Written Evidence Submitted by the Lord Dowding Fund for Humane Research (C190095)

About the LDF

The Lord Dowding Fund for Humane Research (LDF) supports and funds advanced methods of scientific and medical research and training, which replace the use of animals or lead to the adoption of non-animal research methodologies. The LDF present evidence here to illustrate why the UK must prioritise New Approach Methodologies (NAMs) for vaccine and drug development in order to respond more rapidly and effectively to the current and future pandemics.

Summary points

- New approach methodologies (NAMs), which focus on human biological processes to investigate disease and potential treatments, have been identified as disruptive technologies with the potential to revolutionise disease research and drug development, bringing safer and more effective treatments to the market more quickly and at a lower cost than traditional methods.
- The capacity and capability of the UK to respond to the current and future emergencies would be significantly enhanced if the UK research base had a stronger foundation for deploying NAMs for the development and testing of vaccines and therapeutics.
- Actions are required by Government to encourage the development and uptake of NAMs in the UK, ensuring that only the most effective and safe human-based methods are used in vaccine and drug development. These actions include: building supportive infrastructure that facilitates the adoption of NAMs; ensuring that funding is strategic, and directed towards NAMs that could yield significant public health benefits; building a strong skills base in NAMs to enable more rapid discovery of novel vaccines and therapeutics; incentivising collaboration across industries and disciplines; and, crucially, engagement with regulators to encourage flexibility within regulatory guidelines, so that NAMs data can be accepted in place of traditional research methods.
- With the rapid deployment of funding and resources given for COVID-19 research it is vital to undertake reviews to evaluate the quality of the traditional research methods used to understand and control the SARS-CoV-2 virus, the benefits to public health and the financial cost to the public purse compared to more advanced research methods, such as NAMs.
- The UK requires a preparedness strategy to respond to the current and future health emergencies that facilitates the uptake of biomedical technologies and research methods that can bring about a rapid response to vaccine and drug development. On an international level, for over a decade, regulatory agencies, governments and funding bodies have been encouraging a shift towards NAMs, with many producing roadmaps, consisting of targets, deadlines and actions to progress their development and uptake. The UK is at risk of falling behind on global developments in this field and missing opportunities for growth of an innovative industry that can also benefit public health and the economy.

The capacity and capability of the UK research base in providing a response to the outbreak, in terms of: advice to government, public bodies and others on managing the outbreak; the development of testing, diagnostic methods and technologies; the development and testing of vaccines; and the development and testing of therapeutics.

The capacity and capability of the UK research base in providing a response to the outbreak in terms of the development and testing of vaccines and therapeutics

1. While it is good that the UK is making progress towards the development and testing of vaccines and therapeutics for COVID-19, there are ways that the UK research base could be significantly enhanced in order to provide a more rapid response to the current and future outbreaks. For over a decade, regulatory agencies, governments and funding bodies have been encouraging a shift towards New Approach

Methodologies (NAMs) in biomedical research and testing.[1, 2, 3, 4, 5, 6, 7, 8] NAMs are defined as "new scientific approaches that focus on human biological processes to investigate disease and potential treatments, using human cells, tissues, organs and existing data".[9] NAMs have been identified as disruptive technologies,[10] which have the potential to revolutionise disease research and drug development, bringing safer and more effective treatments to the market at a lower cost, and, as vitally important to speeding up the development of vaccines and therapeutics, more quickly compared to traditional models that use animals or animal tissue.[11 , 12, 13, 14]

2. Such advanced research techniques are already being deployed around the world to investigate vaccines and drugs for COVID-19, but require more support. These include: artificial intelligence models to predict which drugs could be used to prevent or treat COVID-19;[15, 16, 17] human organ-on-a-chip technology for emulating human lung infection,[18] and in vitro 3D human airway cell models for evaluating drugs.[19] In addition, NAMs are also being deployed to investigate the virus and the disease it causes, including: mathematical modelling to study how the virus transmits and replicates;[20] patient lung fluid cultures to study the virus genome;[21] patient biopsy samples to investigate how the virus damages the body;[22] and organoids to investigate how the disease infects human tissue.[23]

3. The capacity and capability of the UK to respond to the current and future emergencies would be significantly enhanced if the UK research base had a stronger foundation for deploying NAMs for the development and testing of vaccines and therapeutics. [The specific foundations needed for supporting the development and uptake of NAMs in UK biomedical sciences are outlined later.] These sophisticated research methods have the potential to deliver safer, more effective vaccines and treatments to the market more quickly, and at a lower cost[24] compared to traditional methods, but they require more support to accelerate their progress for research into COVID-19 and future pandemics. Consequently, there is a risk that the UK research base is less prepared in responding to the current and future outbreaks by continuing to focus resources in traditional research methods, resulting in significant delays in the development and testing of vaccines and therapeutics, as well as being of risk to patients and volunteers.

Problems caused by focusing on traditional models for development of vaccines and therapeutics, which could slow down UK's ability to respond

4. While there has been an unprecedented surge in collaboration and funding of research and testing to find vaccines and treatments for COVID-19, the current requirement of regulatory bodies for data from animal models may be responsible for causing significant delays in responding to the current pandemic.

5. The World Health Organization-China Joint Mission has advised that the "ideal animal model for studying routes of virus transmission, pathogenesis, antiviral therapy, vaccine and immune responses has yet to be found",[25] and the US National Institute of Allergy and Infectious Diseases report that "replicating human disease, particularly its more severe manifestations, in an animal model may be challenging."[26] In a move to accelerate the process, the International Coalition of Medicines Regulatory Authorities (ICMRA) has advised that the usual animal disease models to test the efficacy of potential vaccines for the virus are not required before proceeding to human clinical trials.[27] Despite this, such tests are still taking place, and in some cases in parallel with clinical trials,[28] which is a use of precious resources.

6. In the UK animal models are being used for vaccine testing, including in rodents,[29, 30] ferrets and primates,[31] and for therapeutic antibody production;[32] UK researchers are also partnering with researchers outside of the UK using animal models[33]. Internationally animal models are being used for drug testing,[34] to study how different species are affected by the disease,[35] how the disease transmits[36] and ventilator testing.[37]

7. Significant funding and precious time are being spent using animal models, with known species differences affecting the translation of research data to humans. Mice are one of the most commonly used species in drug and vaccine research.[38] In addition to major differences between human and mouse respiratory systems,[39, 40, 41] species differences specific to research for SARS-COV-2 include that mice do not naturally

have the same receptor gene (ACE2) the virus uses to infect human cells.[42] Researchers are now attempting to use "humanized" mice to ensure they contract the virus.[43] While other species, including non-human primates, do not experience the disease in the same way as humans, with the species tested only showing a mild illness.[44, 45]

8. Furthermore, vaccine research and development typically takes 15-20 years,[46] with animal research, currently, a major part of the process and more than 90% of drugs which prove promising in animal trials fail in humans, either due to lack of effectiveness or safety concerns.[47] While oral evidence has already been presented to the Science and Technology Committee on how safety studies in animals as part of vaccine development supposedly protects against adverse drug events,[48] this is not always the case. Animal studies do not necessarily demonstrate that an appropriate immune response is triggered by the therapeutic intervention, as can be seen by the tragic events of the TGN-1412 clinical trials in which healthy volunteers were administered compounds, previously found to be safe in animals (including at doses 500 times higher in primates), triggering a massive immune response nearly killing the volunteers.[49, 50] Similarly, animal studies do not predict the safe or optimal dosage for patients as evidenced by the trial for BIA 10-2474 by French company Biotrial, which saw six volunteers hospitalised displaying neurological symptoms, one lost all his fingers and toes and one died. An investigation confirmed that high doses had been administered over long periods to monkeys, dogs, mice and rats with no comparable effects. Doses in some monkeys are estimated at around 100 times higher without causing neurological toxicity like that in humans.[51]

9. It is vital not to further burden our NHS with patients suffering adverse drug reactions (ADR) at this critical time, particularly when vaccines and therapeutics are heading to clinical trials more rapidly. Many therapeutics already in the market for other conditions have suboptimal efficacy or adverse effects that can result in serious illness, sometimes even fatal.[52, 53, 54] In the UK, hospital admissions caused by ADR account for 4% of bed capacity and are responsible for 10,000 deaths a year,[55] and in England alone cost the NHS up to £1.6 billion per year.[56] This is despite huge investment in traditional animal research methods within the biomedical sciences.[57] The inefficiencies in the current system of vaccine and drug development in general requires urgent addressing, so that the UK is more prepared to respond rapidly and effectively to future pandemics. Currently, preclinical testing is costly, time consuming and resource intensive, and there is a need for testing methods which predict human safety and efficacy more quickly and reliably.[58] NAMs, which incorporate human tissue and data, have specifically been identified as having the capability to enable the "more rapid discovery and development of medicines"[59].

Prioritise NAMs to accelerate the development of vaccines and therapeutics

10. In order to respond more rapidly and effectively to the current and future pandemics, it is important for the UK to focus on research methods that employ human data for vaccine and drug development. NAMs have been identified as important to speeding up the development of vaccines and treatments for disease and bringing safer and more effective treatments to the market at a lower cost and more quickly than compared to traditional animal methods.[60, 61, 62, 63]

11. Alongside over 100 experts, academics, and other concerned parties, the LDF have signed an open letter urging the World Health Organization, national governments, funding bodies, regulators, and the scientific community as a whole to prioritise funding and resources for advanced non-animal scientific methods to accelerate the discovery and use of effective vaccines and treatments for COVID-19 and other human diseases.[64]

The flexibility and agility of institutions, Government departments and public bodies, and processes to respond appropriately during the crisis including: the availability and responsiveness of funding; and the optimal functioning of regulatory and ethical processes; the availability and influence of scientific advice

in all Government departments and public bodies—including by departmental Chief Scientific Advisers; and the extent to which decisions taken drew on that advice.

12. For UK institutions and Government to respond appropriately during emergencies such as the COVID-19 pandemic, it is vital that the UK biomedical sciences industry is adequately supported and equipped with infrastructure that will enable an efficient and effective response. With NAMs, which incorporate human tissue and data, predicted to enable the more rapid[65] and effective[66] development and discovery of vaccines and therapeutics, it is vital that the UK is strategic in building a supportive infrastructure for the deployment of these methods. This includes infrastructure that supports NAMs through strategic funding, enables regulatory flexibility for using data generated from NAMs, and building confidence in scientific advice and decisions which are based on NAMs data.

13. The LDF have recently co-authored a white paper as part of the Alliance for Human Relevant Science, alongside NAM experts and businesses, which outlines actions required by the UK Government and agencies to encourage and support the uptake of NAMs by UK scientists.[67] This will ensure that only the most effective and safe human-based research methods are used in vaccine development and drug evaluation and provide a more resource-efficient means to responding to the current and future public health emergencies. Some of the actions recommended, which would enable greater flexibility and agility, particularly in the event of future public health emergencies, are:

- **Supportive infrastructure:** a central government-backed body is needed to enable the strategic coordination of the development and uptake of NAMs, and to provide access to resources (equipment, data, e-infrastructures, etc.) and communication networks. This body would facilitate access to funding and equipment, as well as supporting communication networks, knowledge transfer and sharing of resources across disciplines and industries – resources, of which, are all vital in responding to future emergencies, allowing for Government to make measured and fully informed decisions.
- **Strategic funding:** to facilitate research and development of, and incentivise full engagement with, NAMs, such as those which could be beneficial in the overcoming or preventing future pandemics, funding priorities need to be strategic. Funding should be directed towards NAMs that could yield significant public health and economic benefits, with high market potential that might attract business investment. Basic research will require significant funding, but with a focus on areas that demonstrate strong translation to human biology. Capital funding is also needed to invest in research centres dedicated to developing NAMs, that can coordinate responding to future health emergencies.
- **Improved education:** to improve the UK responsiveness to future pandemics through the deployment of NAMs, there needs to be an increase in training opportunities for emerging and established scientists to engage with NAMs in their current research. This will enable a strong foundation in skills that could lead to more rapid discovery of vaccines and therapeutics. It is also important to recognise that barriers can exist in adopting such new technologies. Therefore, changing perceptions and building confidence in NAMs in the scientific and regulatory community[68] is vital for their acceptance, and in using their data to make effective health decisions in future emergencies.
- **Multidisciplinary collaboration:** collaboration between industries and disciplines is essential for achieving the best scientific, and consequently health, outcomes, as well as for effective Government decision making that is based on more comprehensive sources. Deployment of NAMs in such decision making will require increased opportunities for collaboration between disciplines and industries, as well as the forging of new partnerships between basic and applied researchers, industry and end-users. Collaboration of researchers across disciplines could establish new and innovative ways of asking research questions and the methods used for answering them. This can help to bring together the best minds to deliver rapid health solutions using advanced human relevant technologies.
- **Engagement with regulators:** crucially, for Government to respond rapidly to the current future health crises, regulatory processes need to be adaptable to public health needs. While NAMs have the ability to speed up vaccine and drug development, a lack of regulatory flexibility in the development process will lead to delays in Government decisions. Early engagement with regulators is, therefore, vital to facilitate the adoption of data generated from NAMs into regulatory guidelines[69], rather than a

requirement for data relying on traditional methods, which can cause delays to health interventions reaching the public. The UK's response to the current global pandemic could have been more strategic: despite the ICMRA advising that, to accelerate the vaccine development process, the usual animal disease models to test the efficacy of potential vaccines for the virus are not required before proceeding to human clinical trials,[70] such tests are still taking place in the UK, and in some cases in parallel with clinical trials.[71]

14. The UK has world-leading universities and is home to some of the largest pharmaceutical companies in the world. By building on and strengthening our current capacity, government backing to put these structures in place would enable a more efficient response to the current pandemic, and more rapid deployment of NAMs technologies for future health emergencies.

The capturing during the crisis of data of the quantity and quality needed to inform: decisions made during the crisis; and to maximise the learnings afterwards.

15. With the rapid deployment of funding and resources currently being given for research into COVID-19 it is vital to undertake reviews to evaluate the contribution of this research to understanding and controlling the SARS-CoV-2 virus, the benefits to public health and the financial cost to the public purse compared to other methods.

16. The view of animal models as the "gold standard", against which all new technologies should be compared, threatens to impede NAMs from being adopted[72, 73] in the UK. The scientific value of using animals in comparison to non-animal methods in research has not been evaluated by an independent body in order for their value to be assessed, while systematic reviews of animal studies demonstrate poor clinical relevance[74, 75] and NAMs, such as machine learning, have been shown to outperform animal methods for toxicology testing.[76] Despite decades of research relying on the rationale that "extrapolating results to other species is based on the extensive homology and evolutionary similarity between morphological structures and physiological processes among different animal species and between animals and humans", this hypothesis has not been verified.[77]

17. A 2011 review by Professor Patrick Bateson evaluated the quality, outputs and impacts of ten years of publicly funded UK research using non-human primates, and found that "in most cases... little direct evidence was available of actual medical benefit in the form of changes in clinical practice or new treatments".[78] In a later discussion, Bateson goes on to state that "there was a tendency among researchers to make overoptimistic and unsubstantiated claims for their work and how it might improve the treatment of brain disorders, presumably to strengthen their case for funding".[79] In prioritising and allocating funding, as well as reviewing the contribution, of any animal research to the current pandemic, it is vital that such unsubstantiated scientific claims do not continue to be repeated, in order to maximise the learnings.

18. As well as the major scientific and, consequently, public health concerns over the use of animal models in responding to health emergencies, there are also issues at an economic level over the use of animal models. The continued funding of animal research carries both economic and societal costs. Animal research is costly in terms of expense and time, and has low predictive value for humans.[80, 81] Poor translation of animal models to human research can hinder progress in the development of effective and safe treatments for patients,[82] with resource intense animal models repeatedly failing to predict severe side effects in humans, resulting in ADR and drug trail disasters,[83, 84, 85, 86, 87] and withdrawn medicines.[88] Animal research has poor scientific validity, putting patient safety at risk; 80-90% of drugs that have proved promising in animal trials fail in human trials due to safety or efficacy concerns[89, 90] resulting in huge economic and scientific costs. Prior to the UK's exit from the EU, in 2008 the European Commission estimated that, for drugs which make it to market, ADR are one of the leading causes of death, killing 197,000 people in the EU each year and costing €79bn.[91] In England alone it is estimated that hospital admissions related to ADR cost the NHS in excess of £1.6 billion annually.[92]

19. Ultimately animal models are a poor model in terms of science and, consequently, economics; the quality of scientific output suffers, and resources are wasted when animals are used as models for humans. On the other hand, NAMs have been identified as disruptive technologies,[93] with the potential to revolutionise disease research and drug development, bringing safer and more effective treatments to the market at a lower cost compared to traditional animal methods.[94, 95, 96, 97] As part of building strong foundations for responding to future emergencies, it is essential that the necessary structures and financial support are in place to advance these disruptive technologies, which have the potential for both health and economic benefits.[98]

The mechanisms for communication of scientific evidence internationally, within national governments and with the public: including the handling of conflicting scientific opinions.

20. Only approximately 0.036% of research and development expenditure in the EU has been specifically invested into non-animal research methods (figures for the UK are not available).[99] Despite the underfunding of NAMs, they are revealing themselves as essential tools in the speedy fight against COVID-19, as well as contributing to a better understanding of disease in general.[100.]

21. Animal research is viewed as controversial by the general public, with the majority of the public (60%) wanting to know more about alternatives to animals used in research.[101] With animal researchers seeking to gain public approval of their methods, it is widely acknowledged that the benefits of animal models are overstated.[102, 103, 104, 105, 106, 107] In reporting of COVID-19 research, and science communication in general, it is vital that the public are well informed about the important contribution human based methods of research are making to speed up the process of research and development of effective treatments and vaccines to fight the virus causing COVID-19.

The UK's readiness for future outbreaks, including a consideration of: the National Risk Register; the UK Pandemic Influenza Strategy; and PHE's Global Health and Infectious Diseases Strategy.

22. The UK requires a preparedness strategy to respond to the current and future health emergencies that facilitates the uptake of biomedical technologies and research methods that can bring about a rapid response to vaccine and drug development. The development and uptake of NAMs, which are promised to deliver "improved decision-making tools that result in more rapid discovery and development of medicines, agrichemicals, chemicals and consumer products"[108], will be vital for considering the preparedness of the scientific community in responding rapidly and effectively, and for supporting Government decision making.

23. For the UK to remain a world leader in science and ready to adapt to future emergencies, it is vital that efforts into research and development are strategic and aligned with international research priorities. Protecting and enhancing current, and future, public health must be a key research funding priority, particularly considering the current health crisis. As well as emerging diseases, such as COVID-19, many major existing diseases remain poorly understood and lack adequate treatments.[109] The lack of available treatments places substantial economic burden on healthcare systems, which face increasing pressure from a growing population that is living longer. Of the treatments that are available, effectiveness is suboptimal, with many causing adverse outcomes or even serious illness, further burdening our healthcare system,[110, 111, 112] something which affects the future readiness to respond to a public health crisis.

24. To address this ongoing global healthcare crisis, agencies across the world are prioritizing the growth of NAMs in biomedical research and testing, which have the potential to revolutionise disease research and drug development, bringing safer and more effective treatments to the market, more quickly and at a lower cost, compared to traditional animal methods.[113, 114, 115, 116]

25. In the past several years, NAMs have progressed exponentially across the world, with significant advancements being made in the fields of *in vitro* and *in silico* science. For example, the Wyss Institute in the US is now a global leader in Organ-on-a-Chip, which is fast becoming a disruptive technology within cell culture science across the world.[117] Given that data obtained by Organ-on-a-Chip are more accurate, can be achieved at a lower cost and with higher throughput compared to traditional animal based methods, in 2016, the Director of the US National Institutes of Health predicted that within 10 years this method will mostly replace traditional methods of testing drug toxicity.[118] The predicted business opportunities for NAMs are substantial: Organ-on-a-Chip technologies could save up to a quarter (~$700 million) of total drug development costs,[119] and they are expected to be worth between $60-117 million by 2022;[120] cell-based assays are expected to reach $18.9 billion by 2024;[121] stem cell technologies to reach $28 billion by 2029;[122] and *in vitro* toxicity testing expected to reach $14.4 billion by 2025.[123]

26. In order to advance predictive biology in the UK, a 2015 collaborative report was published by Innovate UK, NC3Rs, BBSRC, DSTL, EPSRC and the MRC. This economics-based report identified NAMs as disruptive technologies with "the potential to drive future UK economic growth" and attract investment into UK industries. The report outlines how UK strengths in the pharmaceutical sector, consumer goods and personal care companies, contract research organisations and academic researchers have the ability to deploy NAMs and position the UK as the "global powerhouse in this area".[124] Following this, in 2018 and 2019 the Medicines BioIndustry Discovery Catapult and BioIndustry Association (funded by Innovate UK) published the 2018 and 2019 reports "State of the Discovery Nation", with recommendations to develop technologies to humanise drug discovery through NAMs in order to improve research productivity for industry.[125] Unfortunately, no specific actions have been taken by the Government on these reports towards advancing NAMs and human-focused biomedical research methods,[126] including in the preparedness strategies of the National Risk Register, the UK Pandemic Influenza Strategy, and Public Health England's Global Health and Infectious Diseases Strategy.

27. On an international level, for over a decade, regulatory agencies, governments and funding bodies have been encouraging a shift towards NAMs, with many producing roadmaps, consisting of targets, deadlines and actions to progress their development and uptake. Some of these include:

    - United States National Research Council (2007): Toxicity Testing in the 21st Century: A Vision and a Strategy.[127]
    - Transatlantic Think Tank for Toxicology (2012): Roadmap for the Development of Alternative (Non-Animal) Methods for Systemic Toxicity Testing.[128]
    - Netherlands National Committee for the protection of animals used for scientific purposes (2016): Transition to Non-Animal Research.[129]
    - United States Environmental Protection Agency (2016; 2019): Strategic Plan.[130]
    - United States Food and Drug Administration (2017): Predictive Toxicology Roadmap.[131]
    - The Interagency Coordinating Committee on the Validation of Alternative Methods (2018): Strategic Roadmap for Establishing New Approaches to Evaluate the Safety of Chemicals and Medical Products in the US.[132]

28. With the international competition in driving forward NAMs in the biomedical sciences, the UK is at risk of falling behind on global developments in this field and missing opportunities for growth of an innovative industry that can also benefit public health and the economy. After the UK's decision to leave the EU, the Department of Business, Energy and Industrial Strategy published a Green Paper, "Building our Industrial Strategy" [133]. With uncertainties around access to EU funds and data/knowledge sharing, the Green Paper reports that it is vital that we "embrace innovation to keep ahead of the competition, create more good jobs, and make sure jobs in the UK are secure", particularly at a time when "the pace of scientific discovery and innovation is quickening across the world". The UK needs to keep "at the cutting edge of new technologies and developing solutions to global challenges".[134]

29. To be a strong competitor in the global race to create the most innovative and efficient technologies for investigating disease and developing drugs, especially those which contribute to solving global disease outbreaks, it is essential that the UK prioritises its investment in NAMs as disruptive technologies, through dedicated funding. With Governmental support, we now have the unique opportunity to take the lead in biomedical sciences, enhancing the quality of science and industry in the UK. With its world-leading universities and home to some of the largest pharmaceutical companies in the world, the UK is in a strong position to build an economy that can compete with global innovation, reaping rewards for public health.

30. Following the report from Innovate UK and others, the LDF co-authored a white paper as part of the Alliance for Human Relevant Science, alongside NAM experts and businesses which further outlined five core actions required by the UK to capitalise on the health and economic benefits of NAMs (previously outlined above and reiterated here), including:

- **supportive infrastructure** to enable strategic coordination of the development and uptake of NAMs, and to provide access to resources and communication networks
- **strategic funding** to incentivise full engagement with NAMs, particularly those with market potential that might attract business investment
- **improved education** on the benefits of NAMs, alongside skills training for new and established scientists
- **multidisciplinary collaboration** and forging of new partnerships between basic and applied researchers, industry and end-users
- **engagement with regulators** to promote the adoption of data generated from NAMs into regulatory guidelines. [135]

31. In this regard, the LDF calls on the Science and Technology Committee to prioritise the growth of NAMs in the UK in order to speed up and increase the success rate of vaccine development for COVID-19 and prepare for future emergencies.

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