Bringing Back the Human: Transitioning from Animal Research to Human Relevant Science in the UK

REPORT OF THE ALL-PARTY PARLIAMENTARY GROUP FOR HUMAN RELEVANT SCIENCE

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This inquiry was supported, and the report compiled, by the APPG's secretariat, the Alliance for Human Relevant Science (www.HumanRelevantScience.org), an inclusive collaboration of like-minded organisations working together to accelerate innovation and create positive change in biomedical research and testing.

The All Party Parliamentary Group (APPG) on Human Relevant Science is a cross-party group of Peers and MPs which was founded in 2020 and is currently chaired by Grahame Morris MP. Its agreed purpose is to bring together MPs and Peers of all parties to accelerate the development and uptake of human relevant science in the UK.

Its secretariat is the Alliance for Human Relevant Science, whose purpose is to support better science for better health, to save lives – human and animal – through improved safety and efficacy testing of medicines and other chemicals and to save money through more relevant research.

Alliance for Human Relevant Science

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FOREWORD FROM THE CHAIR OF THE ALL-PARTY PARLIAMENTARY GROUP ON HUMAN RELEVANT SCIENCE

With a renewed Government focus on stimulating the life sciences industry, there has never been a better time to examine the contribution that human relevant science can make to driving economic growth and tackling the most serious health challenges in the UK. Despite huge investment into disease research and drug development, many debilitating and life-threatening diseases still lack effective treatments. Drug discovery is highly inefficient and 92% of drugs evaluated in animals fail in clinical trials.[1,2] This has resulted in very high costs for new medicines, overburdened healthcare systems and tragically, individual suffering and lost lives. In addition, the UK public consistently agree (75% of those polled in 2018) that greater effort needs to be put into developing alternatives to using animals in research.[3] New approach methodologies (NAMs) are defined here as 'non-animal, scientific approaches that focus on human biological processes to investigate disease and potential treatments, using cells from human tissues and organs, as well as existing data.'[4] NAMs may also include artificial intelligence, computer simulations and genomics. They can be combined with data from real world clinical and epidemiological studies and have been forecast to contribute £2.54B to GDP in terms of Gross Value Added (GVA)[5] and promise to deliver safer and more effective medicines, faster and at less cost.

Countries such as the Netherlands and the United States (US) have already recognised the great potential of NAMs and human relevant technologies, and are investing substantially in their development and implementation. Currently, this level of investment far exceeds that being made in the UK. Government-backed action is urgently required to enable the UK to become a global leader in NAMs research and innovation, and to ensure it does not fall any further behind other countries.

This report from the APPG for Human Relevant Science is an account of evidence submitted during four meetings in 2020-2021 on the status of UK funding for biomedical research using NAMs, and on the regulatory implications for the adoption and application of these methods for the testing of medicines in the UK. We recommend measures to further maximise human relevant science, and thereby accelerate medical progress.

Investment in human relevant research offers a golden opportunity for the UK to make more effective use of its substantial expenditure on the biomedical sciences, to enhance the productivity of industry, improve public health, cement its status as a global science superpower and conserve its reputation for leadership in animal protection.

[1] https://www.bio.org/clinical-development-success-rates-and-contributing-factors-2011-2020

[2] Wong CH, Siah KW, Lo AW. Estimation of clinical trial success rates and related parameters. Biostatistics. 2019;20(2):273-86

[3] https://www.ipsos.com/en-uk/public-attitudes-animal-research-2018

[4] https://www.humanrelevantscience.org/wp-content/uploads/Accelerating-the-Growth-of-Human-Relevant-Sciences-in-the-UK_2020-final.pdf

[5] https://www.animalfreeresearchuk.org/wp-content/uploads/2021/09/Animal-Free-Research-UK_Economic-Report-2.pdf

EXECUTIVE SUMMARY

A series of evidence sessions held by the APPG for Human Relevant Science in 2020-2021 heard that human-relevant approaches and technologies, known collectively as 'new approach methodologies', or NAMs, are needed to advance the development of treatments for human diseases. Experts from relevant funding bodies (the MRC and NC3Rs), as well as some of their research beneficiaries, presented evidence on the scientific validity of NAMs, but scientists described a UK climate in which limited funding opportunities exist for NAMs research. This lack of funding was contrasted with the extensive resources available for research using established technologies and practices which are primarily based on animal experiments. It emerged that human relevant NAMs funding represents between 0.2% and 0.6% of total biomedical research funding in the UK and ~0.02% of the total public expenditure (£10.45B for 2019-2020) on R&D. This is woefully inadequate and will impede the UK's efforts to improve human health and retain its status as a world leader in the life sciences arena.

A member of the UK's medicines regulator, the Medicines and Healthcare products Regulatory Agency (MHRA) provided the APPG with an assessment of current regulatory requirements for pharmaceutical safety and a view on how NAMs data might be incorporated into regulatory decision making for new medicines. The current legal environment regarding the use of animals and NAMs in biomedical research and regulated testing was also discussed. Finally, the APPG was told how the transition to human relevant, animal-free research is being encouraged and managed in the Netherlands.

The evidence presented to the APPG indicated that important factors which restrict the routine use of NAMs in disease research and drug testing are a lack of awareness of their potential and a widely held belief that in vivo animal research is the only scientifically credible way to discover, develop and test new medicines. A culture of animal use is perpetuated within academia, industry, and regulatory agencies, with outdated guidelines hampering the adoption of NAMs for the safety testing of drugs and prolonging the use of poorly performing animal methods in basic research. This has catastrophic results for the UK's health and for the modernisation of biomedical research.

Increased funding in strategic areas devoted to the development and adoption of NAMs is patently needed. Until the development and use of NAMs is prioritised by the Government, UK science and the health of our nation will lag behind those of other countries, with devastating consequences. The APPG strongly believes that human relevant science offers a golden opportunity for the UK to make more effective use of its substantial expenditure on biomedical sciences to enhance the productivity of industry, improve public health and cement its status as a global science superpower.

RECOMMENDATIONS

FUNDING

We recommend that:

- the Government commits to increasing the funding of NAMs by strategically diverting resources away from animal-based approaches and towards NAMs.
- animal researchers should be legally obliged and financially supported to proactively shift their focus away from animal use and towards the development and use of NAMs, in line with current legislative requirements.

REGULATORY

We recommend that:

- the Home Office commits to a more robust application of the harm-benefit analysis when assessing project license applications for animal research and requires robust evidence that the use of NAMs has been thoroughly considered.
- an aspiration for animal free science is reintroduced into UK legislation.
- the Government commits to reviewing the current regulatory guidelines for animal research and pharmaceutical testing, with a view to updating these such that human relevant methods are recommended where appropriate in research and during the development and licensing of medicines.

STRATEGIC GUIDANCE AND SUPPORTIVE INFRASTRUCTURE

We recommend that the Government commits to:

- creating a dedicated ministerial position to lead an ambitious and detailed programme of work across all relevant departments to transition to human relevant NAMs with appropriate milestones, timelines, funding and deliverables.
- establishing a UK Transition Programme for Innovation without animals to prioritise awareness of NAMs and to incentivise collaboration between stakeholder groups, including academic researchers, industry, funders, and regulators.
- evaluating preclinical research for its clinical relevance and allocating funds accordingly.

INTRODUCTION

Despite a perception that the best way to investigate human diseases and their treatments is by using animal experiments, the relevance to human medicine of many animal studies is in doubt.[6,7,8,9,10] Lack of efficacy and safety are major contributory reasons why 92% of candidate drugs fail when tested in clinical trials, despite having undergone extensive investigations in animals prior to human trials. And despite decades of animal research, many debilitating and life-threatening diseases still lack effective treatments.

Over the last 20-30 years, significant advances in science and technology have generated a plethora of new research methods based on the use of human tissues and cells. These are increasingly being employed by researchers to gain unique and valuable insights into human biology and disease processes, and to identify and develop effective new treatments. These 'New Approach Methodologies' (NAMs) are defined here as 'non-animal, scientific approaches that focus on human biological processes to investigate disease and potential treatments, using cells from human tissues and organs, as well as existing data.' [11] Organ-on-chip (Figure 1) is an example of a NAM, but NAMs may also include artificial intelligence, computer simulations and genomics. Since NAMs focus directly on human biology and on disease mechanisms that occur in humans, they circumvent the significant limitations (species variability and/or poor model relevance) inherent in animal studies.

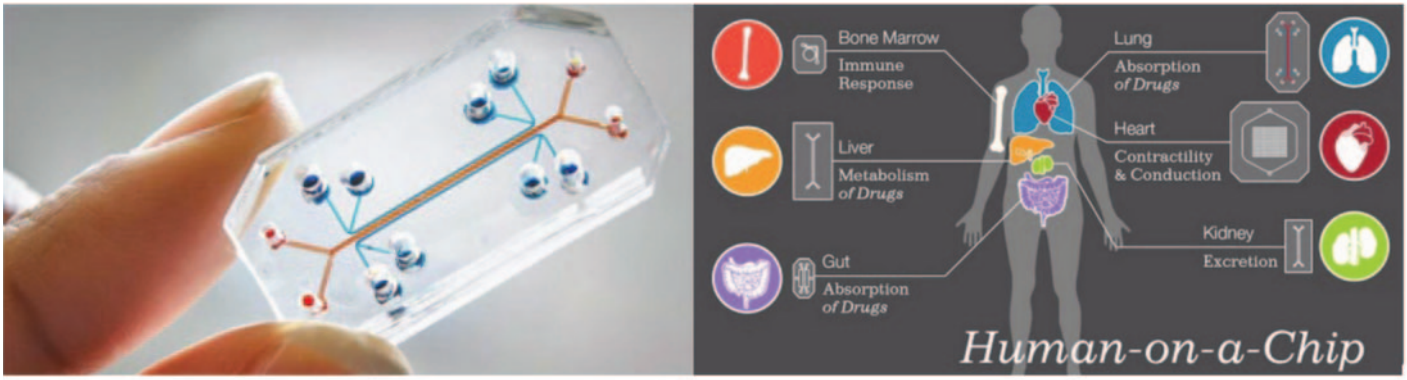

Figure 1: Organ-on-chips. Single or multi organ-on-chips can be generated to test human cells and tissues from different organs with potential drugs. Credit: Wyss Institute.

[6] Dirven, H., Vist, G.E., Bandhakavi, S. et al. Performance of preclinical models in predicting drug-induced liver injury in humans: a systematic review. Sci Rep 11, 6403 (2021). https://doi.org/10.1038/s41598-021-85708-2

[7] Marshall, L.J.; Triunfol, M.; Seidle, T. Patient-Derived Xenograft vs. Organoids: A Preliminary Analysis of Cancer Research Output, Funding and Human Health Impact in 2014–2019. Animals 2020, 10, 1923. https://doi.org/10.3390/ani10101923

[8] Pound, P., Ritskes-Hoitinga, M. Is it possible to overcome issues of external validity in preclinical animal research? Why most animal models are bound to fail. J Transl Med 16, 304 (2018). https://doi.org/10.1186/s12967-018-1678-1

[9] Pound P, Ebrahim S, Sandercock P, Bracken M B, Roberts I. Where is the evidence that animal research benefits humans? BMJ 2004; 328 :514 doi:10.1136/bmj.328.7438.514

[10] Ioannidis JP. Extrapolating from animals to humans. Sci Transl Med. 2012 Sep 12;4(151):151ps15. doi: 10.1126/scitranslmed.3004631. PMID: 22972841

[11] https://www.humanrelevantscience.org/wp-content/uploads/Accelerating-the-Growth-of-Human-Relevant-Sciences-in-the-UK_2020-final.pdf

The APPG for Human Relevant Science explored two areas previously identified by the Alliance for Human Relevant Science as barriers to the uptake and use of human relevant NAMs for medical research in the UK, namely funding and regulation.[8] Over the course of late 2020 - 2021, this APPG held a series of four evidence sessions with experts in the field of NAMs, examining the funding and regulatory environment for these innovative approaches, the legal barriers to their adoption for the regulated testing of medicines, and examples from other countries of initiatives for actively accelerating the transition from animal experiments to human relevant science. This report presents some of the key insights emerging from the sessions, as well as some additional research conducted by the APPG.

There has never been a better or more vital time to build a regulatory framework that improves human health whilst reducing and replacing animal experiments. The Government Taskforce on Innovation, Growth and Regulatory Reform recognises the potential of the UK's departure from the EU as a one-off opportunity to set a bold new UK regulatory framework to boost global innovation opportunities.[12] The APPG believes that human relevant science has a key role to play in driving innovation and in this report makes policy recommendations to support the Government in promoting the development and application of human relevant methods in biomedical science, to both enable major public health challenges to be better addressed and to ensure that the UK remains a global leader in the life sciences industry.

[12] https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/994125/FINAL_TIGRR_REPORT__1_.pdf

1. CURRENT NAMS FUNDING IN THE UK

1.1. UKRI funding

Responsibility for scientific research sits within the Department for Business, Energy & Industrial Strategy (BEIS). BEIS provides funding for UK Research and Innovation (UKRI), which incorporates seven research councils, as well as Research England and Innovate UK (Fig. 2). Total public spending on Research and Development (R&D), including the research councils and devolved higher education councils, was £10.45B in 2019, the majority of which came from BEIS and UKRI. Evidence from the first APPG session suggested around 20% of UKRI projects cite a relevance to human health, amounting to approximately £1.3B of funds in 2019-2020. Two of the key councils funding medical research are the Medical Research Council (MRC) and the Biotechnology and Biological Sciences Research Council (BBSRC), while Innovate UK (IUK) is an important source of funding for the translation of research ideas into practical applications in diagnostics, disease treatments and healthcare in general. Together, the MRC, BBSRC and Innovate UK awarded ~£1.14B (£323M MRC; £175M BBSRC; IUK £646M) in 2019-2020:

Figure 2: UKRI encompasses seven disciplinary research councils, Research England, responsible for supporting research and knowledge exchange at higher education institutions in England, and the UK's innovation agency, Innovate UK. UKRI is a non-departmental public body sponsored by the Department for Business, Energy and Industrial Strategy (BEIS). Values of competitive funding awards made in 2019-2020 for each council are shown (taken from the Competitive Funding Dashboard Dec 2021 https://www.ukri.org/our-work/what-we-have-funded/competitive-funding-decisions/).

1.2. MRC funding

The MRC's remit is to improve the health of people in the UK and around the world by supporting excellent science and by training the very best scientists. The APPG heard that MRC gross expenditure on research in 2019-2020 was £849M. Two thirds of MRC funding supports basic biomedical discovery research, the hope being that this will ultimately translate into medical products, while the remaining third supports trials and other clinical work. The APPG heard that NAMs funding *per se* is not tracked.

1.2.1. MRC experimental medicine

The first APPG session in 2020 heard how the MRC's Experimental Medicine (EM) initiative "now allows us to approach the human as the ultimate experimental animal for improving human health".[13] EM was described as basic or discovery science in humans, to distinguish it from clinical trials and from basic or discovery science using animals. Established in 2015 as part of the MRC's Translational Research Strategy,[14] the aim of EM is to address gaps in our understanding of human disease so that effective new therapies can be developed. At the time, it was acknowledged that the necessary tools, such as medical imaging and 'omics' technologies (e.g., genomics, proteomics, and metabolomics) for identifying disease (biomarkers) in blood or urine samples, were already available. The reciprocal relationships between EM and other research approaches are shown in Figure 3. The APPG was told that despite an upscale in human models and human volunteers, and an uplift in funding, there was underinvestment in EM.

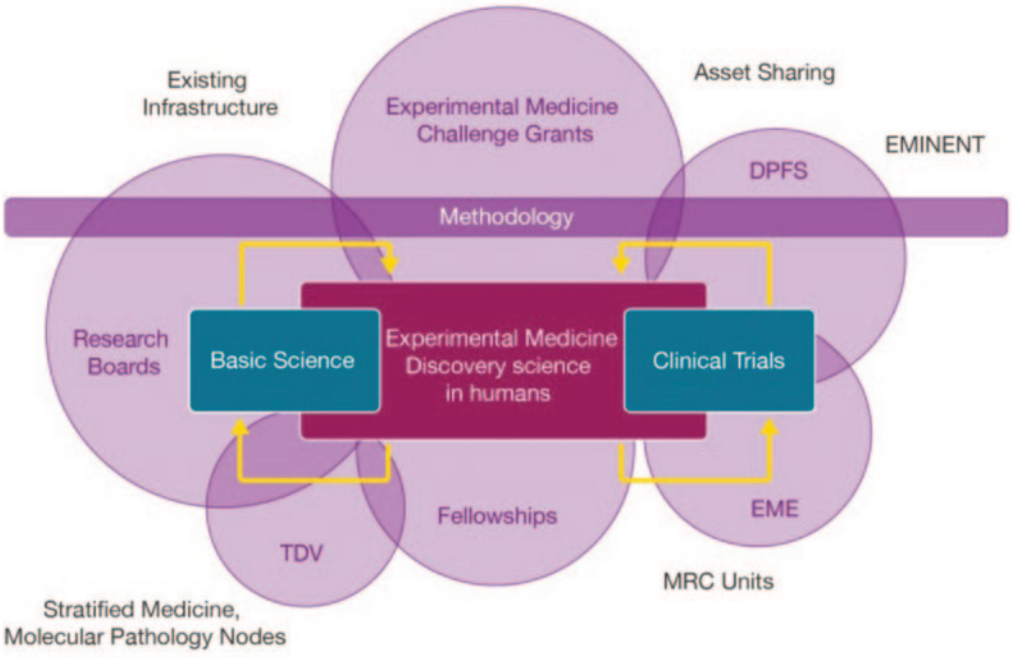

Figure 3: The network of reciprocal interactions between experimental medicine and other research approaches. DPFS - Developmental Pathway Funding Scheme; TDV – Target Discovery and Validation; EME - The Efficacy and Mechanism Evaluation Programme (in partnership with the National Institute of Health Research (NIHR)); EMINENT: Experimental Medicine INitiative to Explore New Therapies. https://mrc.ukri.org/research/initiatives/experimental-medicine/ Accessed on 18/01/22

The APPG heard that, "EM plays a critical role in realising the potential of a number of research disciplines and approaches (funded by the MRC), is a core element of the MRC's translational research strategy and is of strategic importance to MRC and to UK biomedical science". Nevertheless, the MRC member acknowledged that there was a need to reduce bureaucracy so that EM could progress and that lessons could be learned from the way research had been hastened in the case of COVID-19.

> ***"Experimental Medicine ... now allows us to approach the human as the ultimate experimental animal for improving human health."***

[13] https://mrc.ukri.org/research/initiatives/experimental-medicine/

[14] https://mrc.ukri.org/funding/science-areas/translation/

1.2.2. NC3Rs funding

The MRC is a major funder of the National Centre for the Replacement, Refinement and Reduction of Animals in Research (NC3Rs). The 3Rs are principles that aim to minimise the number of animals used in experiments (reduce), lessen animal suffering, and improve experimental animal welfare (refine) and avoid or replace the use of animals altogether (replace).

Through a series of letters and parliamentary questions to BEIS Ministers throughout the year,[15,16,17] the APPG was repeatedly told that government funding for the development of alternative methods to the use of animals was via the NC3Rs.[18] The Chief Executive of the NC3Rs reported to the APPG that their core budget was between £10.5M and £11M per year, with most coming directly from the MRC and BBSRC, and some from charities and industry. Between 2015 to 2019, the MRC funded NC3Rs research grants to the tune of £15M, of which £10M was for replacement technologies (~£2.5M per year). Non-core funding for the NC3Rs from other public bodies provided additional capital amounting to £7.25M over the last 5 years (£1.45M per year). In total, NC3Rs reported receiving over £100M since its inception in 2004 (~£5.9M per year), primarily through the MRC. Of this, £72.3M was awarded to researchers to develop 3Rs models and tools where the primary end use is in academic laboratories, and usually the developer's own research group. Sixty-five percent (~£47M) of this was for replacement methods. It was estimated that 16% of all replacement funding (£7.5M in total or ~£440K per annum) focused on research for application to human health. This represents ~0.004% of total public R&D funding in 2019-2020.

> ***"It was estimated that 16% of all replacement funding focused on research for application to human health, representing ~0.004% of total public R&D funding in 2019-2020."***

From its core budget, the NC3Rs also funds human relevant NAMs development and adoption, through its 'CRACK-IT' challenges, which aim to improve business processes or develop an innovative commercial product that solves an unmet need using 3Rs approaches. The CRACK-IT challenges attempt to address the gap between academic research and industrial commercialisation to ensure that technological innovations are transferred to industry and society. The APPG heard that CRACK-IT funding has amounted to £28.4M over the 10 years since 2011, of which £22M (77%) was for replacement and approximately £15.9M (56% or £1.6M per year) was for the development of NAMs.

[15] Letter to Alok Sharma, 11 August 2020, https://www.humanrelevantscience.org/all-party-parliamentary-group/correspondence-with-government-ministers/

[16] Letter from Amanda Solloway, 28 August 2020, https://www.humanrelevantscience.org/all-party-parliamentary-group/correspondence-with-government-ministers/

[17] Letter to Amanda Solloway and Nadhim Zahawi, 14 December 2020, https://www.humanrelevantscience.org/all-party-parliamentary-group/correspondence-with-government-ministers/

[18] Letter from Amanda Solloway Nadhim Zahawi, 1 February 2021, https://www.humanrelevantscience.org/all-party-parliamentary-group/correspondence-with-government-ministers/

[19] Available on request from media@crueltyfreeinternational.org

1.3. European funding

Access to the EU's key funding programme for research and innovation, Horizon Europe, with a budget of €95.5 billion is still available to UK scientists following the UK's exit from the EU in January 2020. The previous incarnation of this scheme was Horizon 2020, which the APPG was told provided around 20% of funding to the UK science community prior to Brexit. Despite uncertainty at the time of the APPG sessions in 2021, the Government announced in its October 2021 spending review that the UK had set aside £6.9B for its contribution to Horizon Europe until 2025. The proportion of funding available for human relevant NAMs is unclear, but a recent analysis of funding for Horizon projects in 2020 found that those developing non-animal methods represented just 0.1% of the €80 billion Horizon 2020 programme.[19]

1.4. Other funding streams

Third sector funding and private investment for NAMs development and validation was described as minuscule compared to public sector funding for research. APPG Members heard that many research groups end up applying to the third sector when they fail to gain funding through routine channels. However, all the researchers providing evidence agreed that developing and validating NAMs was expensive, and that third sector groups have very little money relative to other funding sources. Private investment for NAMs in regulated testing settings was also highlighted as being dependent on the current testing guidelines, and as animal tests are still perceived to be necessary to progress a drug through the regulatory process (see Section 2), private investors can be reluctant to invest in companies wishing to replace animal models with NAMs, due to a perceived risk of failure.

1.5. Competition for awards

Recipients of awards from public funding bodies such as the BBSRC, MRC and NC3Rs reported that while specialist funding sources exist within the UKRI and NC3Rs for NAMs development, most of the funding goes to those using established methodologies based on animal studies. The APPG heard that animal use is usually taken for granted and one researcher stated that "human relevant research requires the applicant to be much more creative and come up with innovative solutions to problems that would be relatively easy to address in an animal model". A lack of awareness and knowledge of NAMs on funding boards, and by reviewers of grant applications, was identified as a potential barrier to increasing NAMs funded projects, with the result that traditional (i.e. animal) methods typically predominate. Research by one expert contributor to the APPG sessions, for example, found that between 2014-2019 in the US, between $7M and $11M per year in funding was provided for animal research into breast cancer, but research using human-derived methods received less than $2M.[20] The MRC representative stated that they do not instruct the various boards how to allocate the funding they are given, and the NC3Rs confirmed that it is the boards themselves that decide this.

> ***"Human relevant research requires the applicant to be much more creative and come up with innovative solutions to problems that would be relatively easy to address in an animal model."***

[19] Available on request from media@crueltyfreeinternational.org

[20] Marshall LJ, Triunfol M, Seidle T. Patient-Derived Xenograft vs. Organoids: A Preliminary Analysis of Cancer Research Output, Funding and Human Health Impact in 2014-2019. Animals (Basel). 2020 Oct 20;10(10):1923. doi: 10.3390/ani10101923. PMID: 33092060; PMCID: PMC7593921.

1.6. Tracking NAMs funding

It was clear from the evidence sessions and from the science minister's response to a letter from the chair of the APPG in February 2021,[21] that NAMs funding outside of the contribution to the NC3Rs is not actively tracked in the BEIS or UKRI systems because research is not routinely categorised in this way. The science minister noted that MRC awards are categorised using automated coding and that one way of tracking NAMs projects might be to use Medical Subject Headings (MeSH) terms.

1.7. Summary of NAMs funding in the UK

Evidence presented at the APPG meetings in 2020-2021 indicates that UK funding for human relevant NAMs in 2019 amounted to ~£2M per annum through the NC3Rs organisation, comprising ~£1.6M from the CRACK-IT challenges and £0.4M from direct NC3Rs funding. This is less than 0.2% of the total budget for MRC, BBSRC and Innovate UK combined (£1.144B) and ~0.02% of the UK's total public expenditure on R&D of £10.45B (Fig. 4).

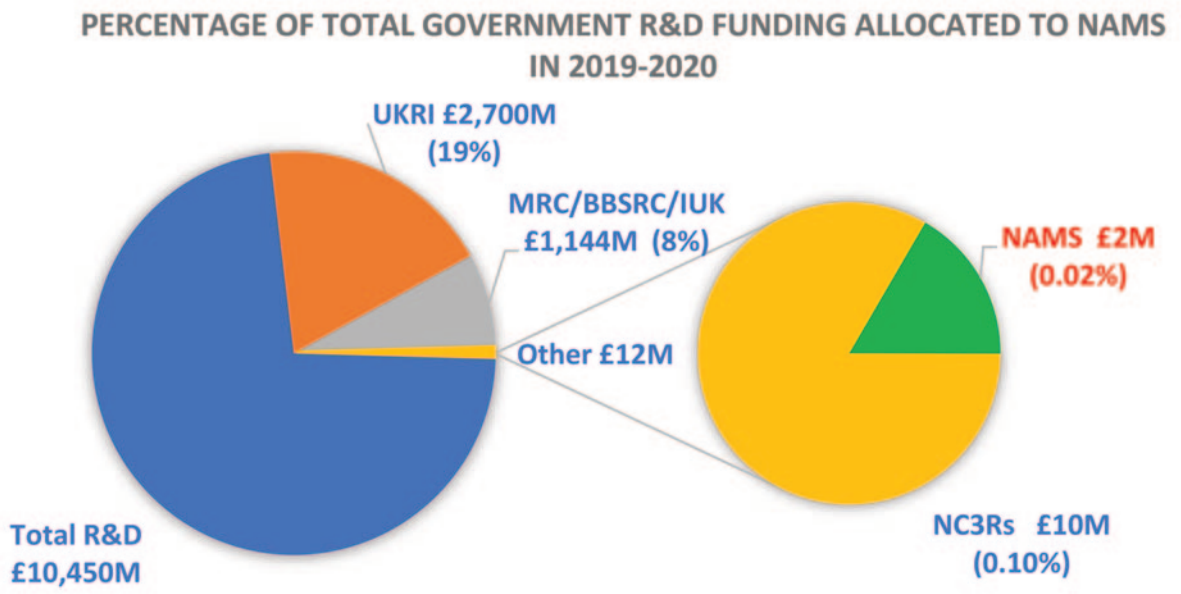

Figure 4: Proportion of research funding allocated to NAMs as a percentage of the total public R&D funding in 2019-2020 (£10.45B). UKRI funding was £2.7B, MRC/BBSRC/IUK combined funding was £1.144B, NC3Rs ~£10M and NAMs ~£2M.

> ***"UK funding for human relevant NAMs in 2019 amounted to ~0.02% of the UK's total public expenditure on R&D of £10.45B."***

[21] Letter from Amanda Solloway Nadhim Zahawi, 1 February 2021, https://www.humanrelevantscience.org/all-party-parliamentary-group/correspondence-with-government-ministers/

RECOMMENDATIONS

FUNDING

We recommend that the Government commits to increasing the funding of NAMs by strategically diverting resources away from animal-based approaches and towards NAMs.

- **Prioritisation**
  Funding of NAMs should be prioritised when allocating research budgets and increased support should be available to companies and academics developing NAMs, as well as for human-focused translational research through the appropriate research councils (MRC, Innovate UK etc). New funding would not be required as resources could be diverted from existing poorly performing animal-based approaches. A reprioritisation of such funding streams would therefore be financially neutral.

- **Using tax relief to incentivise the development and implementation of NAMs**
  Implementation of tax relief for R&D which uses non-animal methods, or which seeks to further the development of these technologies, could provide a means of incentivising human relevant, animal free R&D, while disincentivising research relying on animal use.

- **Tracking**
  Funding of NAMs should be tracked and reported. A first step is to provide a robust definition for NAMs (specifying what the term includes and excludes) built up of specific terms from the MeSH thesaurus.[22] The use of MeSH would allow NAMs to be effectively identified in the existing UKRI database of competitive funding decisions[23] and ensure that a reprioritisation of funding streams is supported.

We recommend that animal researchers should be legally obliged and financially supported to proactively shift their focus away from animal use and towards the development and use of NAMs, in line with current legislative requirements.

- **Proactive employment of NAMs**
  Allocation of funding specifically for the development of NAMs and for research employing NAMs should be prioritised (see above). All funders should clarify and emphasise the legal position regarding the requirement to use animals only if non-animal methods are not available (see section 2 and recommendations). There should be a shift from a presumption of animal use to an assumption that animals will not be used and funders should request robust explanations in the event that scientists propose to use animals. Scientists should be encouraged to reframe their research questions such that the use of animals becomes unnecessary, and a database of accepted NAMs should be made available for scientists at the stage at which they are formulating their research question and seeking funding.

[22] https://www.nlm.nih.gov/mesh/meshhome.html

[23] https://www.ukri.org/our-work/what-we-have-funded/competitive-funding-decisions/

2. CURRENT REGULATORY REQUIREMENTS FOR RESEARCH INVOLVING ANIMALS AND PHARMACEUTICAL APPROVAL IN THE UK

2.1. Research using animals in the UK

The law governing the use of animals in experiments in the UK is the Animals (Scientific Procedures) Act 1986, known as ASPA, which is enforced by Home Office's Animals in Science Regulation Unit (ASRU). Under ASPA, those conducting animal research must apply for three separate licenses: for their research institution, for the research project and for the researcher. ASPA also enshrines the 3Rs principles into UK law and creates a duty to conduct a harm-benefit analysis (harms to animals vs. benefit to humans) when applications for project licenses are assessed. Applications for project licences to conduct experiments on animals are rarely if ever refused in the UK; certainly, none was refused in 2020.[24,25] A leading academic expert on NAMs and former adviser to the Government during the drafting and passage of ASPA, gave evidence to the APPG calling for reform to the application of ASPA, in particular, a better assessment of the justifications for using animals. The application of the harm-benefit analysis focuses on harms to animals as opposed to benefits to humans, he reported, with the benefit to humans simply being assumed because of the severity of the disease being investigated as opposed to being based on the merits of the research proposed. It was suggested that for the harm-benefit analysis to be properly conducted, experts with knowledge of the specific research in question, and/or of relevant NAMs, would need to have greater input. This sentiment was echoed by an expert in animal law who told the APPG that the Home Office could evaluate the likely success or clinical relevance of a particular animal study far more rigorously than it does at present.

2.2. Implications for approving animal work in the UK after exiting the EU

The APPG heard how ASPA 1986 was revised and updated in 2012 to conform to European Directive 2010/63/EU[26] on the use of animals in science. European Directive 2010/63/EU was formally introduced in 2013 and established measures for the protection of animals used for scientific or educational purposes. On leaving the EU in 2020, the APPG heard, Directive 2010/63 was retained in UK law as an amendment to ASPA and this included the legal duty that 'wherever possible, a scientifically satisfactory method or testing strategy not entailing the use of live animals, shall be used instead of a procedure'.* However, the APPG heard that at present there is no legal obligation to proactively take steps to develop these 'scientifically satisfactory method(s) or testing strategy(ies)', nor has the Directive's aspiration of animal-free science been formally incorporated into UK law. Consequently, there is little impetus to increase the use of human relevant NAMs in basic research in the UK.

[24] Busquet F, Kleensang A, Rovida C, Herrmann K, Leist M, Hartung T. New European Union statistics on laboratory animal use – what really counts! ALTEX. 2020;37(2):167-186. doi:10.14573/altex.2003241

[25] https://questions-statements.parliament.uk/written-questions/detail/2021-03-02/161856/

[26] https://www.legislation.gov.uk/eudr/2010/63/contents
*'Procedure' means any use, invasive or non-invasive, of an animal for experimental or other scientific purposes.

2.3. Pathway to pharmaceutical regulatory approval

The APPG heard from scientists as well as an employee from the MHRA (speaking in a personal capacity), all of whom provided an overview of the regulatory process for pharmaceuticals.

All potential drugs are required to undergo regulated testing to determine their safety and effectiveness before being tested in humans in formal clinical trials (Fig. 5). If the pre-clinical stages are successful, the drug then progresses to three phases of clinical trials starting with (typically) healthy people in Phase 1, through to patient volunteers in Phase 3. Preclinical and clinical trials are designed to assess the efficacy and long-term effects of new drugs before marketing approval is granted by the relevant regulatory body.

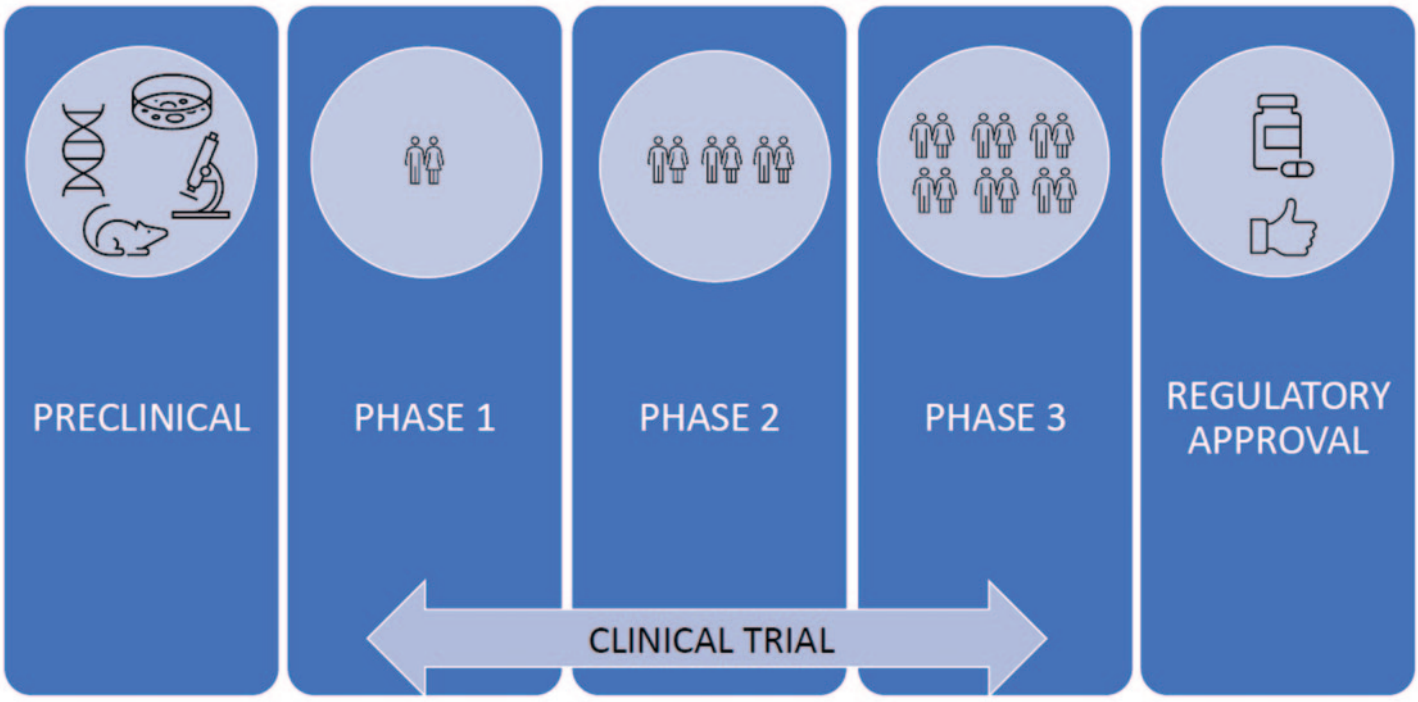

Figure 5: The drug testing process. Preclinical studies provide information on dosing and toxicity and may use in vivo (animal), in vitro (cells and tissues) and in silico (computational) methods. Phase 1 clinical trials primarily evaluate safety in a small number of participants; Phase 2 trials monitor effectiveness, side effects and the best dose to use in a larger number of participants; Phase 3 trials in a patient population confirm effectiveness and continue to monitor safety. Regulatory approval for a new drug to enter the wider population follows successful clinical trials.

2.4. Guidance on preclinical testing

The APPG heard how data from various tests during the preclinical stages of drug development are used by regulators to assess whether a drug should be allowed to progress to studies in humans. These data may come from in vivo tests (carried out in whole, living organisms, usually animals), in vitro tests (studies of biological properties conducted outside of a living organism e.g. in cell culture), and/or in silico tests (biological studies performed on a computer, or computer simulations or modelling).[27] Guidance on the preclinical testing of new drugs for pharmaceutical companies is provided by the various regulatory agencies worldwide and harmonised by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). [28]

[27] https://www.humanrelevantscience.org/wp-content/uploads/Accelerating-the-Growth-of-Human-Relevant-Sciences-in-the-UK_2020-final.pdf

[28] https://www.ich.org/

Representatives of newly established UK biotech companies told the APPG that current ICH guidelines generate an expectation that animal tests should be routinely used in the preclinical assessment of drugs. Despite this, the MHRA employee confirmed that there is no requirement that animal studies be used, which was confirmed by an expert in EU and international animal law. He also stated that the MHRA accepted alternatives to animal studies, that animal studies should not be the default, and that it made this clear to all sponsors of clinical trials. However, this does not reflect the experience of scientists reporting to the APPG, and as the NC3Rs states, "it has been common practice for more than 40 years to perform toxicity tests of pharmaceutical drugs in two animal species (a rodent and a non-rodent) for conventional drugs or so called "small molecules" [and] this principle is included in international regulatory guidelines [such as] ICH M3."[29] In 2020, 473,000 (33%) of all UK experimental procedures on animals were conducted to satisfy regulatory requirements.[30] The MHRA employee stated that the Government encourages the use and development of in vitro methods in place of animal testing and that the MHRA itself encourages this for the preclinical assessment of all new drugs. He also expressed his view that animal studies should only be conducted to evaluate safety concerns that cannot be adequately addressed another way, a position in line with the European Directive 2010/63/EU (see section 2.2) and stated his view that conducting an animal study simply to provide reassurance prior to exposing humans was wholly unacceptable. Speakers from both the MHRA and NC3Rs acknowledged that the guidelines need updating as a matter of urgency, since they fail to indicate how NAMs may be employed and create an impression that only animal methods are acceptable.

The need for updated guidelines was corroborated by representatives from both new enterprises embarking on regulated testing for the first time, and experienced industry representatives with extensive knowledge of the guidelines, who told the APPG they were concerned that the wording of current regulatory guidance almost exclusively refers to animal use for these tests, driving the expectation that animal tests are required for regulatory approval. The MHRA employee drew attention to the MHRA Innovation Office which provides advice and guidance on test selection for drug sponsors but acknowledged that academia and SMEs may be unaware of this facility. In addition, it was noted that the NC3Rs website at the time (May 2021) predominantly described animal methods and welfare, with only one of its 24 microsites referring to NAMs.

> ***"The wording of current regulatory guidance almost exclusively refers to animal use for these tests, driving the expectation that animal tests are required for regulatory approval."***

2.5. Opportunities for change

In recent years, new types of drugs such as biopharmaceuticals or biologics which specifically interact with proteins on human (and not animal) cells have been developed. Consequently, the argument for testing these drugs in animals is not persuasive and the current guideline for biopharmaceuticals (ICH S6) acknowledges this, stating, 'Conventional approaches to toxicity testing of pharmaceuticals may not be appropriate for biopharmaceuticals due to the unique and diverse structural and biological properties of the latter' that may include species specificity, immunogenicity, and unpredicted (...) activities'.[31] The APPG heard that the same approach could be applied to the safety assessment of other drug types and that ICH S6 could potentially serve as a template in such contexts.

[29] https://nc3rs.org.uk/news/opportunities-use-single-species-drug-development

[30] https://www.gov.uk/government/statistics/statistics-of-scientific-procedures-on-living-animals-great-britain-2020

[31] https://database.ich.org/sites/default/files/S6_R1_Guideline_0.pdf

2.6. New approaches in preclinical testing

All participants agreed that if NAMs were to be used for regulatory testing they should be able to answer the specific questions requested by regulators. They also noted that there was no legal requirement for new tests to be fully validated and accepted into test method regulations (such as those produced by the OECD for chemicals[32]), simply that the body of data supporting those tests should be relevant to the question being asked and sufficiently robust to give regulators confidence that they could be used to support clinical decision making and the communication of potential risks. Scientists reported that many scientifically robust NAMs already exist but that the specific regulatory guidance needed to promote their widespread use is lacking. Furthermore, it was agreed that comparing NAMs data against data generated by animal studies was problematic and illogical; NAMs are human-relevant and so would not be expected to agree with the animal data. The APPG heard that combining methods (e.g., in silico modelling of in vitro human data) was a powerful way of generating an understanding of the overall likely human response and that ideally, any comparisons should be against the gold standard of human clinical or real-world data, not animal data.

[31] https://www.oecd.org/chemicalsafety/testing/oecdguidelinesforthetestingofchemicals.htm

RECOMMENDATIONS

REGULATORY

We recommend that the Home Office commits to a more robust application of the harm-benefit analysis when assessing project license applications for animal research and requires robust evidence that the use of NAMs has been thoroughly considered.

- **Assessment of benefit**
  Methods for assessing the likely impact of animal research in terms of its clinical benefits, as well as the research team's track record in this respect, should be developed and rigorously applied as part of the harm-benefit analysis in applications for project licenses to ASRU. Where there is insufficient expertise available within ASRU to perform a proper assessment of benefit an independent opinion should be sought from an expert in the field.

We recommend that an aspiration for animal free science is reintroduced into UK law.

The European Directive's aspiration of animal-free science was not transposed into UK law and therefore there is little impetus to increase the use of human relevant NAMs in basic research in the UK.

We recommend that the Government commits to reviewing the current regulatory guidelines for animal research and pharmaceutical testing, with a view to updating these such that human relevant methods are recommended where appropriate in research and during the development and licensing of medicines.

- **Benchmarking**
  Current guidelines (i.e., ICH M3(R2)[33] and ICH S7[34]) should be reviewed, taking into consideration the existing use of NAMs within pharmaceutical development worldwide and across other sectors such as household products, chemicals, and cosmetics. Some human relevant NAMs have been accepted by regulatory authorities and guidance on how these may be used in the development and licensing of new medicines, should be made available. They might potentially be used as templates for harmonised guidelines.

- **Acceptance criteria**
  Regulatory agencies should clarify to stakeholders which data packages and requirements for the acceptance of human relevant NAMs are necessary. Case studies (anonymised if appropriate) from the MHRA Innovation Office should be shared with the scientific community to educate and raise awareness of how NAMs may be used.

- **Adherence to EU directive 2010/63/EU**
  Guidelines for both animal research and pharmaceutical regulated testing should be updated to clarify that, in accordance with European Directive 2010/63/EU (enshrined in UK law), a scientifically satisfactory method not using live animals should be used wherever possible. There should be a shift from a presumption of animal use to an assumption that animals will not be used. In addition, the Directive should be more robustly emphasised at the funding stage.

[33] https://www.ich.org/page/multidisciplinary-guidelines

[34] https://database.ich.org/sites/default/files/S7A_Guideline.pdf

- **Establishment of MHRA NAMs working group**
  The establishment of an MHRA NAMs working group, like those within the European Medicines Agency (EMA) for 3Rs[35] and the US Food and Drug Administration (FDA) agencies,[36,37] would encourage and expedite the training of regulators in the appropriate use of NAMs and facilitate the revision of current guidelines to include NAMs use.

[35] https://www.ema.europa.eu/en/documents/work-programme/work-plan-2018-joint-cvmp/chmp-working-group-application-3rs-replacement-reduction-refinement-regulatory-testing-medicinal_en.pdf

[36] https://www.fda.gov/science-research/about-science-research-fda/advancing-alternative-methods-fda

[37] https://www.fda.gov/media/144891/download

3. CURRENT CULTURAL MINDSET AND POTENTIAL OUTLOOK FOR BIOMEDICAL RESEARCH AND TESTING IN THE UK

Scientists gave examples of currently available human relevant NAMs that are already being used to perform valuable biomedical research which cannot be undertaken using animal procedures. However, they also highlighted the difficulties they routinely encounter when attempting to secure funding, when reporting their findings in journals and when using their data to support the development of new medicines; namely the problematic practice of being asked to provide animal data to support their research, even though it is not scientifically necessary. Overall, the APPG heard that among many scientists a mindset persists that animal research is essential for medical progress. It was agreed that a greater awareness of the scientific value of NAMs was needed among those who influence funding decisions and review publications. The MRC representative stated that the science community need to be encouraged to consider ways of conducting research that do not involve animals, and that this was a cultural and educational challenge. It was also felt by scientists at the APPG meetings that NAMs training should be embedded early, in secondary and tertiary education, and that needs at each level of education should be identified, and appropriate career structure and guidance employed, to prevent a skills shortage and a future lack of early career NAMs researchers. Others noted that scientists tend to be "creatures of habit", so if animal methodologies are what they are used to, they will tend to continue using them unless forced or incentivised to change. As one contributor observed, "it is easier to build on existing types of data than to create new types".

> ***"Scientists tend to be "creatures of habit", so if animal methodologies are what they are used to, they will tend to continue using them unless forced or incentivised to change."***

3.1. Changing the mindset: bottom-up approach

Some countries have recognised the potential of NAMs and have programmes underway to prioritise their development and uptake. In the Netherlands, Helpathons[38] bring together numerous stakeholders in a 24 hour online and in-person event to share and disseminate potential approaches and solutions to a particular human health research question. Representatives of the Dutch Transition Programme for Innovation without animals (TPI)[39] suggested that Helpathons 'catapult' the transition to NAMs, increasing the chances that a researcher will act on the advice given and build networks to support the use of NAMs. The Helpathons were described as open to everyone, with the collaboration between scientists wanting to transition to NAMs and those already using them being a key factor in their success, allowing scientists working with animals to see what alternatives were possible. The Dutch Primate Research Centre, for example, found the Helpathons to be a confidential forum for discussing its issues, providing an opportunity seldom open to them. The APPG also heard that the "effort and courage" required to move away from animal experiments (e.g., the implications for those previously regarded as experts in their

[38] https://www.tpihelpathon.nl/

[39] https://www.transitieproefdiervrijeinnovatie.nl/

field of "starting from scratch at the publication level" and learning completely new approaches) was acknowledged within Helpathons. Another positive aspect was felt to be the inclusion of non-experts such as members of the public, with this "outsider's view" regarded as invaluable for providing a societal perspective. All Helpathons now have a societal theme running parallel to the scientific theme, with patient organisations, for example, contributing to the discussions.

Helpathons enable dialogue between scientists from the worlds of animal research and NAMs research, leading to new opportunities and a growing number of potential funders. This, in turn, has generated more funding avenues through a new economy created especially by the Dutch Government for this research. The TPI awarded funding which was supplemented with cash and in kind contributions from industry. 'Helpathons' can link to finance solutions and funders who are more willing to take risks in this area. The Dutch Government has also made funding worth millions of euros available through a new finance economy specifically aimed at non-animal technologies, and although it has taken 3 years to get to this point, the APPG heard that €18M is now dedicated to preparing technologies for regulatory acceptance. This preparation involves all the relevant stakeholders, including regulatory groups and funders.

3.2. Changing the mindset: top-down approach

Helpathons are undoubtedly speeding up the transition to animal free, human relevant technologies for biomedical science in the Netherlands, but the APPG heard that both a bottom-up and a top-down approach are considered necessary to change the Dutch mindset around animal experiments. The EMA recently published its Regulatory Science Strategy to 2025,[40] which included recommendations promoting the use and development of non-animal methods and reducing and replacing animals in the testing of human and veterinary medicines. Likewise, the APPG heard how in 2020[41] (and updated in 2021)[42], the US Environmental Protection Agency (EPA) announced its intention to phase out vertebrate animal experimentation in the testing of chemicals for their impact on human health and the environment. This has resulted in a five-point work plan and funding to prioritise agency efforts and resources toward activities that support this aim.

3.3. Policy and targets

A recurring question throughout the APPG sessions was whether government deadlines or targets could influence the development and adoption of NAMs in the UK. The legal expert proposed that the 3Rs principles were fertile ground for the use of targets, which in his view would provide the discipline necessary for changing the behaviour of researchers, funders, and regulators. In this regard a Dutch researcher noted that a Directive from the Minister of Agriculture in the Netherlands, got "all the noses turned in the right direction", creating huge momentum and a change of mindset. While acknowledging that scientific research is immensely complicated and that it is not always possible to predict where it might lead, the legal expert highlighted that targets exist in areas such as climate science and the eradication of child or world poverty, which are also complicated disciplines. Targets, he suggested, do not have to take a numbers approach but must be sophisticated, multifactorial, and bespoke. Experience had also convinced the Dutch transition leader of the need for top-down leadership: "When the undercurrent [of Helpathons etc.] meets the leadership from the top, that's when things start happening". All parties agreed that while change is possible, it would take a lot longer without targets, and that incentivisation was vital for securing real progress. Finally, it was emphasised that targets are perfectly possible now, and without any need for legislative change, but that political will and commitment from the animal research community was lacking, stalling progress. As the UK legal expert noted, paradigm shifts rarely happen in a policy vacuum.

[40] https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/ema-regulatory-science-2025-strategic-reflection_en.pdf

[41] https://www.epa.gov/newsreleases/epa-awards-4-million-develop-new-approaches-evaluating-chemical-toxicokinetics

[42] https://www.epa.gov/system/files/documents/2021-11/nams-work-plan_11_15_21_508-tagged.pdf

> *Paradigm shifts rarely happen in a policy vacuum.*

3.4. UK Roadmap for Non-Animal Technologies

In 2015, a collaboration of the NC3Rs, BBSRC, MRC, Defence Science and Technology Laboratory (DSTL), Engineering and Physical Sciences Research Council (EPSRC), and Innovate UK produced a non-animal technologies roadmap for the UK[43] to guide the efforts of those working in this area. However, the six organisations made it clear that their participation in the roadmap "should not be construed as a commitment to ensuring its delivery". When asked about the status of this roadmap in one of the evidence sessions, the NC3Rs confirmed that the organisations have continued to work together on the programme (e.g. EPSRC and DSTL have co-funded some CRACK-IT Challenges with NC3Rs), that investment in commercial feasibility and collaborative R&D has totalled £7M (for 23 awards), and that the organisations are currently reviewing the situation with a view to future funding and revitalisation of the roadmap. In addition, the Medicines Discovery Catapult was established by Innovate UK to help commercialise and drive the adoption of new tools and technologies for the sector and it remains a key player in the translation of academically developed technologies into robust mainstream platforms. Nevertheless, the APPG heard that the roadmap partners acknowledged the programme lacked focus, for which various reasons were given, primarily related to budget deficiencies and priority changes. These have clearly stalled the UK roadmap to detrimental effect, and it was concluded that it (or an equivalent vision and strategy) desperately needed an injection of cash and incentives to function successfully.

[43] https://nc3rs.org.uk/sites/default/files/documents/NonAnimalTechCO082_RYE_4_nrfinal2.pdf

RECOMMENDATIONS

STRATEGIC GUIDANCE AND SUPPORTIVE INFRASTRUCTURE

We recommend that the Government commits to creating a dedicated ministerial position to lead an ambitious and detailed programme of work across all relevant departments to transition to human relevant NAMs with appropriate milestones, timelines, funding, and deliverables.

The 2015 UK roadmap for non-animal technologies[44] can form the basis for this programme. However, Government level commitment to milestones, timelines, funding and deliverables, as well as an injection of 'thought leadership', is necessary if the UK is to maintain and grow as a global science superpower and leader in the life sciences industry.

- **Implementation**
  The programme should be implemented as a standalone programme, co-ordinated and run independently by a dedicated minister. This would be advantageous for clarity of purpose and visibility and would highlight the strategic importance of such an initiative to the Government and UK science. It would also enable more "blue-skies" funding from a wide range of sources such as the Advanced Research and Invention Agency (ARIA)[45] and through private co-financing.

We recommend that the Government commits to establishing a UK Transition Programme for Innovation without animals (TPI) to prioritise awareness of NAMs and to incentivise collaboration between stakeholder groups, including academic researchers, industry, funders, and regulators.

- **Education, training and collaboration**
  All stakeholders and non-scientists, including the public and policy makers, need to be aware of the nature and value of human relevant NAMs. NAMs training should become embedded in secondary and tertiary education, with needs at each level of education identified.

  Collaborative opportunities must be incentivised between academia and industry, industry sectors, regulatory agencies, and healthcare organisations such as the NIHR, as a core part of this programme. Helpathons could provide fora in which scientists using animals and those using NAMs are able to exchange ideas. The Government, UKRI and private bodies could provide incentives for collaboration, and multi-disciplinary technology centres could be developed in the longer term. Engagement with UK and European programmes should be facilitated, and open data sharing promoted. The development of databases of accepted NAMs, to build confidence in their implementation and enable knowledge exchange, will be key.

  Skill sets should be identified and developed to ensure that a critical mass of specialists is employed in the UK. The development of multidisciplinary scientific skills in NAMs, such as in engineering, mathematics, chemistry, computer science and molecular biology, should be prioritised across research, industry, and healthcare.

[44] https://www.ukri.org/wp-content/uploads/2015/11/IUK-071221-RoadmapNonAnimalTech.pdf

[45] https://www.gov.uk/government/publications/advanced-research-and-invention-agency-aria-statement-of-policy-intent/advanced-research-and-invention-agency-aria-policy-statement#innovative-funding-approaches

We recommend that the Government commits to evaluating preclinical research based on its clinical relevance and allocates funds accordingly.

- **Retrospective review of animal research**
  While retrospective review of some projects is already a requirement of the directive, all UK animal research (from a specified date) that has been granted licenses under ASPA should be evaluated to determine whether clinical benefit has resulted.[46] In addition, bodies of scientific work reporting research on animals in specific disease areas (e.g. cancer or Alzheimer's) should be critically reviewed in terms of their contribution to treating or managing that disease. Research that has not benefitted humans should be deprioritised, with funding diverted to human relevant NAMs.

[46] Pound P, Nicol CJ (2018) Retrospective harm benefit analysis of pre-clinical animal research for six treatment interventions. PLoS ONE 13(3): e0193758. https://doi.org/10.1371/journal.pone.0193758

CONCLUSIONS

The clinical relevance of much preclinical animal research has been in doubt for some time now, with poor translation to humans across a wide range of conditions. In addition, some drugs result in serious adverse drug reactions and even death when released into the general population, despite having been previously tested on animals.

The APPG believes that this cannot continue. Although there is increasing evidence that NAMs produce data that can be extrapolated more accurately to humans, they are not used routinely in drug testing and disease research because of a lack of awareness of their potential and because of the still widely held belief that animal research is the only acceptable way to discover, develop and test new medicines and therapeutics.

Although the APPG was told in ministerial responses to letters and written parliamentary questions that funding for human relevant NAMs was primarily through the NC3Rs organisation, it became evident that only 16% of all NC3Rs funding for replacement was for NAMs intended to have application to human health. This amounts to just £7.5M over 17 years or ~£440K per annum and is simply nowhere near enough to address the current health crisis in the UK.

> ***“Only 16% of all NC3Rs funding for replacement was for NAMs intended to have application to human health.”***

While it is very difficult to accurately identify how much the UK spends in total on human relevant NAMs research, calculations based on the evidence presented suggests that at most this amounts to ~£2M per annum, compared with between £300M and £1.1B on research involving animals. Human relevant NAMs funding therefore represents between 0.2% and 0.6% of total biomedical research funding in the UK and ~0.02% of the total public expenditure (£10.45B for 2019-2020) on R&D. This is woefully inadequate and will impede the UK’s efforts to improve human health and retain its status as a world leader in the life sciences arena.

> ***“While it is difficult to accurately identify how much the UK spends in total on NAMs research, the evidence suggests that at most this amounts to ~£2M per annum, compared with between £300M and £1.1B on research involving animals.”***

Increased funding in strategic areas devoted to the development and adoption of human relevant NAMs is patently needed and it could strongly be argued that the current funding system is actually obstructing biomedical progress in the UK.

> ***“Current human relevant NAMs funding … is woefully inadequate and will impede the UK’s efforts to improve human health and retain its status as a world leader in the life sciences arena.”***

While animals do not have to be used in basic research or for regulatory purposes, evidence presented to the APPG indicates that a culture of animal use is perpetuated within academia, industry, and regulatory agencies. Current regulatory guidelines for the safety assessment of new drugs unquestionably need to be updated to make this position clear, to remove the almost exclusive references to animal use for testing and to reflect the potential of NAMs. It was felt that outdated guidelines currently hamper the adoption of human relevant NAMs for the safety testing of drugs and prolong the use of poorly performing animal methods in basic research, with catastrophic results for the UK's health and for the modernisation of biomedical research. The APPG looks forward to working with the new Policy Function that is being established to focus on animals in science. The APPG would especially welcome the opportunity to provide evidence to feed into the Policy Function's development of the UK's vision for the use of animals in science, focusing on the benefits of transitioning from animal research to human relevant NAMs.

> ***"Outdated guidelines currently hamper the adoption of human relevant NAMs for the safety testing of drugs and prolong the use of poorly performing animal methods in basic research, with catastrophic results for the UK's health and for the modernisation of biomedical research."***

Poor funding levels for NAMs will prevent transformative technologies from addressing the current crisis in research, drug development and life sciences in the UK. As long as animal use is considered necessary for biomedical research, funding will continue to be allocated to ineffectual technologies, with patients continuing to suffer and drug failure rates increasing. Only by diverting significant funds from existing, non-productive technologies will breakthroughs be possible. It is time to re-evaluate the current paradigm. There is no longer any need to rely on animal surrogates. The modernisation of medical research is possible with human relevant NAMs, many of which are being developed by UK institutions and companies today. But effective and courageous leadership is necessary to enable this transformation, as is the adoption of sophisticated targets to support and promote a paradigm change.

The way we do biomedical research in the UK needs to change. Human relevant NAMs can make this change happen but until their development and use is prioritised by the Government, UK science and the health of our nation will lag behind those of other countries, with devastating consequences. The APPG for Human Relevant Science strongly believes that there is a golden opportunity for the UK to make more effective use of its substantial expenditure on biomedical sciences, to enhance the productivity of industry, improve public health and cement its status as a global science superpower.

> ***"The modernisation of medical research is possible with human relevant NAMs, many of which are being developed by UK institutions and companies today."***

APPENDIX

Government funding and initiatives potentially impacting NAMs development and implementation

First announced in July 2020, the Government **R&D roadmap**[47] was described as "a once-in-a-generation opportunity to strengthen our global position in research, unleash a new wave of innovation, enhance our national security and revitalise our international ties". It was stated that the Government would use this opportunity to pursue ambitious new goals – the "moon shots" that would define the next decade and beyond – to create long-lasting economic and societal benefits for the UK. In addition, the Government has repeatedly emphasised its commitment to maintaining and extending Britain's position as a global leader in the life sciences, the most recent iteration being in its July 2021 **Life Sciences Vision**.[48] As part of this commitment, it has set a target for UK investment in Research and Development (R&D) to reach 2.4 per cent of GDP by 2027 and an increased spend to £22B by 2024/2025.

However, members of the scientific community have expressed concerns over the current state of funding for research. The Government's decision to reduce **Official Development Assistance (ODA)** from 0.7 to 0.5 per cent of Gross National Income (GNI) in 2021[49] prompted significant concern from the scientific community.[50] This reduced allocation left UKRI with a shortfall of £120 million between its allocations and commitments. Professor Christopher Smith, UKRI's International Champion, commented that this reduction 'will affect every UKRI Council, including Innovate UK, and will have whole-system impacts in the UK and overseas.'[51] In addition, medical charities playing a significant role in funding scientific research contributed £1.7 billion to R&D in the UK in 2020.[52] However, the COVID-19 pandemic had a devastating financial impact and while the Government announced a £20 million fund to support early career researchers funded by medical research charities,[53] these organisations warned that much more support was needed.[54]

The Government has set up a new agency (with funding of £800 million) to support high-risk, high-reward science; the **Advanced Research and Invention Agency (ARIA)**. ARIA is intended to be more agile and independent than other agencies, but it is still not clear at this stage whether it will choose to focus on medical research.[55]

In June 2021, the Prime Minister announced plans to create a **National Science and Technology Council**, as well as an **Office for Science and Technology Strategy**. The Council is to be chaired by the Prime Minister, while the Office will be led by Sir Patrick Vallance, the Government's Chief Scientific Adviser. These new entities will play a key role in determining the UK's science strategy and deciding which technologies will provide competitive advantage.[56]

[47] https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/896799/UK_Research_and_Development_Roadmap.pdf

[48] https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1000030/life-sciences-vision.pdf

[49] https://commonslibrary.parliament.uk/research-briefings/cbp-9224/

[50] https://hansard.parliament.uk/commons/2021-03-17/debates/E06E89F6-64A1-4B7C-8B90-09481981ECAC/ResearchAndDevelopmentFunding

[51] https://www.ukri.org/our-work/ukri-oda-letter-11-march-2021/

[52] https://www.amrc.org.uk/pages/category/member-directory?Take=20

[53] https://www.gov.uk/government/publications/beis-research-and-development-rd-budget-allocations-2021-to-2022/beis-research-and-development-rd-budget-allocations-2021-to-2022

[54] https://www.amrc.org.uk/news/amrcs-response-to-20-million-government-support-for-early-career-researchers-supported-by-charities

[55] https://www.gov.uk/government/publications/advanced-research-and-invention-agency-aria-statement-of-policy-intent/advanced-research-and-invention-agency-aria-policy-statement

[56] https://www.gov.uk/government/news/prime-minister-sets-out-plans-to-realise-and-maximise-the-opportunities-of-scientific-and-technological-breakthroughs

In July 2021, BEIS published the **UK Innovation Strategy** including details on two major funding initiatives from the British Business Bank. **The Life Sciences Investment Programme** is a £200 million fund that will address the 'growth-stage funding gap' for life sciences companies. **Future Fund: Breakthrough** is a £375 million programme that will run alongside private investment. Its focus will be on breakthrough technologies that can have a transformative impact, including in the field of medicines development.[57]

The UK Innovation Strategy also described the establishment of an **Innovation Missions Programme** to tackle challenges affecting the UK, including those relating to public health. Once these 'missions' have been identified, support will include challenge funding, as well as policy initiatives. In addition, the Strategy identifies seven technology 'families', which represent areas of strength for the UK, including AI, Digital and Advanced Computing; Bioinformatics and Genomics; and Engineering Biology. These are key fields for NAMs, and we believe that future Government policy should specifically recognise these as being animal free, human relevant techniques. The new National Science and Technology Council will be responsible both for identifying key 'missions' and for further prioritisation within the technology families, presenting a key strategic opportunity for funding NAMs.

[57] https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1005000/uk-innovation-strategy.pdf

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