that contract research organisations (CROs) are increasingly active partners in this team science and should not be viewed as contractors for commissioned research.

However, participants noted that differing incentive and reward and career structures across academia, industry and the NHS can present a barrier to team science. Projects with large, multi-disciplinary teams from different sectors are unlikely to align with the traditional academic model of success – such as first authorship on academic papers – and so a broader view of impact is needed beyond these criteria. For example, progression of a therapy to the next stage of clinical development could be seen as equally successful as publication in a high impact journal. Similarly, industry could encourage greater openness in sharing data and high-quality publications with researchers and patients at the earliest opportunity. If such mutual recognition of success can be achieved, then researchers would have more confidence to move between sectors to expand experience and skill sets. It was remarked that some funding bodies still use authorship of academic papers as a key metric for assessing quality of an application, which may deter collaborations without such outputs.

## Building interdisciplinary skill sets

Participants noted that there are a range of skillsets common to industry that are not well established in academia or the NHS, such as medicinal chemistry, drug metabolism and pharmacokinetics, safety evaluation (toxicology) and pharmaceutical sciences. Collaboration between academia and industry (including contract research organisations and the wider industrial sector) can allow academia to benefit from these skills but there is also a case for harnessing them within academia itself to enhance drug discovery programmes. In addition, the UK clinical workforce lacks some capabilities such as experimental medicine clinicians and nurses. Horizon scanning for such potential future gaps is key; for example there may be a lack of clinical academics in rare disease areas to meet demand if the number of trials in these diseases rises significantly.

Participants also noted specific skills gaps with relevance across all sectors including clinical pharmacology, bioinformatics and data science. These may be set to widen as technological

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<sup>3</sup> Academy of Medical Sciences (2016). *Improving recognition of team science contributions in biomedical research careers*. <https://acmedsci.ac.uk/file-download/6924621>

approaches to medicines development change and statisticians and bioinformaticians become key to developing the methodologies for using early data and preclinical models. It was proposed that training for medical students could include informatics and clinical pharmacology. As well as exposing medical students to a diversity of skills, it was felt that clinical academic training programmes could become more widespread in medical training to instil a research culture in the clinical community from the outset.

There are several programmes that are beginning to address these skills gaps such as the Clinical Pharmacology Skills Alliance, set up by the ABPI, British Pharmacological Society, Faculty of Pharmaceutical Medicine and Health Education England, that aims to support the long-term sustainability of the clinical pharmacology skills pipeline. UK Research and Innovation (UKRI) is also now funding data science studentships.

## Case study: The Francis Crick Institute

Dr Veronique Birault, Head of Translation, The Francis Crick Institute, described how the Institute is pioneering a new model for interdisciplinary translational research, linking fundamental biology with experimental medicine to accelerate the development of better treatments, diagnostics and preventative measures of disease. The model at the Crick Institute reflects the importance of overcoming boundaries between disciplines and organisations, and aims to create the next generation of scientific leaders through recruiting early to mid-career researchers and building their portfolio of experiences and skills.

The Institute has three pillars to its strategy for accelerating translational research. The first is clinical insight, which cements experimental medicine as a key source of evidence for basic and exploratory research. The second is '*close distance translation*', which shares insight across disciplines and across the translational pathway. This includes incorporating scientists from different disciplines into teams to generate new insights, and experts can then be embedded into a team to take a project further as necessary, such as entrepreneurs, industry scientists and translational advisers.

Integrated research is key within the Crick Institute and Dr Birault noted that working with industry requires agility that may not be present in a purely academic environment. She described how pre-competitive discovery projects can maximise the complementary skills of industry and academia and enable industry to explore early science to test new concepts. These projects also include a secondment programme to facilitate mobility of researchers across sectors. Finally, the third pillar for the innovation model at the Institute focuses on impact rather than short-term revenue, and a key measure of success for early science projects is either further industry commitment or a successful application for translational funding.

# Collaboration and mobility across sectors

Professor Tim Eisen, Head of Oncology (Translational Medicine Unit), AstraZeneca and Professor of Medical Oncology, University of Cambridge, outlined the value of collaboration across sectors and ways to improve cross-sector working. Although there have been incremental advances in the success of preclinical and clinical research, he described the significant failure of drugs at Phases I and II, and the opportunity for substantial improvements in demonstrating efficacy at Phase II. He advocated the importance of establishing a higher degree of confidence for progressing a drug into Phase II, and the need for different expertise and sectors in enabling this.

## Culture across sectors

Observing the cultural differences between academia, industry and the NHS, Professor Eisen noted the difference in how time and finances are valued; in industry, time is critical, which demands shorter timeframes despite increased costs, whereas academia often focuses on the most effective use of resources, which may increase time. A lack of appreciation of this fundamental difference can impede collaboration. In addition, Professor Eisen noted a potential 'credibility gap' in how academia perceives science within industry, whereas partnerships need a mutual recognition of the complementary expertise across sectors. Approaches to talent development may differ in that industry often prioritises investment in workforce skills, which may not be as well recognised in academia or the NHS – in part, this may be because the NHS has to balance performance across all areas whilst industry can terminate projects or reprioritise where necessary. Finally, there is variation in approach to discovery science across sectors. Industry often prioritises finding and pursuing a promising avenue to allow rapid commercialisation, whilst academia often explores every scientific opportunity for a complete understanding of a biological system. Both of these approaches are important to fulfil sector goals and advance scientific understanding but may not always align when working in partnership, particularly if research questions, outcomes of interest and measures of success differ.

To address these cultural differences, AstraZeneca has developed criteria for assessing the value of academic collaborations. These include the alignment of objectives, value and cost to the company, quality of research, expected timelines and likelihood of success, quality and frequency of communication and credibility of collaborators. Such criteria could be generalised as guidance for organisations seeking collaborations with other sectors.

## Trust and reputation

Trust between sectors was cited as vital to the success of collaborative programmes. However, it was suggested that there may still be an underlying mistrust of industry in the public and other sectors. Patient advocacy groups could be key to building trust, alongside trainees who can foster a culture change around perceptions of industry. In addition, there may be stigma associated with academics who move into, or even collaborate with, industry and any such stigma needs to be broken down to enable the mutual respect required for truly collaborative research.

## Measuring the success of collaborations

The wider benefits of collaborations beyond that of the specific project include job creation, spin-outs, inward investment, licensing deals and more clinical trials. These metrics can be

measured to demonstrate the economic 'health' of a region, and cluster organisations such as MedCity are collecting this data for assessing the effectiveness of programmes that promote collaboration.<sup>4</sup>

## Permeability across sectors

Participants advocated the need to expose the workforce to different sectors to foster a better mutual recognition of the differences and expectations across sectors. Co-location of academia, industry and the NHS is also a key enabler of collaboration. Participants suggested that the lack of permeability between academia, industry and the NHS impedes the development of skilled researchers who can lead interdisciplinary teams. Part of this lack of permeability may be due to the cultural differences between sectors outlined above.

It was proposed that training schemes should incorporate exposure to different sectors by routinely offering secondments or placements. These encourage a diversity of experience and would foster greater collaboration between sectors beyond just that of the trainee. However, this necessitates further funding as although some initiatives do exist, they are often limited in scope and scale. For example, the Clinical Science Fellowships established between AstraZeneca and King's Health Partners enable academics in a variety of roles and career levels at the university to be seconded to AstraZeneca. It was suggested that such secondments are particularly important for clinical researchers and to enable them to take part in these schemes, a change to clinical contracts is required to provide the flexibility for these secondments, as well as anticipating the potential reduction in clinical capacity. Research experience or industry 'exposure' is also valuable early in the career pathway such as during medical training. This has been shown through successful initiatives such as joint training in clinical pharmacology and medical oncology carried out at Edinburgh (which included a placement in industry), and such practice could become more mainstream to include other disease areas and specialisms. There is also an opportunity for industry to engage with the General Medical Council and Royal Colleges to make the case for opportunities during medical training.

### Future priorities

Participants proposed the following as possible priorities for the future:

- Supporting the creation of multidisciplinary early development teams, by accommodating new reward and career structures that will promote an environment of team science; this may also look to consider how we develop 'impact' as a measure and driver for research.
- Identifying and addressing current and emerging key skills gaps, particularly statisticians, bioinformaticians, clinical pharmacologists and those with expertise in methodologies for data, preclinical models and novel trial design.
- Embedding research into medical training to create a research culture in the NHS and develop a new generation of clinical academics.

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<sup>4</sup> [www.medcityhq.com/](http://www.medcityhq.com/)

- Enhancing permeability across sectors by providing opportunities for secondments, placements and exposure across sectors to diversify skills and create an understanding of different ways of working across sectors.

# Infrastructure for research

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## Joining up UK infrastructure

### Access to research infrastructure

Sarah Haywood, Chief Executive Officer, MedCity described the range of infrastructure for translational research in the UK, and MedCity's role in supporting organisations to navigate this infrastructure and locate the right expertise across industry, academia and the NHS. The UK research infrastructure is rich and diverse, however, it is also complex and so can be challenging to understand, particularly for SMEs. For example, in the Golden Triangle alone there are over 3000 SMEs that may struggle to identify and access resources, as well as a plethora of academic and NHS organisations that may be difficult to navigate. Participants recognised the complexity in the current infrastructure and the role of the clusters in signposting organisations to available support. In addition, it was highlighted that SMEs are more likely to rely on collaborations to access necessary expertise, which may present less of a concern for large pharmaceutical companies who have the in-house expertise or the resources to commission research to contact research organisations. Therefore there may be a need for further support that particularly aids SMEs in finding the appropriate collaborations and research infrastructure.

As an example, Ms Haywood described how MedCity worked with the British Standards Institute and DigitalHealth London to explore the evidence base for digital health technologies to support companies in this field.<sup>5</sup> The project is looking at the evidence required to adopt and diffuse digital health technologies, and where the regulatory framework may need to evolve to allow such technologies to meet the necessary standards of evidence. It has also mapped the opportunities to support SMEs around adoption of digital technologies in the NHS and the cluster works closely with the Academic Health Science Networks (AHSNs) more broadly who support early engagement around adoption.

### Building on existing research infrastructure

Given the widespread support for the high-quality UK infrastructure for translational research, participants agreed on the need to continue building upon this to optimise the landscape for experimental medicine. Dr Jane Kinghorn, Director of the Translational Research Office (TRO), UCL, demonstrated how NHS infrastructure and new models of collaborative working can accelerate translational science. First, she discussed the essential role of the NIHR Biomedical Research Centres across the UK in linking NHS research hospitals to academic centres of excellence to drive experimental medicine and translation.

When considering the translational pathway, she highlighted the importance of not only considering 'forward' translation but also feeding clinical knowledge back into biological and scientific discovery. In addition, there are many activities that sit at the preclinical/clinical translational boundary that require a matrixed support team, including preclinical validation, Good Manufacturing Practice, Good Laboratory Practice safety testing, regulatory knowledge and clinical trial infrastructure design and management. The TRO at UCL provides an

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<sup>5</sup> MedCity, DigitalHealth London and the British Standards Institute (2017) *Digital Health Technology and Evidence*. [www.medcityhq.com/wp-content/uploads/2017/09/Digital-Health-Evidence-Report.pdf](http://www.medcityhq.com/wp-content/uploads/2017/09/Digital-Health-Evidence-Report.pdf)

important resource to support academics and their translational projects to navigate this vast amount of required activity that sits within the university and its NHS partners as well as in the different external sectors involved. The TRO has populated its team with industry experienced scientists to enable it to catalyse the links to all resources to help the principal investigators drive a project forward. Dr Kinghorn also described the wealth of translational funding available to catalyse academic preclinical and clinical research through organisations such as the MRC, Wellcome Trust and NIHR. This milestone funding enables the TRO to scope and support the translational pathway for projects, and provides support for bringing in necessary expertise such as appropriate regulatory and commercial advice as well as engaging with other partners such as CROs, contract manufacturing organisations (CMOs) and industry. The technology transfer office at UCL are a key partner of the TRO and the translational ecosystem within UCL. They have had significant success in securing UCL intellectual property, spinning out companies and securing the significant investment required for further translation.

## Case study: Access to AstraZeneca's open innovation screening platform

Dr Jane Kinghorn described AstraZeneca's open innovation screening platform as an example of academia-industry collaboration to advance preclinical studies.<sup>6</sup>

The platform provides academic access to a range of clinical compounds, preclinical research tools and potential therapeutic targets. The goal of accessing this platform, which at the UCL TRO was led by the drug discovery group, is to build a data package, which de-risks the development project to encourage substantial future investment from funders. This project brought together clinical expertise and knowledge around target selection and structural biology to build a hit-lead discovery strategy, assay development, attract seed funding and foster links to the wider drug discovery community. The ultimate outcome of these projects using the platform is to make academic drug discovery more robust and reproducible, to foster collaboration across the sectors, to develop new biological assays and lead compounds for drug discovery and ultimately to develop and commercialise promising projects.

### Piloting new infrastructure and scaling up

It was suggested that the devolved health systems, such as that in the Greater Manchester healthcare system, pose opportunities to pilot integrated schemes at a local level. Using devolved healthcare systems in this manner more widely could provide the flexibility to rapidly trial small, iterative improvements that may be too costly, slow or risky to enact more widely in the system. If such pilots are successful, schemes can be scaled up to drive change based on evidence and disseminate best practice across the system.

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<sup>6</sup> <https://openinnovation.astrazeneca.com/>

## Funding to bridge the gap

One participant highlighted that it is sometimes challenging for industry, especially smaller companies, to fund the studentships to create skilled, interdisciplinary researchers. UKRI has a formalised system for industry partners who wish to support doctoral training programmes. However, some participants felt that the doctoral training landscape can at times be difficult to navigate, even for a large pharmaceutical company, and that it is likely that this is an even greater challenge for SMEs.

Participants also highlighted the relative lack of venture capital in the UK compared to some other countries such as the USA. It was surmised that there were several reasons for this, such as the lack of a commercialisation culture in academia, gaps in funding for generating early clinical evidence to encourage private investment, investment community caution on the commercial potential of biomedical innovation and uncertainty about the willingness of the UK healthcare system to adopt new innovations.

## Improving patient recruitment for experimental medicine

Despite the UK's excellent clinical trials infrastructure, participants highlighted a recent decline in early phase trials. This was attributed, in part, to challenges around patient recruitment. Participants outlined the need to better utilise the patient population, who are often highly motivated and receptive to involvement in research. Engagement with patient groups could be key to improving trial enrolment, especially for experimental medicine studies which might not directly benefit the participant. It was also suggested that some hospitals and disease areas have better recruitment than others, suggesting that there is scope to improve recruitment through disseminating best practice throughout the NHS.

It was noted that the NIHR BioResource aims to build a database of potential research participants – characterised either genotypically, phenotypically or both – for rapid recruitment into clinical trials.<sup>7</sup> To date, it had recruited over 100,000 volunteers with rare diseases and they and their relatives and been used in over 100 experimental medicine studies, largely in academia. There is potential for further engagement with industry to capitalise on this valuable resource, however, this would need data governance issues to be overcome which stem from unwillingness for sharing data or patients by some centres.

## Streamlining trials infrastructure

It was felt that trial set-up in the UK is slow in some places, due to bureaucratic processes such as contract negotiation. It was highlighted that standardised contracts would accelerate this process and increase the attractiveness of the clinical trials environment. Participants felt that the recently updated Model Clinical Trials Agreement (mCTA) would help to support multi-site trials and streamline research by standardising contracts to conduct clinical trials across the devolved nations.<sup>8</sup>

# Innovative trials and regulation

## Novel trial designs to bridge preclinical and clinical research

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<sup>7</sup> <https://bioresource.nihr.ac.uk/>

<sup>8</sup> [www.hra.nhs.uk/about-us/news-updates/new-templates-published-streamline-commercially-sponsored-trials-set-/](http://www.hra.nhs.uk/about-us/news-updates/new-templates-published-streamline-commercially-sponsored-trials-set-/)

Innovative trial design is a rapidly emerging opportunity for the UK. In contrast to traditional trials with a fixed design throughout, innovative trials can be adapted during the trial to act on learning and maximise utility. This enables modifications such as removing or adding treatment arms, changing the balance of randomisation or altering statistical methodologies, without compromising validity. Professor Sallie Lamb FMedSci, Professor and Co-Director of the Oxford Clinical Trials Research Unit, University of Oxford, cited an example of a dose escalation trial looking at the effects of an anti-cancer drug compared with the drug in combination with radiotherapy. This used Bayesian modelling to calculate side effects that are typically not observed until 3-6 months after treatment. This was achieved by entering toxicity data from each clinical review into the model to identify early emergence of any side effects.<sup>9</sup> This allowed dose escalation to proceed more quickly and demonstrates the importance of a cross-disciplinary, skilled workforce such as integrating statisticians and trial methodologists into clinical research, which is a key consideration to enable implementation of new trial designs.

## Creating an agile regulatory system

Participants proposed that the regulatory and governance framework for translational research and early trials should be sufficiently flexible to allow the acceleration of discovery programmes whilst maintaining the quality and reliability of data and biomarkers. This includes allowing for novel trial designs. It was emphasised that regulation should be innovative rather than reactive and so a collaborative approach with regulators is needed to foster a clear understanding of the requirements around new evidence sources such as adaptive trials. In addition, implementing proportionate, flexible regulation may require investment in regulatory science to develop the appropriate tools and safeguards for an internationally competitive preclinical-clinical environment. It was suggested that such regulatory science would be valuable for determining potential opportunities for flexibility and the appropriateness of different regulatory standards for experimental medicine, where the intention of trials is not to diagnose or treat but to answer fundamental scientific questions.

The MHRA's Innovation Office enables researchers to engage with regulators earlier in the development process to better understand the regulatory infrastructure and opportunities and it was suggested that stakeholders need to be more proactive in using this tool. In addition, regulators need to be kept informed of technological developments that are likely to feature in licensing applications such as microphysiological systems (or 'organ on a chip', described later), so that there is an opportunity to discuss reliability and the evidence requirements for such technologies.

## Future priorities

Participants proposed the following as possible priorities for the future:

- More effective use of existing research infrastructure in the UK through facilitating access and better signposting, both nationally and internationally.

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<sup>9</sup> [www.hra.nhs.uk/planning-and-improving-research/application-summaries/research-summaries/vx-970-plus-standard-treatment-in-oesophageal-and-other-cancer-v10/](http://www.hra.nhs.uk/planning-and-improving-research/application-summaries/research-summaries/vx-970-plus-standard-treatment-in-oesophageal-and-other-cancer-v10/)

- Ensuring that regulatory frameworks remain facilitative and proportionate for accommodating innovative trial designs so that the UK remains internationally competitive for clinical research. For example, potentially reviewing the role of ICH-GCP in research.<sup>10</sup>
- Continuing to encourage early engagement and communication of stakeholders with regulators around adaptive and novel trial designs.
- Continued investment in early phase trial infrastructure and establishing mechanisms for enhancing and utilising such investment.
- Ensuring clarity around real vs. perceived barriers to research and myth-busting where necessary.
- Potential investment in regulatory science to ensure that the UK remains competitive in adaptive design and processes that accelerate study timelines.
- Developing internal dedicated support and governance to manage large, interdisciplinary projects, to take them from discovery science through to clinical development and commercialisation.
- Targeted funding for scale-up and commercialisation of promising early clinical research to encourage further private investment and industry investment.

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<sup>10</sup> Academy of Medical Sciences, Bill & Melinda Gates Foundation and Wellcome Trust (2018). *Exploring Good Clinical Practice guidance in clinical trials – meeting summary*. <https://acmedsci.ac.uk/file-download/76367131>

# Science and technology to bridge the boundary

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## Pre-competitive collaborations and open innovation

Pre-competitive collaborations – described as the sharing of knowledge, expertise and resources with collaborative partners without the burden of commercial sensitivities or interests – were highlighted as a significant tool for enhancing preclinical research and experimental medicine. These collaborations are especially suited to basic research on biological mechanisms that lead to better understanding of disease, pharmacology and target discovery. This can enable industry to de-risk projects whilst allowing academia access to new expertise and resources. In these collaborations, results, data and resources are shared across scientific collaborators with the understanding that improving the fundamental knowledge base can benefit the entire research community. Successful collaborations also build partnerships that can transition into commercial collaborations. Participants noted that such collaborations need to be initiated by understanding the mutual benefits to ensure buy-in from all partners, and that cultural barriers need to be overcome to achieve this success.

Open innovation programmes often go beyond pre-competitive collaboration to allow external access to data or resources without the demand to meet a specific outcome or strategic goal. In these cases, the organisation making its resources openly accessible may not directly benefit from others using them, but instead there is an understanding that allowing access can facilitate novel approaches that may otherwise go untested. If these novel approaches successfully provide insights there is then the possibility of a closer collaboration forming.

Whilst open innovation and pre-competitive agreements are highly valuable, it was noted that competitive programmes will continue to require confidentiality and intellectual property agreements. These can disincentivise collaboration and overcoming this may require demonstration of the value of collaboration to both parties.

### **Case study: EMINENT pre-competitive partnership**

Professor Caroline Savage FMedSci, VP and Head Experimental Medicine Unit, GlaxoSmithKline, described the Experimental Medicine Initiative to Explore New

Therapies (EMINENT) programme.<sup>11</sup> This is a collaboration between GSK, the MRC and five universities that brings academia together with industry and allows access to GSK's unlicensed molecules for the purpose of conducting experimental medicine studies around the mechanisms of inflammatory diseases.

EMINENT involves two project types. 'Pathway projects' are multicentre projects to conduct an experimental medicine study such as new indications for immunosuppressive medications. On the other hand, 'starter projects' are single centre projects that focus on developing evidence to support experimental medicine studies such as a mechanistic study of therapies for rheumatoid arthritis. Overall, the initiative will support the development of a cohort of excellence and leaders in experimental medicine with researchers who are experienced working across academia and industry.

## Technologies to enhance translation

### Using novel preclinical science to support translation

Dr Mick Fellows, Principal Scientist, AstraZeneca described the need for improved mechanistic and predictive models to reduce attrition in trials and accelerate development by offering insight into disease and effects of therapies. There are already a number of new preclinical technologies in development to support progression into clinical studies and they will become increasingly embedded in preclinical research. He used the example of MPS to demonstrate how these scientific advances can improve translation. MPS – or 'organ on a chip' – are 3D cell or tissue structures that mimic the complexities of tissues and organs. These include aspects such as a vascular system, extracellular matrix or immune cells, or mimic the physical environment through mechanical forces. The models allow greater understanding of tissue response before clinical studies and are intended to provide more relevance to the real world than a simple cell culture or assay.

For example, Dr Fellows described AstraZeneca's work in developing an MPS to explore the impact of insulin resistance in the liver on beta cells in the pancreas.<sup>12</sup> The system has been used to model both prediabetic and diabetic systems in a more relevant way than pancreatic or liver cells in isolation, and has been shown to replicate normal physiology. Such models have also been used to model pharmacokinetics and pharmacodynamics (PKPD) of a drug, potentially providing insight into the likelihood of drug interactions and contraindications prior to trials.<sup>13</sup> In the future, there may be potential for these models to supplement or even replace animal models. However, Dr Fellows highlighted that it is too early to know whether they could be used for toxicity screening to complement or supplant toxicity trials in humans, but they provide a useful tool at present for guiding decision-making around clinical studies.

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<sup>11</sup> [www.ucl.ac.uk/eminent-consortium](http://www.ucl.ac.uk/eminent-consortium)

<sup>12</sup> Bauer S, et al. (2017). *Functional coupling of human pancreatic islets and liver spheroids on-a-chip: towards a novel human ex vivo type 2 diabetes model*. *Scientific Reports* **7**, 14620.

<sup>13</sup> McAleer C, et al. (2018) (manuscript in preparation)

## Case study: Imaging technology to bridge the boundary

Professor David Edwards FMedSci, Professor of Paediatrics and Neonatal Medicine, King's College London, indicated the key role that medical imaging can play in translational research. He described how premature children often have brain development problems and there are few treatments available and no reliable animal models for detecting or predicting the developmental effects of premature birth. However, recent research has shown that risk of brain injury is associated with specific gene mutations.<sup>14</sup> This approach, known as 'genetic imaging', allows the identification of gene pathways that have significant association with brain injury in preterm infants.<sup>15</sup> Differences in the genetics of children with and without injury were compared to identify a number of signalling pathways key to the risk of brain injury. This was then further used to identify 47 genes as key risk factors, including a pathway that has presented a potential target for repurposing of a licensed drug.<sup>16, 17</sup>

Professor Edwards described this as a key example of how medical imaging techniques can be used in experimental medicine beyond just providing biomarkers. Utilising medical imaging in this way requires data scientists and clinical informaticians who can provide the bridge to biology and drug discovery programs, and the realisation of the potential of medical imaging for experimental medicine depends on the development of these expertise.

## Future priorities

Participants proposed the following as possible priorities for the future:

- Establishing further pre-competitive consortia and open innovation models to reduce drug development attrition (i.e. unsuccessful drug development projects) and 'de-risk' translational research through sharing of knowledge, skills and expertise to advance fundamental research.
- Embracing new technologies and approaches, including preclinical models such as organoids and microphysiological systems and clinical

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<sup>14</sup> Boardman JP, et al. (2014). *Common genetic variants and risk of brain injury after preterm birth*. *Paediatrics* **133(6)**, e1655.

<sup>15</sup> Krishnan ML, et al. (2016). *Possible relationship between common genetic variation and white matter development in a pilot study of preterm infants* *Brain Behav* **6(7)**, e00434.

<sup>16</sup> Krishnan ML, et al. *Proc Nat Acad Sci USA (in Press)*.

<sup>17</sup> Krishnan ML, et al. (2017). *Integrative genomics of microglia implicates DLG4 (PSD95) in the white matter development of preterm infants*. *Nature Communications* **8**, 428.

tools such as innovative imaging techniques and novel trial design, to enhance the evidence base at the preclinical-clinical boundary.

# Conclusion

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Dr Chris Powell, Vice President, Translational Medicine & Comparative Pathobiology, GlaxoSmithKline, co-chair of the workshop, concluded the workshop by highlighting that it was clear that the UK was outstanding in terms of drug discovery, translational and experimental medicine, and clinical trials. However, he stressed that improvements are necessary to maintain and build upon this excellence. Enhancing the attractiveness of the UK as a place to conduct clinical trials and experimental medicine should be a priority. This can be supported by ensuring an appropriate regulatory structure that encourages innovative approaches, filling essential skills gaps and targeting funding towards promising preclinical and early clinical research programmes to encourage scale up, translation and adoption.

He noted that the regulatory structure should accommodate novel trial designs and minimise the burden of setting up multi-site clinical trials. Building the skilled workforce will require investment in areas such as clinical pharmacology, statistics, bioinformatics, molecular pathology and pharmaceutical science. Targeted funding for promising projects to build the evidence base is important to attract further investment from venture capital and industry and this should also be a priority to capitalise on the strength of UK science.

Dr Powell also emphasised that to further capitalise on the UK's strengths, changes are needed to the traditional siloing of work between sectors. This could be achieved by encouraging movement of researchers between sectors, which would allow the next generation of research leaders to understand the cultural differences and requirements of different disciplines and sectors. In addition, further collaborations through team science, open innovation and pre-competitive collaborations can capitalise on the respective expertise of sectors to improve target selection and validation, and answer fundamental biological questions. Finally, such collaboration and permeability between sectors can be encouraged by reassessing the reward structures and career pathways for researchers in different sectors to recognise and incentivise the respective contributions of partners in interdisciplinary teams.

# Annex I - Agenda

Friday 9 March 2018, 09.30-17.00

Academy of Medical Sciences, 41 Portland Place, London, W1B 1QH

09.30-10.00	<b>Registration and refreshments</b>
10.00-10.05	<b>Welcome and introduction</b> Professor Geraint Rees FMedSci, Dean of Life Sciences, UCL
<b>Translation and integration across the preclinical-clinical boundary</b> <i>Chair: by Professor Geraint Rees FMedSci, Dean of Life Sciences, UCL</i>	
10.05-10.30	<b>The UK translational landscape for discovery and development</b> Professor Paul-Peter Tak FMedSci, Chief Immunology Officer and Senior Vice President R&D Pipeline, GSK
10.30-10.50	<b>1. Driving an integrated and skilled workforce</b> Professor Tim Eisen, Head of Oncology, Translational Medicine Unit, AstraZeneca and Professor of Medical Oncology, University of Cambridge
10.50-11.10	<b>Case study: building an integrated workforce and translational skills</b> Dr Veronique Birault, Head of Translation at the Francis Crick Institute
11.10-11.35	<b>Tea and coffee</b>
11.35-11.50	<b>2. Infrastructure to bridge the preclinical-clinical boundary</b> Sarah Haywood, Chief Executive Officer, MedCity
11.50-12.20	<b>Case study: BRC infrastructure for translation</b> Dr Jane Kinghorn, Director, Translational Research Office, UCL
12.20-13.00	<b>Lunch</b>
<b>Translation and integration across the preclinical-clinical boundary</b> <i>Chair: Dr Chris Powell, VP Translational Medicine &amp; Comparative Pathobiology, GSK</i>	
13.00-13.20	<b>3. Technological advances to support translation</b> Dr Mick Fellows, Principal Scientist New Modalities, Drug Safety and Metabolism, AstraZeneca
13.20-13.40	<b>Case study: new technologies to support discovery and development</b> Professor David Edwards FMedSci, Professor of Paediatrics and Neonatal Medicine, King's College London
13.40-14.00	<b>4. The regulatory and clinical research framework</b> Professor Sallie Lamb FMedSci, Professor and Co-Director of the Oxford Clinical Trials Research Unit, University of Oxford
14.00-14.20	<b>Case study: creating an agile, flexible framework for clinical research</b> Professor Caroline Savage FMedSci, VP and Head Experimental Medicine, GSK
14.20-14.40	<b>Tea and coffee</b>
<b>What is needed to ensure that the UK remains a leader in discovery and development of innovative treatments?</b>	
14.40-14.45	<b>Introduction to afternoon session</b> Dr Chris Powell, VP Translational Medicine & Comparative Pathobiology, GSK
14.45-16.00	<b>Break-out session: How can we ensure we remain at the forefront of discovering and developing medicines?</b>
16.00-16.55	<b>Feedback and panel discussion: Next steps for the UK</b> Panellists: <ol style="list-style-type: none"> <li>1. Dr Anne-Marie Coriat, Head of Research Careers, Wellcome Trust</li> <li>2. Professor Alan Melcher, Team Leader, Translational Immunotherapy, Institute of Cancer Research</li> <li>3. Dr Richard Butt, Chief Executive Officer, Apollo Therapeutics</li> <li>4. Henry Stemplewski, Expert Non-clinical Assessor, MHRA</li> </ol>

	5. Dr Lisa Cotterill, Director for the NIHR Trainees Coordinating Centre, NIHR
16.55-17.00	<b>Summary</b> Dr Chris Powell, VP Translational Medicine & Comparative Pathobiology, GSK

# Annex II - Participant list

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## Co-Chairs

**Dr Christopher Powell**, Vice President, Translational Medicine & Comparative Pathobiology, GlaxoSmithKline

**Professor Geraint Rees FMedSci**, Dean of the UCL Faculty of Life Sciences, University College London

## Speakers and panellists

**Dr Veronique Birault**, Head of Translation, Francis Crick Institute

**Dr Richard Butt**, Chief Executive Officer, Apollo Therapeutics

**Dr Anne-Marie Coriat**, Head of Research Careers, Wellcome Trust

**Dr Lisa Cotterill**, Director for the NIHR Trainees Coordinating Centre, National Institute for Health Research

**Professor David Edwards FMedSci**, Director of the Centre for the Developing Brain and Professor of Paediatrics and Neonatal Medicine, King's College London

**Professor Timothy Eisen**, Professor of Medical Oncology, University of Cambridge

**Dr Mick Fellows**, Principal Scientist New Modalities, Drug Safety and Metabolism, AstraZeneca

**Ms Sarah Haywood**, Chief Executive Officer, MedCity

**Dr Jane Kinghorn**, Director, Translational Research Office, University College London

**Professor Sallie Lamb FMedSci**, Professor and Co-Director of the Oxford Clinical Trials Research Unit, University of Oxford

**Professor Alan Melcher**, Team Leader, Translational Immunotherapy, Institute of Cancer Research

**Professor Caroline Savage FMedSci**, VP and Head Experimental Medicine Unit, GlaxoSmithKline

**Mr Henry Stemplewski**, Expert Non-clinical Assessor, Medicines and Healthcare products Regulatory Agency

**Professor Paul-Peter Tak FMedSci**, Chief Immunology Officer and Senior Vice President R&D Pipeline, GlaxoSmithKline

## Participants

**Dr Dave Allen**, Chief Chemist and Head of Respiratory R&D, GlaxoSmithKline

**Ms Elizabeth Allen**, Vice President, Early Clinical Development, IQVIA

**Professor Deborah Ashby OBE FMedSci**, Professor of Medical Statistics and Clinical Trials, Co-Director of Clinical Trials Unit, Imperial College London

**Dr Sue Bailey**, Disease Area Head, Oncology, Bristol-Myers Squibb

**Dr Jacqueline Barry**, Chief Clinical Officer, Cell and Gene Therapy Catapult

**Professor John Bradley**, Director, NIHR Cambridge BRC

**Professor Ian Bruce**, Director, NIHR Manchester BRC

**Dr Kevin Cox**, Chief Executive Officer, Hammersmith Medicines Research

**Professor Caroline Dive FMedSci**, Professor of Cancer Pharmacology and Deputy Director, Cancer Research UK Manchester Institute, University of Manchester

**Professor Jeff Evans**, Professor of Translational Cancer Research, University of Glasgow

**Mr Richard Hebdon**, Senior Innovation Lead for Health Technologies, Innovate UK

**Dr Nicola Heron**, Head of Collaborative R&D, Medicines Discovery Catapult

**Dr Meena Jain**, Director of Clinical Development, MedImmune

**Dr Louise Jones**, Head of Translational Research, Medical Research Council

**Professor Sir Peng Tee Khaw FMedSci**, Director, NIHR Moorfields BRC

**Ms Louise Knowles**, Head of Research Policy: NIHR Infrastructure and Growth, Science, Research and Evidence Directorate, Department of Health and Social Care

**Ms Emma Lowe**, Research Policy Senior Manager – Industry Relations & Growth, Science, Research and Evidence Directorate, Department of Health and Social Care

**Professor Sara Marshall**, Head of Clinical and Physiological Sciences, Wellcome Trust

**Dr Fiona Marshall FMedSci**, VP Head of Discovery UK, MSD

**Mr Robert Meadowcroft**, Chief Executive, Muscular Dystrophy UK

**Dr Cesar Mendoza Martinez**, Newton International Fellow, University of Edinburgh

**Dr Paul Mercer**, Principal Research Associate & EMINENT Programme Manager, University College London

**Dr Declan Mulkeen**, Director of Strategy, Medical Research Council

**Dr Alex Pemberton**, Head of Therapeutic Discovery Funding, Cancer Research UK

**Dr Peter Phillips**, Head of Clinical Immuno-Inflammation in Translational Medicine, UCB

**Professor John Pickard FMedSci**, Director, NIHR Brain Injury Healthcare Technology Co-operative

**Dr Sarah Rudkin**, Head of Clinical Studies and Experimental Medicine, Arthritis Research UK

**Ms Annette Rusling**, Senior Policy Advisor, Office for Life Sciences

**Professor Avan Sayer**, Director, NIHR Newcastle BRC

**Dr Christian Schneider**, Director, National Institute for Biological Standards and Control (NIBSC)

**Dr Malcolm Skingle CBE**, Director of Academic Liaison, GlaxoSmithKline

**Professor Trevor Smart FMedSci**, Schild Professor of Pharmacology, University College London

**Professor Mark Thursz**, Interim Director, NIHR Imperial BRC

**Dr Estee Torok**, Senior Research Associate and Honorary Consultant, University of Cambridge

**Dr Frank Wiegand**, Medical Director UK & Ireland, Janssen

**Dr Matthew Wintle**, Managing Director, Zestmedica

#### **Academy and ABPI staff**

**Ms Ola Bykowska**, Policy Intern, Academy of Medical Sciences

**Ms Liberty Dixon**, FORUM Policy Manager, Academy of Medical Sciences

**Dr Ali Hansford**, Head of Science Policy, Association of the British Pharmaceutical Industry

**Ms Florence Mowlem**, Policy Intern, Academy of Medical Sciences

**Dr Sheuli Porkess**, Interim Executive Director, Research, Medical & Innovation, Association of the British Pharmaceutical Industry

**Dr James Squires**, Policy Officer, Academy of Medical Sciences

**Dr Emma St Clair Pearce**, Research and Collaboration Policy Officer, Association of the British Pharmaceutical Industry

**Mr Mike Thompson**, Chief Executive, Association of the British Pharmaceutical Industry



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