Accelerating the Growth of Human Relevant Life Sciences in the United Kingdom

A White Paper by the Alliance for Human Relevant Science

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Executive summary

Significant advances in science and technology have provided a variety of new research methods that are based on the use of human tissues and cells. These are increasingly being used by researchers to gain unique and valuable insights into human biology and disease and to develop new treatments. With numerous human diseases remaining poorly understood and lacking effective treatments, urgent action is needed to develop and implement these new human relevant methods. Animal models are limited in their ability to translate to humans – of the drugs that have proved promising in animal trials, 86-90% fail in human trials. It is now time to invest in methods that focus on human biology, to transform our ability to understand human disease and develop new medicines.

To accelerate the development and uptake of human relevant methods and technologies in the UK, this white paper calls for:

- Government-backed infrastructure to provide practical support in transitioning towards human relevant approaches
- Strategic funding to incentivise the development and usage of human relevant methods and technologies
- Improved education at all levels on the potential of human relevant technologies, as well as skills training in their use
- Drawing together of multidisciplinary expertise
- Incorporation of human relevant methods into regulatory guidelines on medicines development

Achieving these objectives will require support from the UK government, universities, pharmaceutical companies and regulatory agencies. The outcome will directly benefit the UK science base, help improve human health and wellbeing, and enhance the efficiency and profitability of industries which make vital contributions to the UK economy.

Key Terms

Adverse drug reaction (ADR): a harmful reaction caused by administration of a pharmaceutical drug

Clinical trials: trials to evaluate the effectiveness and safety of medicines (or medical devices) in humans

Drug efficacy: the ability of a drug or treatment to produce the intended result

Induced pluripotent stem cells (iPSC): adult (mature) cells (derived from skin or blood) that have been reprogrammed into a stem cell like state, then grown into an unlimited source of any type of human cell

In silico: biological studies that are performed on a computer or using computer simulation or modelling

In vitro: studies of biological properties that are conducted outside of a living organism, e.g. in a cell culture

In vivo: studies conducted on whole, living organisms, usually animals

New approach methodologies (NAMs): new scientific approaches that focus on human biological processes to investigate disease and potential treatments, using human cells, tissues, organs and existing data

Organs-on-a-chip (OOC): more correctly termed microphysiological systems (MPS), are isolated human tissue cultures on a microchip that replicate organ function and interactions among cell types and tissues

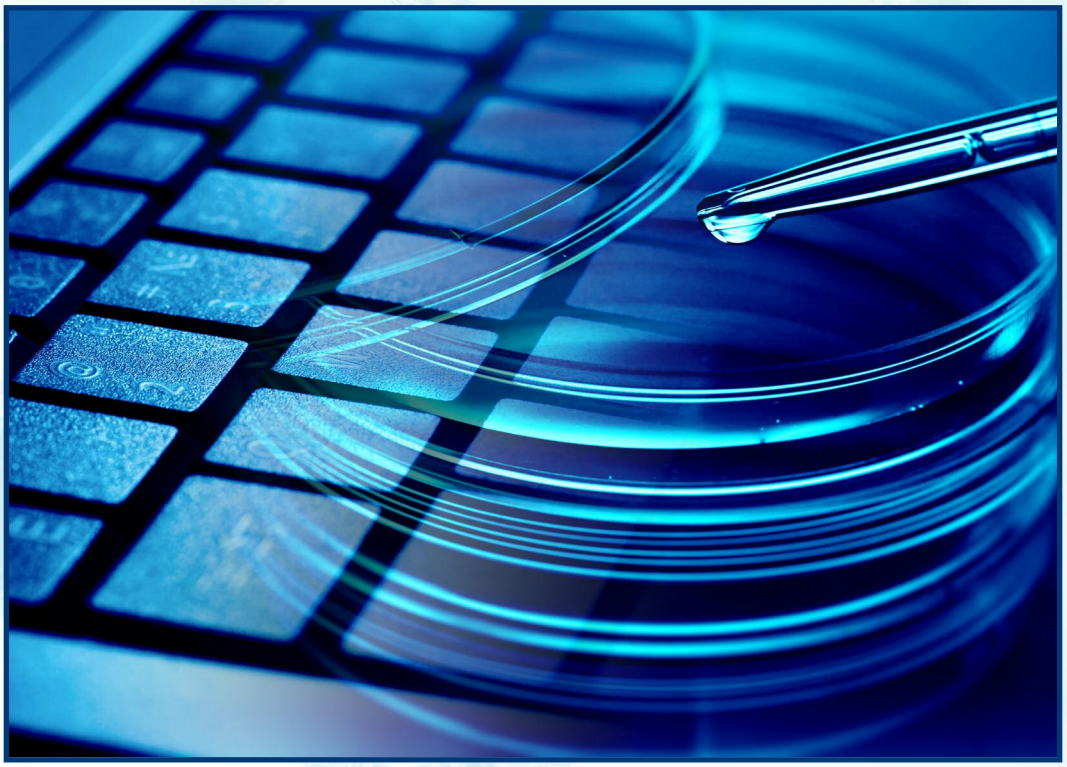
Pharmacokinetics (PK): the study of the bodily absorption, distribution, metabolism, and excretion of drugs, and the proportion of drug that reaches its site of action

Preclinical studies: tests conducted ***in vitro***, ***in silico*** and/or ***in vivo*** (in animals) before trials may be carried out in humans. Sometimes referred to as non-clinical trials

Introduction

Unmet need

Many of the major diseases of our time, such as stroke, cancer, heart disease, Alzheimer's and other dementias, remain poorly understood and lack adequate treatments. Although several thousand diseases affect humans, only about 500 are estimated to have any approved treatments[1]. Despite huge investment into disease research and drug development, the lack of available treatments leads to considerable unmet need and places substantial economic burden on the healthcare system. The worldwide cost of dementia care, for example, is more than $604 billion[2] and in the UK the NHS picks up £4.3 billion of the costs[3]. The number of people suffering from Alzheimer's is expected to triple by 2050[2] yet there are no medications to target the underlying causes of the disease or to slow its progression[3]. The economic burden of stroke in Europe (including healthcare and non-healthcare costs) was €45 billion in 2015[4]. In England, Wales and Northern Ireland the total cost of health and social care for patients with acute stroke each year is estimated to be £3.6 billion (mean per patient cost £46,039) in the first five years following admission[5]. Population growth and ageing is likely to result in a greater number of people at risk of stroke[6], yet apart from thrombolysis for a minority of stroke patients, there are no specific drugs available for targeting acute stroke[5].



Adverse drug reactions

Many currently used medicines have suboptimal efficacy, while others may cause adverse effects which restrict their use and can result in serious illnesses[7, 8, 9]. It has been estimated that adverse drug reactions (ADRs) kill more than 10,000 people in the UK[10] and 100,000 in the United States (US)[11] each year. In addition, ADRs are reported to account for 6.5% of hospital admissions in the UK (i.e. more than a million per year) and 3.6% in Europe[12]. In the UK it is calculated that one in seven hospital inpatients will have an ADR during their stay[13].

As well as causing significant individual suffering, ADRs place a high economic burden on hospitals and result in substantial lost economic productivity. In the UK, admissions caused by ADRs account for 4% of hospital bed capacity[10] and in England cost the NHS up to £1.6 billion annually[14]. In the US and Europe, the costs of ADRs are estimated to range from €2,851 to €9,015 per hospital admission, while the average indirect healthcare costs of ADRs (i.e. time off work, reduced productivity at work) are estimated to be €1,712 per ADR admission for people under age 65[15]. Overall, the total annual societal cost of ADRs in the European Union (EU) is calculated to be €79 billion[16].

Key information

Adverse drug reactions:

- Account for 4% of hospital bed capacity in the UK
- Cost the NHS in England up to £1.6 billion annually
- Cost between €2,851 – €9,015 per hospital admission in the US and Europe
- Cost €1,712 per ADR admission in indirect costs
- Cost the EU €79 billion a year

Studies in animals

Annual investment into biomedical research worldwide is estimated to be well in excess of $100 billion[17, 18], with a significant proportion spent on animal research. Animal studies are undertaken to investigate disease mechanisms, and to gain insight into the therapeutic efficacy and safety of new medicines. In the US, in 2012 it was reported that up to 47% of projects funded by the National Institutes of Health and 70% of projects funded by the National Institute of Neurological Disorders and Stroke had an animal research-based component[19]. In 2007 the Medical Research Council (MRC), the UK's largest funder of biomedical research, invested around 30% of its budget into animal research, which is regarded as foundational to all other biomedical research[20]. In 2017, UK research and development spend was £34.8 billion[21], of which 40% was for basic research[22], which uses a greater number of animals than any other research category.

Despite this substantial funding, animal studies demonstrate limited relevance to many human diseases. Furthermore, they are also unable to detect many important human ADRs[23, 24, 25, 26]. Some examples are illustrated in Table 1.

Table 1. Limited value of animal studies for investigation of human disease and safety assessment of human medicines

Outcomes associated with animal models	Public health impacts	Financial impacts
Poor translation of basic and applied animal research: *Animal models do not adequately represent the human condition*	A large proportion of animal research does not translate into benefits for humans[27]. High rates of translational failures from animal models include: Alzheimer's disease[28]; motor neuron disease[23]; arthritis[29]; asthma[30]; attention deficit hyperactivity disorder[31]; cancer[32]; HIV/ AIDS[33]; major depressive disorder[31]; multiple sclerosis[34]; myocardial infarction[27]; Parkinson's disease[27]; sepsis[35]; stroke[36]; Type 1 diabetes[37].	UK research and development spend in 2017 was £34.8 billion[21] with 40% of this for basic research, which uses many animals[22] and is largely publicly funded. Benefits of animal studies can be overstated[38] which is concerning as public support for animal research is conditional upon there being benefits for humans[39].
Predictive failures in toxicology testing: *Testing drugs in animals does not reliably predict human safety or efficacy, which can lead to drugs that are not safe or effective being tested in humans, or to drugs being rejected after animal testing that might have been safe or effective in humans*	86-90% of drugs that have proved promising in animal trials fail in human trials, either due to lack of effectiveness or safety concerns[40, 41]. Some candidates that could have been safe and effective human medicines are rejected during animal testing for not showing promise[42], thereby hindering the progress of new treatments[8]. Drug failure rates are particularly high for cancer research[43], Alzheimer's disease[44] and HIV research[45], despite these being areas of high investment[46]. Motor neuron disease[23], stroke[36], Crohn's disease[47] and sepsis[35] also have high drug failure rates.	Animal models are costly in terms of time and expense[8, 42]. The average cost of developing a successful new drug is estimated to be $2.6 billion[48] and each new drug can take up to 10 years to develop[49]. Preclinical studies account for 32% of drug discovery costs[50], with animal studies comprising much preclinical research. Despite increased funding for drug development, there are not more drugs coming to market. In the UK, the cost per new drug produced is estimated to have grown at an annual compound rate of 13.4% since the 1950s[51].
Clinical trial disasters: *Sometimes drugs do not show toxicity in animal studies but are hazardous for humans, resulting in humans being exposed to harmful substances in clinical trials*	Thousands of people participating in clinical trials globally suffer from ADRs and a significant number die[52]. Examples of high-profile cases where toxicity which was not identified in animal models has led to tragic outcomes include: BIA 10-2474[9], TGN-1412[53], Fialuridine[54], Torcetrapib[55] and Sildenafil[56].	The financial costs of failed clinical trials are considerable, estimated from $800 million to £1.4 billion per trial[57]. Failed clinical trials significantly set back research progress and can lead to companies' stock prices plummeting, resulting in a need to reduce the workforce and close research sites[57].
ADRs and withdrawn medicines: *Even after preclinical testing in animals and clinical trials in humans, medicines that reach the market are not guaranteed to be safe for humans*	In a study of 43 medicines that caused serious harm to patients, prior animal tests only identified 19% of those harms. Of the 93 serious ADRs caused by those drugs in humans, 63% had no counterpart in the animal tests[58]. ADRs in the wider population can range from minor side effects, such as discomfort or dysfunction, to major harms, such as liver failure, birth defects and death[59].	Despite safety testing in animals, it has been estimated that ADRs kill 197,000 people in the EU each year and are one of the leading causes of death, costing €79 billion of public funds[16]. In England it is estimated that ADRs may cost the NHS up to £1.6 billion annually[14]. Safety issues lead to around 50% of drugs having warnings or being withdrawn from the market post approval[7] costing the industry millions. During the Vioxx disaster, Merck paid out more than $8.5billion in settlements alone[42].

Inefficiencies in the current system of drug discovery and development

Discovery and development of new drugs is complex and time-consuming. Early drug discovery involves identifying a mechanism of disease and designing and selecting a drug that can intervene in that mechanism and thereby benefit patients. Prior to clinical trials, detailed studies are undertaken to explore expected efficacy and safety, typically using animal models. Later phases of drug development are conducted in human patient populations (typically involving many hundreds of patients) as well as in animals (these are longer term and more specialised safety studies, mandated by regulatory guidelines e.g.[60, 61]). These late phases provide efficacy and safety data prior to licensing a drug for commercial use. After drug licensing, additional post-marketing studies are often undertaken to more fully understand the efficacy and safety of the drug in the human population. The key steps are illustrated in Figure 1.

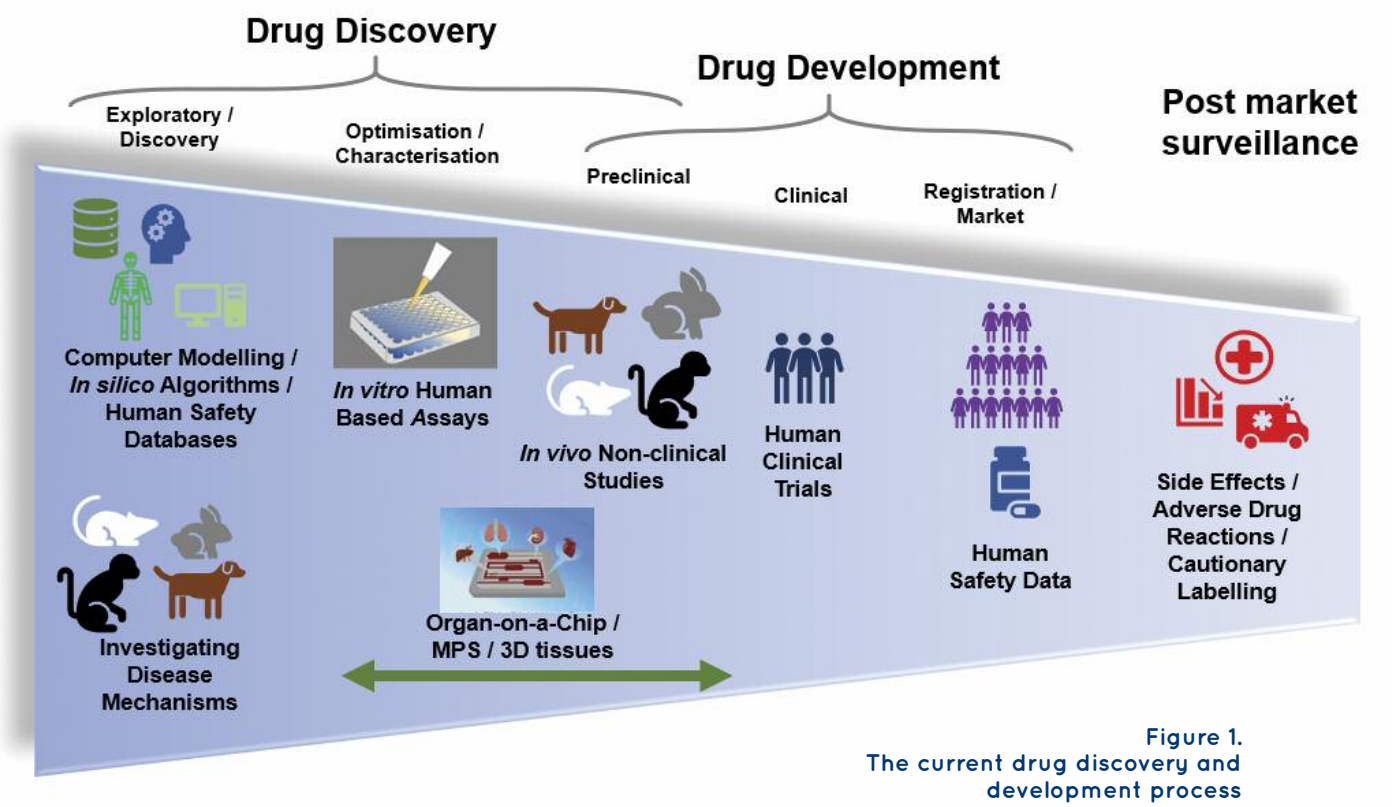


Figure 1.
The current drug discovery and development process

The limitations of animal studies outlined in Table 1 help explain why the current drug discovery and development process is highly inefficient. A common cause of failure to progress potentially promising drugs into clinical trials is unacceptable toxicity in animals[24,62]. However, the toxicity affecting animals may not manifest in humans at all, or to the same extent,[63,64] resulting in potentially valuable medicines being needlessly discarded. Even drugs which enter clinical trials have only a one in ten (9.6%) chance of progressing to market approval[42]. In mid and late stage clinical trials, the majority of failures are due to inadequate efficacy and safety (52% and 24% respectively)[65], further emphasising the limited human relevance of many animal studies. Since clinical trials represent the most expensive part of the pipeline, failures in clinical development have a huge financial impact, and human trial participants are exposed to risk[66]. There is an unmet need for test methods which more reliably predict both human efficacy and safety.

Developing a new prescription drug from a research idea to market approval has been estimated to take at least 10 years and to cost, on average, $2.6 billion per successful launch, taking into account the high frequency and cost of failure[48, 49]. Consequently, the pharmaceutical industry is now in the midst of a productivity crisis[26, 50 ,67, 68, 69, 70].

Key information

- Of the thousands of diseases affecting humans, only about 500 are estimated to have any approved treatments
- Developing a single successful new drug is estimated to cost $2.6 billion (incorporating failures along the way) and can take 10 years or more
- The overall failure rate for new drugs in clinical development is around 90%

Human relevant methods

A substantial international effort over the last decade has produced many different experimental models that use human cells and reproduce key features of human biology. These new approach methodologies (NAMs) do not use animals, thus circumventing the problem of animal-human species differences that can confound data interpretation[71,72]. Their development has been driven by the need to produce cost-effective tools that can be used to support the efficient development of effective new medicines. NAMs use advanced ***in vitro*** and ***in silico*** technologies to model diseases, test treatments and investigate biological processes in humans[73]. These include methods that use isolated human tissues and that recapitulate the physiological conditions encountered ***in vivo***[74]. Such microphysiological systems, often called 'organ-on-a-chip' (OOC), have enabled investigations of important mechanisms that cannot be explored using animal studies, such as the infection of human liver cells by malaria parasites[75]. Examples of these and other useful NAMs are outlined in Table 2.

Table 2. A selection of available human relevant test methods currently in use or development

Method	Description
Genomics	Application of a biomarker, which readily distinguishes DNA damage-inducing (DDI) agents from non-DDI agents, to assess the relevance of *in vitro* positive results from genotoxicity assay data to carcinogenic hazard[76]
	Screening of >2,000 ToxCast chemicals to understand defined pathways and then select appropriate assays to discover adverse outcome pathways (AOPs)[77]
Stem cells	*In silico* modelling to link activities in stem cell derived cardiac cells to the prediction of pro-arrhythmic risk[78]
	Developmental toxicity models[79]
	Stem cell models of human brain development[80]
3D models	Investigation of drug-induced changes in cardiac cell contractility[81]
	Neurodevelopmental disorders arising from disruption of the growth of neural progenitor cells in Zika virus infected microcephaly cases[82]
	Neurite outgrowth and abnormal neuronal differentiation caused by exposure to nicotine during early stages of human brain development[83]
	3D platform using primary brain cancer cells to study drug development and personalised medicine[84]
	Kidney organoids to allow identification of possible renal failure complications upon drug exposure[85]
	Prediction of drug-induced diarrhoea using gastro-intestinal micro-tissue model[86]
	Perfused 3D platform to study complex disease of the human liver – including hepatitis B and non-alcoholic fatty liver disease[87]
Primary cells/ cell lines	Human cell lines used in regulated tests to determine hormonal (oestrogenic and endocrine) effects[88,89,90,91]
	Human cell lines used in regulated tests for gene mutation and chromosome aberrations[92,93,94,95]
	Human cells used in regulated tests for skin sensitisation[96]
	Human cornea-like cells used in regulated tests for eye irritation[97]
	Panel of cell lines to allow selection of drug candidates with reduced propensity to cause adverse drug reactions in humans[98]
	Functionally stable model of primary human hepatocytes for predictions of clinical drug induced liver injury (DILI)[99]
	Testing for Replication Competent Retrovirus (RCR) in retroviral vector-based human gene therapy products using appropriate cell lines and polymerase chain reaction[100]
Human tissues	Freshly excised human skin used in regulatory studies for dermal absorption[101,102]
	Reconstructed human skin model used in regulated tests for skin corrosion and irritation[103,104]
	Reconstructed human corneal epithelial tissue used to evaluate its usefulness to identify chemicals as either classified or not for serious eye damage/eye irritation[105]
In silico	Model demonstrated to perform better than animal tests for predicting cardiotoxicity and used to simulate virtual clinical trials[106]
	Human model successfully applied to predict the plasma changes observed after dose reduction in a clinical trial in schizophrenic patients[107]
	Model to detect impurities in pharmaceutical products to support an initial hazard classification[108]
	Models to predict inter-species and inter-ethnic human differences in liver toxicity[109]
	Utilisation of quantitative systems toxicology (QST) methods to interpret *in vitro* experimental results leading to an improved understanding of the clinically relevant mechanisms underlying drug-induced liver toxicity[110]
	Mechanistic modelling of bilirubin disposition to elucidate underlying mechanisms of drug-induced hyperbilirubinemia (liver injury) and distinguish benign from clinically important elevations in serum bilirubin[111]
	Scientific Committee on Consumer Safety (SCCS) Memorandum on the use of *In Silico* Methods for Assessment of Chemical Hazard[112]
	Guidance Document on the validation of quantitative structure-activity relationship (QSAR) Models[113]
	World Health Organization guidance on physiologically based pharmacokinetic (PBPK) modelling in risk assessment of chemicals[114]
	Guidance on prediction of human pharmacokinetics and drug interaction risk using PBPK models[115,116]
	Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products[117]

In vitro technologies have provided invaluable new insights into human biology, physiology and disease processes, and have markedly improved our ability to understand and predict human toxicities caused by medicines and other chemicals[70]. Mathematical, statistical, modelling, and computer science tools (collectively known as ***in silico*** methods) enable investigation of the relationships between chemical structure, biological activity and toxicity[118], further enhancing our understanding of how medicines can cause both desirable therapeutic effects and undesirable toxicities. In particular, ***in silico*** Physiologically Based Pharmacokinetic (PBPK) modelling methods enable simulation of the ways in which drugs are distributed within and eliminated from the human body, as well as variability in these processes within the human population. PBPK models are used routinely to support predictions of human drug efficacy and undesired interactions between drugs. In addition, PBPK models are now increasingly used to improve prediction and understanding of adverse drug effects that occur in humans. Although the processes by which these adverse effects occur can be investigated using ***in vitro*** technologies, interpretation of the ***in vivo*** relevance of the data they provide is challenging. Such '***in vitro-in vivo*** extrapolation' is greatly improved when PBPK models are used to aid analysis of ***in vitro*** data[119,120,121.122].

Opportunities offered by human relevant methods

The use of NAMs in drug discovery, i.e. prior to clinical drug development (Figure 1), has substantial potential to provide data more predictive of desired efficacy, and undesired toxicity, than the approaches currently used[123,124,125,126,127,128]. Data that accurately predict efficacy and safety would improve the efficiency of drug development and reduce ADRs[25,73], meaning that patients would benefit from safer and more effective medicines. Furthermore, the business opportunity is potentially huge, as suggested by these global market forecasts:

- Cell-based assays to reach $18.9 billion by 2024[129]
- Stem cell technologies and applications to reach $28 billion by 2029[130]
- OOCs to reach between $60-176 million by 2022[131]
- *In vitro* toxicity testing expected to grow at a Compound Annual Growth Rate (CAGR) of 9% to reach $14.4 billion by 2025[132]

In 2016, the Director of the US National Institutes of Health predicted that within 10 years human OOCs will "mostly replace animal testing for drug toxicity.... giving results that are more accurate, at lower cost and with higher throughput."[133] A recent study estimated that OOC technologies could save up to 25% (~$700 million) of total drug development costs[134] and there is evidence that the commercial market value of NAMs may already be greater than that of animal test methods[42].

Humans are unique and differ from one another due to complex genetically inherited and non-genetic factors, which remain poorly understood. These differences affect health status, disease susceptibility, the types of diseases that may develop and responsiveness to treatment. Human relevant methods can be devised that use cells and tissues derived from different human populations and from individuals with different disease genotypes and phenotypes. Human induced pluripotent stem cell (iPSC) technology could be especially useful for this purpose[135]. Such methods can be expected to provide novel insights into mechanisms that influence disease susceptibility, as well as aid the potential development of 'precision medicine'

strategies that can individualise and hence optimise the effectiveness of drug treatments. Individualised approaches are already routinely used to treat some cancers[136] and in the future may be applied to other diseases. The global precision medicine market is anticipated to reach $217 billion by 2028[137]. In the UK, the Medicines and Healthcare products Regulatory Agency (MHRA) has pledged to collaborate with relevant partners to develop a clear regulatory pathway for genomic medicines and tests by March 2021. Their aim is to accelerate developments in precision medicine, so that treatments can be directly targeted to patients based on their genetic profile[138].

In the UK, we have world-leading universities, are home to two of the largest pharmaceutical companies in the world and are currently regarded as one of the world's best locations for developing new, targeted, high value medicines[73]. Our pharmaceutical sector, consumer goods and personal care companies, contract research organisations and academia all have the ability to deploy advanced NAMs and to position the UK as a 'global powerhouse' in this field[73]. There is an opportunity, therefore, for the UK to take a lead in developing and evaluating NAMs and other new technologies that are needed to humanise drug discovery[26,73,139].

Key information

- The benefits of transitioning to NAMs are increasingly recognised
- NAMs have potential to increase drug safety and to reduce ADRs, as well as their costs to business and society
- NAMs represent a huge business opportunity for the UK

Challenges to be addressed

A number of countries, including the UK, have produced roadmaps (Table 3) to progress the transition to NAMs. The UK roadmaps are optimistic about the benefits of NAMs for the UK and highlight their potential to attract business investment and drive economic growth [26, 73, 139].

Table 3. Roadmaps to encourage adoption of NAMs

		Aims	Targets
2007 	**Toxicity Testing in the 21st Century: A Vision and a Strategy** US National Research Council	A new toxicity-testing system that uses new methods in computational biology and a comprehensive array of *in vitro* tests based on human biology	No targets stated, although the vision was for major change within 10 years and a fully human relevant paradigm within 20 years. This pivotal report led to all the following initiatives
2012 	**Roadmap for Development of Alternative (Non-Animal) Methods for Systemic Toxicity Testing** Transatlantic Think Tank for Toxicology (T^4)	To overcome the acknowledged scientific gaps for the full replacement of systemic toxicity testing using animals	No targets stated but many good recommendations. No significant government or regulatory support
2015 	**Non-Animal Technologies Roadmap for the UK** Innovate UK, NC3Rs, BBSRC, DSTL, EPSRC and the MRC	To encourage UK to lead the way in non-animal methods that are biologically relevant for humans	Target of 2030. Innovate UK is a government agency but no specific action has been taken by government on this roadmap
2016 	**Transition to Non-Animal Research** Netherlands National Committee for the protection of animals used for scientific purposes	To phase out specific types of animal use in research and to promote education in NAMs in the Netherlands. To be world leader in the area	Target of 2025 with goals and timelines. Dutch Minister of Agriculture commissioned the report
2016 and 2019 	**Strategic Plan** US Environmental Protection Agency (EPA)	To reduce and replace the use of mammals in testing of chemicals and to promote, develop and incorporate non-animal methods	Revised target of 2035 with goals and timelines. EPA is an agency of the US federal government
2017 	**Predictive Toxicology Roadmap** US Food and Drug Administration (FDA)	To strengthen FDA's commitment to promoting use of new technologies to better predict human / animal / environmental responses to substances	No targets stated but many positive actions proposed. FDA is a US federal government agency
2018 	**Strategic Roadmap for Establishing New Approaches to Evaluate the Safety of Chemicals and Medical Products in the US** The Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM)	To enable development of new approaches to toxicity testing that improve human health relevance and reduce or eliminate the need for testing in animals	No targets stated but many positive actions proposed. ICCVAM comprises 16 federal government agencies, including the FDA and EPA
2018 and 2019 	**State of the Discovery Nation 2018 and State of the Discovery Nation 2019** Medicines BioIndustry Discovery Catapult and BioIndustry Association	To develop technologies to humanise drug discovery in order to improve research productivity for industry	No targets stated but many good recommendations. The Medicines Discovery Catapult is funded by Innovate UK, an agency of the UK government

Government and regulatory support are necessary to drive progress in adopting and exploiting the business potential of NAMs, but a 2018 House of Lords Science and Technology Committee report[140] on UK life sciences missed the opportunity to highlight the potential of NAMs, as did the government's 2018 Life Sciences Sector deal[138]. It is notable that, although the UK produces 25% more scientific citations than the US per $billion research spend, we are less effective at realising the value of this output in terms of private follow-on investment, number of biotech companies and sector wage pool. All of these are lower in the UK than, for example, in California or Massachusetts[26].

There is considerable 'lock in' to animal research; for example, the editorial policies of scientific journals worldwide can hamper the adoption of NAMs by requiring authors of NAM-related papers to validate their approaches against the very same animal models which have proven sub-optimal. Pragmatic changes to the requirements for validation or qualification of NAMs, driven by governmental directives, could potentially break down such barriers to realising the business and scientific potential of NAMs.

Internationally, a number of governmental organisations, such as the US Environmental Protection Agency (EPA) and the US Food and Drug Administration, are recognising the scientific, public health and economic benefits of transitioning from animal models to NAMs. These agencies have developed roadmaps to encourage this transition, some of which incorporate specific goals and deadlines (Table 3). Without government support, infrastructure and funding, and the implementation of its own goals and deadlines, the UK risks falling behind international developments in NAMs and losing its position as a global leader in research and innovation.

> *"Without government support, infrastructure and funding, the UK risks falling behind international developments in NAMs and losing its position as a global leader in research and innovation."*

The way forward for the UK

Supportive infrastructure

In the US and the Netherlands, it is recognised that government agencies need to take the lead if progress is to occur[141,142]. For example, the US government provides funding and incentives to test chemicals using NAMs[143] and in 2019 the US EPA announced funding of $4.25 million for research methods and strategies that reduce, refine, and/or replace vertebrate animal testing, aiming to eliminate all requests and funding for studies using mammals by 2035[144]. Meanwhile, five ministries within the Dutch government are collaborating with funders, scientists and businesses to organise conferences, workshops and funding proposals to accelerate the transition to NAMs[145].

By contrast, progress in the UK is less coordinated and more supportive infrastructure is needed. A central government-backed body could support and coordinate the excellent work being undertaken by Innovate UK, the Medicines Discovery Catapult, National Centre for the Replacement, Refinement and Reduction of Animals in Research (NC3Rs), academic researchers and biomedical industries. Such a body could support the growth of human relevant science across the UK by providing equipment, resources and e-infrastructures, by fostering communication networks to facilitate collaboration and knowledge transfer between academia, science, industry and regulators, and by funding the commercialisation of NAMs. Government support is also needed for the transition to NAMs, in terms of jobs, training and infrastructure. Figure 2 summarises actions that are needed in the UK in order to keep pace with international progress in NAMs.

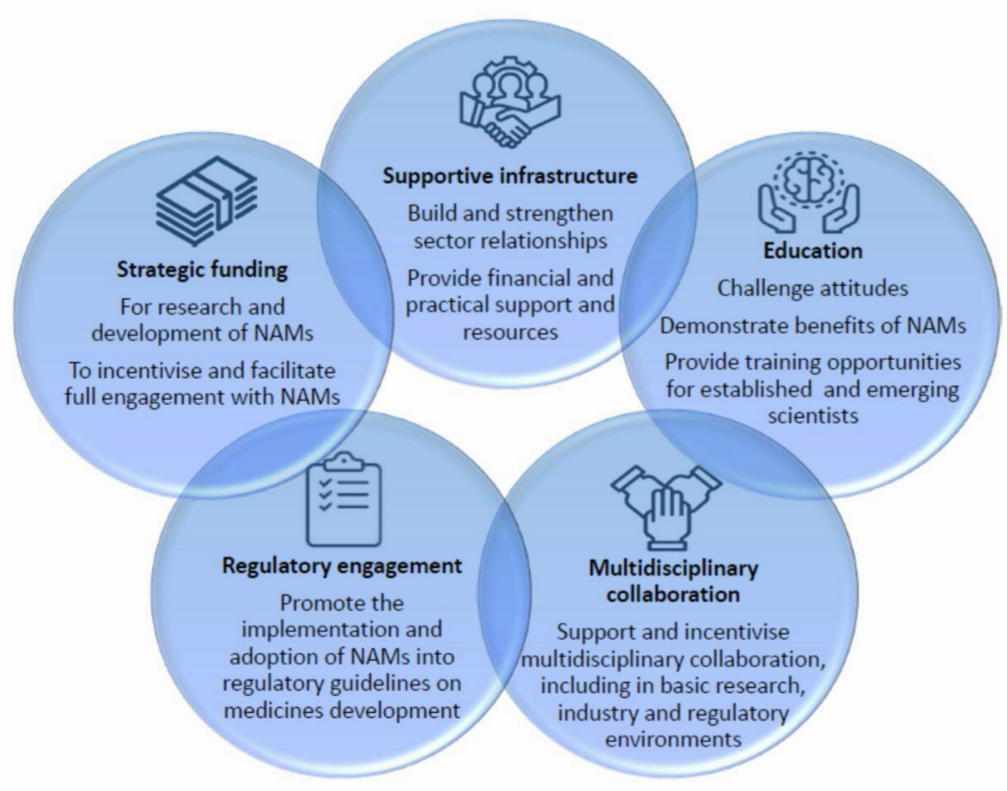


Figure 2.
Recommended actions required for the UK to keep pace with international scientific progress in humanised disease modelling and drug discovery

Strategic funding

NAMs have been significantly underfunded, with only an estimated 0.036% of science research and development expenditure in the EU specifically invested into non-animal methods[146]. Strategic funding is required to develop and evaluate NAMs, particularly those with commercial and market potential (e.g. toxicity testing and drug discovery). This could be achieved without the need for additional capital by diverting existing resources from poorly performing animal studies. Such funding, capitalising on the UK's strengths and expertise, would drive progress in NAMs and enable the UK to be a strong competitor in the worldwide market, with the potential to drive economic growth by attracting business investment and international collaboration[73]. The UK government has acknowledged the need to invest in more effective and efficient science by moving away from animal models[147]. In a welcome move, major UK funders stated in 2019 that their long-term ambition is to fund exploration of emerging technologies such as 3D tissue models and organoids[148], as well as new approaches to reduce the use of animals and provide more effective tools for studying animal and human biology[149]. Strategic funding is essential to create incentives for researchers to develop and test NAMs, and to direct the current focus in many institutions away from animal research[150].

Education

There is a need for educational initiatives within the UK which increase the opportunities available for emerging scientists to specialise in human relevant research methods, as well as opportunities for established scientists to widen their skills beyond traditional animal use. In the US, the Physicians Committee for Responsible Medicine is providing training and seminars to promote the use of non-animal approaches for regulatory purposes[151] and the EU has announced their intention to develop online modules for training in non-animal approaches[152]. Education is needed in the UK to help scientists understand the limitations of animal methods and learn about the wide range of new technologies that can be used instead[73, 153]. Building confidence in NAMs, challenging current attitudes about animal models and recognising their limitations, are important steps towards a human relevant life sciences industry.

Multidisciplinary collaboration

The UK needs to draw together relevant industries and expertise if there is to be progress[73]. At present, academia and industry are somewhat siloed. Collaboration between the two would forge partnerships, encourage the commercialisation of NAMs and ensure that basic research has practical application. A supportive infrastructure could help build networks and facilitate the flow of knowledge and resources between sectors and disciplines. Furthermore, international collaboration between scientists using animal models and those using NAMs would encourage greater understanding of the wide range of ***in vitro*** and ***in silico*** technologies available. In the Netherlands, transition facilitators bring together a range of stakeholders, including researchers, funders and lay people, in workshops called 'Helpathons', where researchers bring their research questions and work collaboratively to devise ways of answering these without using animals[154]. This innovative approach has been well received and

provides an excellent model for other countries wishing to move away from animal use. In the UK we also need to cross disciplinary boundaries and forge new partnerships in order to progress the transition to human relevant approaches.

Regulatory engagement

In order for NAMs to support regulatory decisions on the progression of drugs into clinical trials, and on drug licensing and labelling, it is critically important that their development is undertaken in close collaboration with regulatory agencies such as the UK's MHRA and relevant regulatory agencies in the EU, US and elsewhere. An important goal should be the provision of evidence which demonstrates the scientific validity and human clinical relevance of NAM data to regulatory scientists. To accommodate rapidly advancing human relevant approaches, agencies from around the globe should review and update regulations in a timely manner. This will improve the delivery of effective and safe new medicines, by ensuring that only the most effective human-based NAMs are used in drug safety evaluation[155].

Alliance for Human Relevant Science

The Alliance for Human Relevant Science is an inclusive collaboration of like-minded companies, charities, organisations and individuals, who work together to accelerate awareness and use of human relevant approaches within industry and the scientific research community. Established in 2017, the Alliance is well positioned to act alongside organisations such as Innovate UK, NC3Rs and the Medicines Discovery Catapult as an independent coordinator and facilitator of projects and activities emerging from UK government-based initiatives, in order to speed up the transition to NAMs. Members conduct research to develop valid and reliable human relevant approaches and to improve the evidence-base for these approaches. In addition, we work with regulators, funding bodies and industry to generate the evidence needed to develop and use NAMs. Further information on the Alliance, its members and how to contact us can be found at: www.HumanRelevantScience.org.

The Alliance for Human Relevant Science calls for:

- Government-backed infrastructure to support the transition to NAMs
- Strategic funding to incentivise the development and testing of NAMs
- Improved education on the potential of NAMs
- Multidisciplinary collaboration and new partnerships to progress the transition to NAMs
- Close collaboration with regulators to promote implementation and adoption of NAMs in regulatory guidelines

Conclusion

The pharmaceutical industry is in the midst of a productivity crisis. Many patients lack treatments for their diseases, healthcare systems are overburdened and the economy and society are negatively impacted.

New approaches based on human biology promise to deliver safer and more effective medicines, more quickly and at less cost. Other countries have recognised the potential of these NAMs and already have ambitious programmes underway to implement them, something which is lacking in the UK. Government-backed action is required for the UK to become a global leader in NAMs research and innovation, and to prevent it falling behind other countries.

We need: coordinated infrastructure; strategic re-allocation of research funding; investment in education and skills training at all levels; collaboration between all stakeholders and earlier engagement with regulators.

It is time for a fresh approach to biomedical research and drug discovery. Investment in human relevant methods offers a golden opportunity to revitalise translational research, save money, create wealth and, crucially, improve public health.

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The Alliance for Human Relevant Science is an inclusive collaboration of like-minded companies, charities, organisations and individuals, who work together to accelerate awareness and use of human relevant approaches within industry and the scientific research community. Partners include:

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