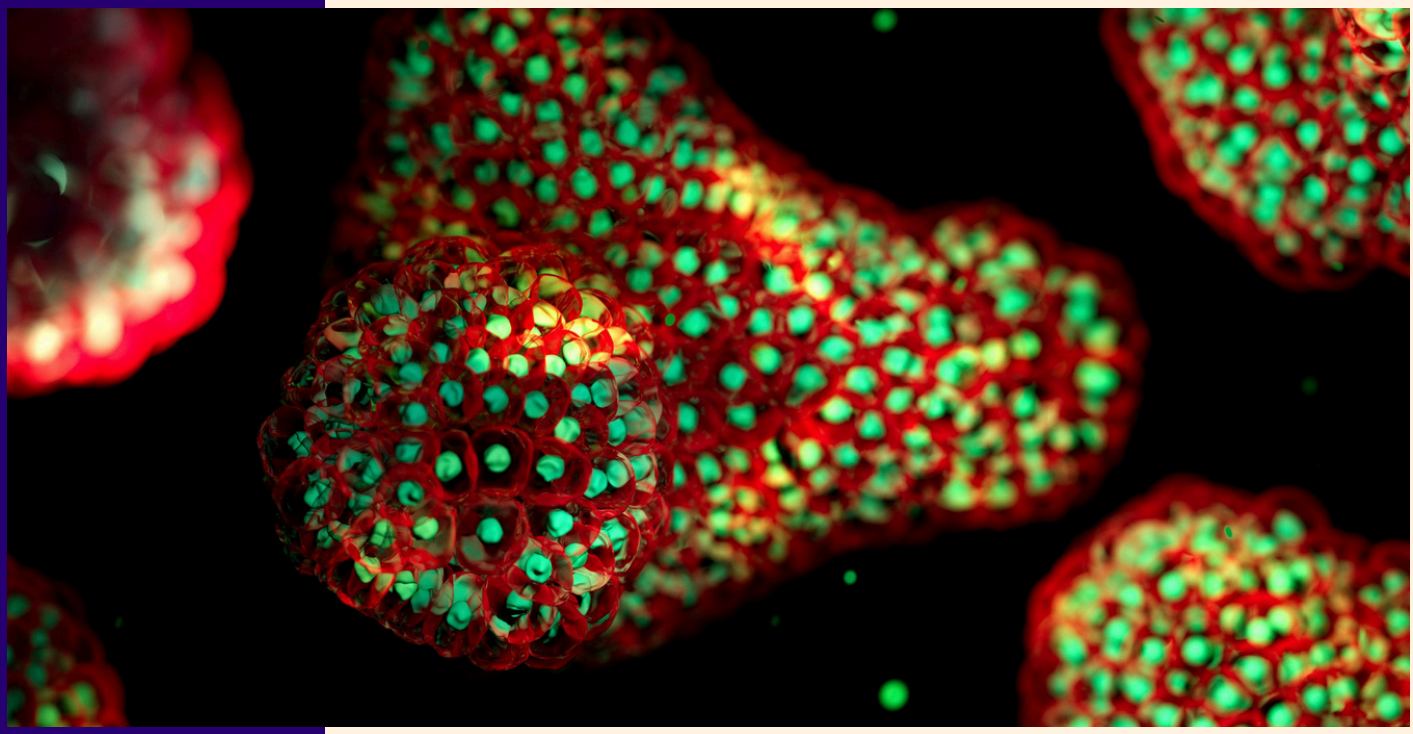
RSPCA
ANIMALS IN SCIENCE

Supporting Replacement in Academia

Exploring barriers around the acceptance and uptake of non-animal methods in science in UK academia



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“I would say I never had a discussion on like, does it have to be an animal?”

“There’s obviously the fear of the unknown, and people feeling comfortable with certain methods or models.”

“There’s a definite push to try and get away from animals, but I don’t think the pull is strong enough...”

“I am aware that these [NAMs] exist out there somewhere, but I don’t know where they are or how much they cost or where they may be beneficial...”

“We also need the skills, and we don’t have the skills”

Quotes from study participants

Cover image: Illustration based on fluorescence light micrographs of organoids - Science Photo Library / Alamy Stock Photo

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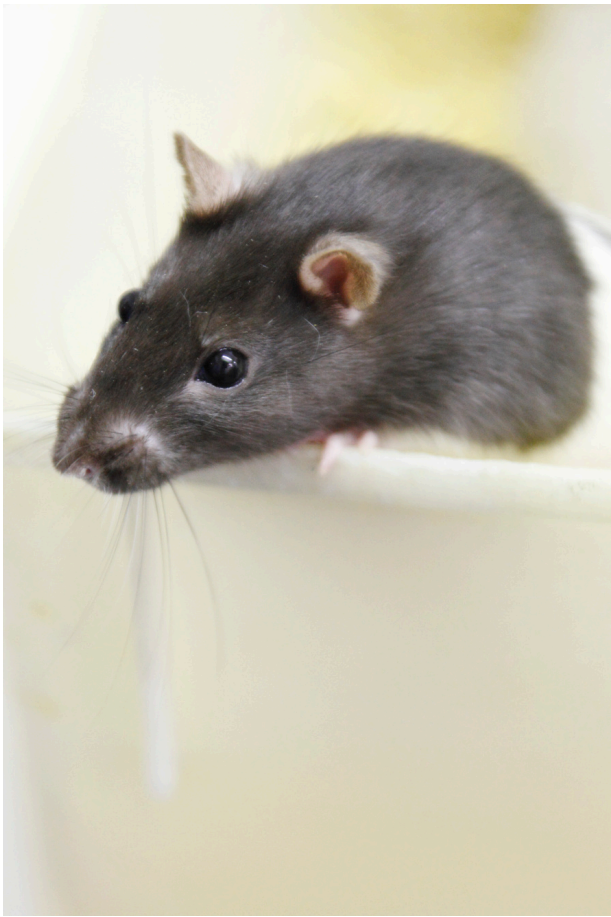
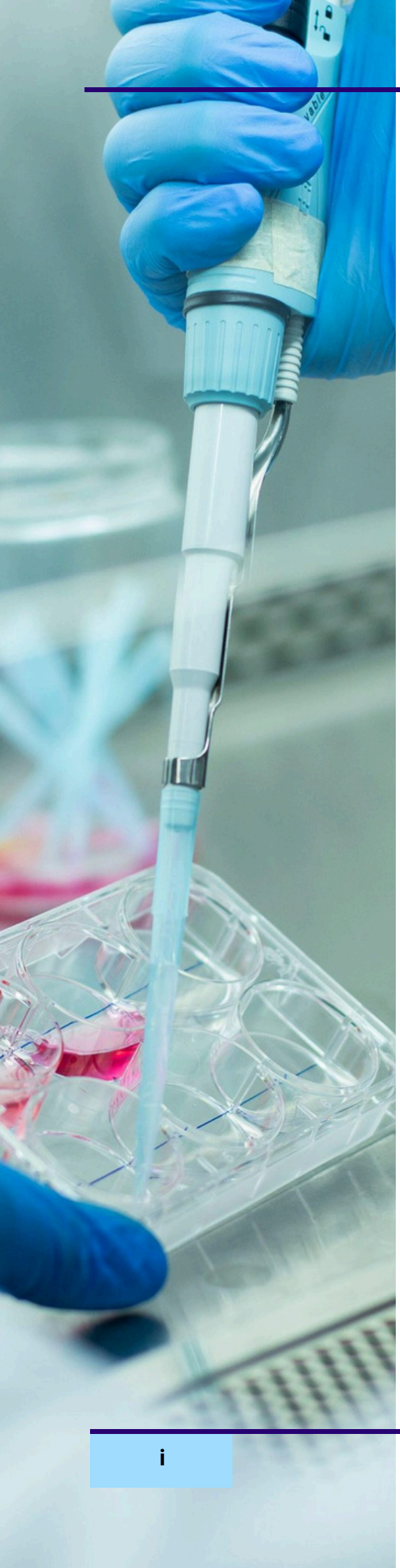


Image: Rat - Andrew Forsyth/RSPCA Photolibrary



Executive summary

The last decade has seen a significant increase in ambition and activity aimed at facilitating a transition away from the use of animals in research and testing, towards the development and uptake of alternative non-animal approaches and methods for answering important scientific questions and generating sought after information or data.

When it comes to making further and faster progress, real scientific challenges remain. For example, the alternative methods may not currently be available. Significant efforts continue to be needed for these, often technological barriers, to be overcome. Much of the focus to date, has been on the area of regulatory testing (e.g. of potential new medicines, vaccines, chemicals or other substances).

But there are also critically important **sociocultural issues** around 'the way science is currently done' that act as barriers and brakes on the capacity and speed at which animal use is being avoided or replaced in science. These play a particularly significant role in relation to research undertaken within **academia**. These are the focus of this present RSPCA work.

This report details findings from a qualitative study of sociocultural factors impacting on the acceptance and uptake of non-animal methods (NAMs) in science in UK universities and medical schools. Based on an analysis of 32 in-depth interviews with Biosciences students and researchers using animal models, **this study offers insights into key barriers around the use of NAMs, and drivers of animal models in academia**.

The eleven **key themes** arising during the interviews (summarised on the next page, and considered in more detail within the report) will form **the basis for future multi-stakeholder work aimed at facilitating opportunities for overcoming some of the challenges and barriers identified**. Through examination and highlighting of these issues, we hope that everyone can work together towards making faster progress with moving towards non-animal methods and approaches in science.

Image: Cell culture - Murat Idikut / Alamy Stock Photo

Key themes

1 Knowledge, expertise, and experience

a) acquiring the required skillset
b) familiarity with the model
c) building skills, status and research interests around particular animal models
d) considered success with animal models
e) *in vivo* skills seen as being sought after both by academia and industry

2 Training in NAMs

a) lack of access to training in NAMs
b) lack of formalised training programmes around NAMs

3 Funding

a) need for experience and expertise around NAMs to access funding
b) the length of funding grants

4 Access to NAMs

a) perceptions of cost
b) limited access to required infrastructure

5 Career progression

a) pressure to publish
b) pressure to validate NAM data against *in vivo* data

6 Communication and collaboration

a) lack of communication across fields and between those using NAMs/animals
b) development of alternatives needs to be informed by the *in vivo* context

7 Awareness of NAMs

a) need for better communication of the benefits and opportunities of NAMs
b) imbalance in the promotion and implementation of each of the 3Rs

8 Institutional commitment to replacing animals

a) continuing prioritised investment in animal facilities
b) implementation and engagement with 3Rs perceived as tokenistic

9 Use of NAMs in conjunction with animal models

a) use of NAMs seen as refining and/or reducing, rather than replacing animal use
b) lack of confidence in the feasibility of full replacement

10 Perceived technological or scientific limitations of NAMs

a) complexity of NAMs

11 The established nature of (particular) animal models

a) history of use and characterisation
b) 'Gold standard' status of animal models

Introduction

In 2022, 2.76 million scientific procedures involving animals were carried out in Great Britain [1]. In addition to the ethical and animal welfare concerns that this raises, there is increasing recognition of the significant scientific limitations of many animal 'models' and tests, with attention particularly focussed on the reproducibility, validity and translatability of animal studies.

In the UK, across Europe, and internationally, there is a building momentum towards transitioning to non-animal technologies, and new approach methodologies - collectively referred to for the purposes of this report as non-animal methods (NAMs) - with much discussion of how this can best be supported. In 2015, Innovate UK, the UK's innovation agency, produced a collaborative roadmap for non-animal technologies in the UK, with involvement from the National Centre for the 3Rs and several major research councils. As well as highlighting scientific advantages and opportunities, the roadmap also highlighted potential economic benefits, citing the large market potential of these new technologies (Innovate UK 2015). To capitalise on this, the roadmap recommended *'increased support for NATs R&D, and the greater coordination and integration of activities from a number of organisations and sectors'*.

At a 2016 European Commission Scientific Conference on non-animal approaches involving scientists and a range of stakeholders, it was reported that the '*desire for change in the use of animals in science, and the elimination of unnecessary and unproductive testing, was common across all stakeholders'*, with recognition of *'the opportunity, and need, for a paradigm shift in the way science is performed, moving away from entrenched dogma and ways of thinking'* (European Commission 2017). In 2022, a working group commissioned by the US National Institutes of Health (NIH) stated that now is '*an ideal time to invest strategically in the development and use of novel alternative methods'* (NIH ACD Working Group 2023).

It is clear that NAMs are gaining prominence on scientific and political agendas. But while there are complex technological challenges to overcome - which have attracted much of the focus to date - there are also a range of critically important sociocultural issues that need to be addressed to optimally facilitate a transition to scientific methods which do not involve the use or harming of animals.

[1] https://www.gov.uk/government/collections/animals-in-science-statistics

Whilst the 'phasing out' of animal use in research and testing, alongside the 'phasing in' of NAMs, is gaining worldwide attention (e.g. Muller 2024), much of the focus to date has been in the area of regulatory testing. Although there will be overlap between many of the challenges of integrating NAMs into regulatory testing and stimulating its uptake in academic research, including both scientific aspects like relevance and accuracy, and sociocultural aspects such as familiarity, trust, and confidence (e.g. see van der Zalm et al. 2022, Holden et al. 2024, Sewell et al. 2024), animal use in academia presents particular barriers. These are the specific focus of this study.

Around 50% of animal use in the UK takes place within universities and medical schools [2]. In reviewing grey and academic literature around the transition to non-animal alternatives, several potential key challenges were identified for the acceptance and uptake of NAMs in academia. These include: disciplinary silos (Carusi et al. 2019; Zuang et al. 2020); limited institutional support and strategy around Replacement (Lund et al. 2018); limited access to required infrastructure, expertise, and resources (BBSRC 2021; van Mulders et al. 2022; Rawle 2023); limited access to required education and training (Abarkan et al. 2022; Andreoli et al. 2022); insufficient scrutiny of opportunities for Replacement (Rawle 2023); biases towards animal models in publication processes (Ingber 2020; Del Pace et al. 2022; Krebs et al. 2022); a need for greater funding of research involving NAMs and dissemination of new methods (Rawle 2023); associations of NAMs with risk (Fitzpatrick et al 2018; Krebs et al. 2022; Rawle 2023); and a self-reinforcing cycle of animal use promoted by the development of skills, familiarity, status, and networks (Lohse 2021; Abarkan et al. 2022).

As well as challenges specifically linked to the implementation of NAMs, there are also broader structural constraints and pressures that are likely to impact upon research practice in academia. A 2020 report by Wellcome on research culture indicated that researchers across disciplines faced challenges relating to insecure employment, the metrics used to assess performance, increased competition, workload and working hours, and funding for example (Wellcome 2020). These raise further clear challenges where shifts to novel research approaches are required, and it will be crucial to address these in order to support researchers to transition away from animal use.

On the issue of conservativism in research, Lohse (2021) writes of a 'scientific inertia' across the life sciences around the implementation of non-animal approaches. Lohse identifies two key drivers of this inertia, the first being the 'secondary epistemic

[2] https://www.gov.uk/government/collections/animals-in-science-statistics - see data for 2019, Table 11, page 24.

functions' that animal models may have, indirectly supporting research by providing guidance as well as cultural and infrastructural 'anchors' for research communities and establishing collective standards (ibid). Alongside this, the use of animal models can be seen as part of a 'risk-spreading' strategy in which the risks of failure associated with novel approaches are mitigated by pursuing them alongside traditional approaches (ibid). Similarly, a survey by Del Pace et al. (2022) examining the perspectives of researchers across Europe on model choice and external factors influencing their research found that an '*overwhelming majority posed high value in working within an established environment with its accepted models and methods*'. Finally, a 2022 survey on the use of models in research from the Biotechnology and Biological Sciences Research Council (BBSRC) indicated '*a tendency to use the model that is available rather than the best model for the question*', with researchers often being unsure of who to approach for training around a new model and there being a '*lack of 'in-house' resources*' to facilitate the use of novel models (BBSRC 2022). Overall, such work suggests how **characteristic aspects of current academia environments, and of animal models themselves, can work together to drive the continued use of animals in research, and present barriers to the use of novel methods**.

Project aims

To further explore the sociocultural factors which may impact upon the acceptance and uptake of NAMs in UK academia, this report offers insights into the experiences and views of students and researchers across career stages. Based on an analysis of 32 in-depth qualitative interviews, this study aims to develop a better understanding of the current key challenges around implementing NAMs in academia. Overall, the ambition is to help support the creation of a research community that is:

Aims

- **aware** of available alternative approaches to the use of animals, including how and where to find out about them
- **confident** in using alternative approaches and interpreting the data that comes from them
- **enthusiastic** about the use of non-animal approaches and reaching a point where the use of animals in research and testing is avoided or replaced

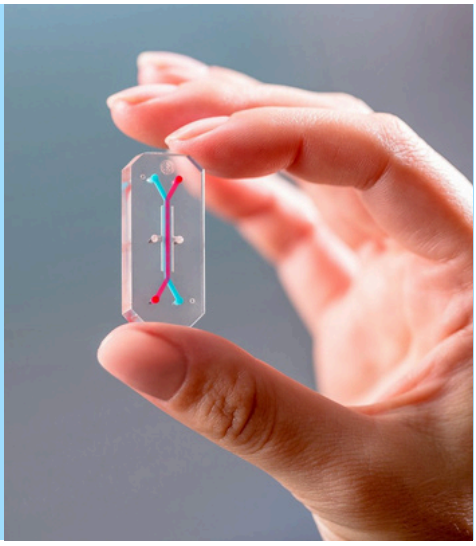


Image: Organ-on-a-Chip - Emulate Inc.

Methodology

Study design

This study involved a qualitative interview design to explore students' and researchers' views and experiences around animal use and non-animal methods (NAMs) in scientific research. The study aimed to gather in-depth insights into the views, experiences, and decision-making processes of students across the Biosciences and researchers who use, or have used, animal models. The design of this study was informed by a one-day stakeholder workshop, and input from a stakeholder steering group who also assisted with recruitment and gave feedback on the drafting of interview guides. Sampling of participants was based on key career stages, being organised into three groups: undergraduate and master's students; PhD students and Early Career Researchers (ECRs); and mid- to late-career researchers. Accordingly, the recruitment call specified that we were looking to speak to 'students in their final year of either an undergraduate, master's, or PhD level degree within the biosciences, and researchers of early, mid, or late career stages undertaking procedures using animals that are regulated under the Animals (Scientific Procedures) Act (ASPA) 1986'.

To facilitate in-depth discussions on these topics, semi-structured interview guides were developed for each sample group. The Undergraduate and Master's student interview guide was structured around three key sections: 1) education; 2) choosing models and methods; and 3) the goal of replacement: motivations and expectations. The same interview guide was used for the other two groups and this was structured around two key sections: 1) choosing models and methods and 2) academic environment and research culture. All interview guides had warm-up and closing questions, aiming to ease the participant into the interview and provide an opportunity to raise topics not covered by the interview guide or return to particular points.

Before contacting participants and beginning any empirical work, the research plan was reviewed by the RSPCA's Data Protection Department to ensure compliance with legal and ethical standards. This involved outlining the scope of data collection, specifying the types of data we were aiming to gather, and detailing the methods of storage, handling, and disposal of data. This information was provided to all participants within the participant information sheet.

Recruitment

Participants were recruited via contacting academic institutions across the UK, and through an open call for participation shared via RSPCA social media accounts, the Animals in Science team's professional affiliations and those of the project's stakeholder group. When contacting academic institutions, emails were sent to universities' Biological Service Units, relevant academic faculties and departments, and known academics and laboratory personnel within our professional network. In total, emails were sent to 50 academic establishments across the UK, with specific focus to ensure that the institutions with the highest numbers of animal use [3] were contacted.

Recruitment emails asked for assistance in circulating the call for participation and included both a recruitment poster and participant information sheet. The participant information sheet included detailed information on the study's aims and purpose, what kinds of topics the interview would cover, who can take part, what participation would involve, withdrawing from the study, how information would be used, and data protection and confidentiality. The lead researcher's email address was provided to enable contacts to ask any questions or receive further information. Those interested were asked to email our general departmental email address for further information and/or to arrange participation. Upon emailing, potential participants were again provided with the participant information sheet and a consent form. All participants signed a consent form before participating in an interview. Online interviews were arranged at a date and time of the participant's convenience.

Participants

A total of 32 participants were recruited for the study. All career stages were represented, apart from undergraduate students. The lack of undergraduate students presents a limitation of the study in restricting insights into current curricula and undergraduate views towards animal use and NAMs. With more focus on examining research experiences and decision-making around model usage, this was not deemed a major limitation for the current study. However, future studies focussing specifically on the experiences and views of undergraduates around NAMs, may provide helpful insights into current education and training needs.

[3] Ten organisations account for half of all animal research in Great Britain in 2021: Understanding Animal Research.

In terms of the gender split, 20 women and 12 men were recruited for interviews. Looking at career stages and roles, a fairly even spread across research career stages was achieved (Figure 1). As noted earlier, only a limited number of postgraduate students were recruited and no undergraduate students were recruited.

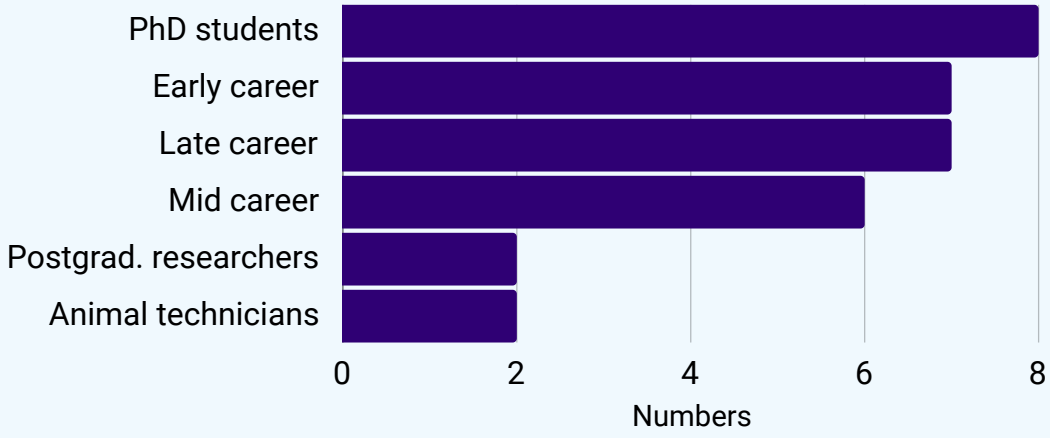


Figure 1: Career stages and roles of participants recruited
Early career: postdoctoral researchers and experimental Managers; mid: senior lecturers, associate professors, group leaders, and clinicians; late: professors, senior lecturers, and principal investigators

The majority of individuals were aged between 25-34 (9), followed by participants within the age brackets of 18-24 and 45-54 (7 each), 35-44 (6), 55-64 (2), and 65+ (1) (Figure 2).

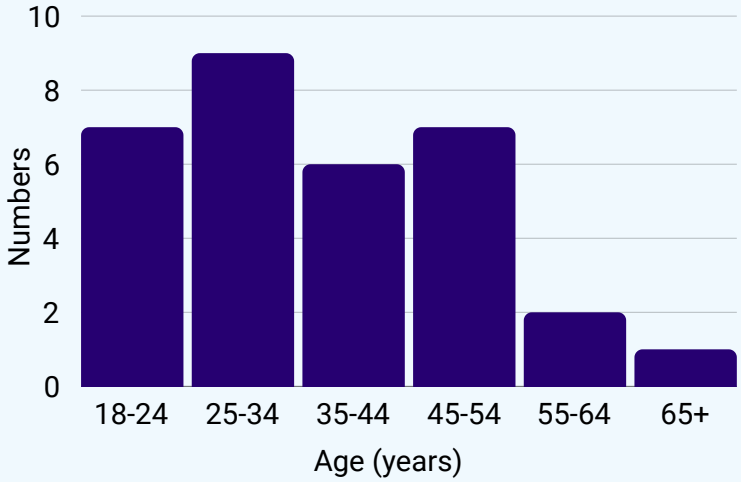


Figure 2: Age brackets of participants recruited

Participants came from a range of disciplines, such as Medicine, Bioengineering, Neuroscience, Nutrition, Physiology, Toxicology, Agriculture, Cancer Biology and Imaging, Immunology and Immunobiology, Genetics, Biochemistry, Pharmaceutical Chemistry, Developmental Biology.

[2] Ten organisations account for half of all animal research in Great Britain in 2021: Understanding Animal Research.

Data collection

Data was collected through semi-structured interviews undertaken between September 2023 and March 2024. Interviews were conducted via Google Meet, a video conferencing service, and ranged from between 30 and 70 minutes in length, with the majority of interviews (20) lasting longer than 50 minutes. With interviews being conducted through a semi-structured approach, the interview guide described earlier was used to steer conversation and provide prompts, but was not implemented in a rigid manner. Therefore, though all interviews ultimately covered the same topics, they did not necessarily all play out in the same order. This allowed participants to follow their own directions and go on 'tangents' they felt were relevant to the discussion. Interviews were audio-recorded with participants' consent and transcribed by the lead researcher and a private transcription service under a confidentiality agreement.

Data analysis

Data was analysed using a thematic analytical approach. This followed Braun and Clarke's (2006) six-phase framework: 1) reading full transcripts to become familiar with the data; 2) generating initial codes across the dataset; 3) grouping codes into overarching themes; 4) reviewing and reorganising themes; 5) defining themes; and 6) writing up the report. Initial codes were generated via an inductive approach which aimed to reflect the content of the data rather than limiting analysis to specific pre-defined interests. For instance, factors influencing model choice generally were coded in detail although this report focuses specifically on barriers to the use of non-animal methods. This enabled a fuller appreciation of challenges around the use of novel models and non-animal approaches, as well as drivers of animal use. Upon grouping codes into broader themes, the analysis turned to focus more narrowly on potential barriers around the acceptance and uptake of NAMs, leading to the categorisation of the 11 key themes laid out in this report.

Findings

From the interviews, several key barriers around the acceptance and uptake of NAMs in academic settings were identified. These cover knowledge, expertise, and experience; training and education; funding; access to NAMs; career progression; communication and collaboration; awareness of alternatives; institutional commitment to and strategy around Replacement; use of NAMs in conjunction with animal models; perceived technological and scientific limitations of NAMs; and the established nature of animal models. Although many of these themes overlap due to their interrelated nature, they are organised separately here for clarity.

1 Knowledge, expertise, and experience

Barriers relating to knowledge, expertise, and experience with models comprised a major part of the interview discussions. This involved not only the methodological and technical skills that promoted use of particular models, whilst preventing moves into new areas, but also the importance of gaining experience around broader aspects of model usage and the building of professional status. In examining the impact of knowledge, expertise, and experience on the uptake of NAMs, this section will cover acquiring the required skillset; familiarity; building skills, professional status, and research interests around particular animal models; success with animal models; and the perceived value of *in vivo* skills.

1a) Acquiring the required skillset

Knowledge, expertise, and experience around certain models and approaches were discussed as significant barriers to using NAMs as well as drivers of using familiar and established animal models. Several participants discussed a lack of the appropriate skills required to enable transitions away from animal use and, as will be discussed later around funding, the ability to move into new methodological areas was therefore linked to collaborating with others with the needed skillset.

Indeed, whilst in this first example actually discussing a move from one animal model (mice) to another (flies, organisms not regulated by UK animal research law), this Postdoctoral researcher indicates the need to gain the required understanding of the model, how to provide the necessary care, and how to analyse the data generated:

"Usually, the models you're trained on, it's very difficult to say, 'Oh, now I'm going to start doing stuff in flies'. I don't have the knowledge to do fly husbandry, how to do the phenotyping, how to do the analysis. So, I need to work alongside somebody that does fly work. So, that's the other limitation. But my hope is, in the long term, when we appreciate that we can use simpler models, simpler organisms to ask the same questions, people will start moving away from vertebrates, from mammalian species."
(Participant 28, Postdoctoral Fellow, Biochemistry, Early-career)

As well as the importance of gaining experience and expertise in each of these aspects of model usage, some participants also highlighted the difficulty of building a team with the right set of skills to enable the use of more complex *in vitro* technologies:

"We also need the skills, and we don't have the skills. We need far more tissue engineers than what we have because cell biologists cannot really easily pick up, because moving from single cells to proper organoid, you know, you need tissue engineer skills and not single cell biology. People use 2D, 3D tri-culture, but moving to organoid is very different."
(Participant 08, Senior Lecturer, Toxicology, Late-career)

"I think the challenge is just the availability of people with experience in a given cell line because, in my experience, people that work with the kidney cell lines are experts in it, but they know nothing about liver cell lines. So, it's just difficult finding those sorts of people, and it's almost become as specialised as that in a sense."
(Participant 06, Professor of Physiology, Late-career)

Having members of the team with the required skillset to enable use of NAMs was not only expressed as important on a practical, technical level but also on the level of enabling confidence in the reliability and accuracy of the work, as the following participant's experience suggests:

"I would choose to work with people that really know what they're doing, and believe what they're doing, and question themselves that what they are looking at is genuinely what you want it to be, type thing. So that puts me off a little bit. And then, I just, essentially, don't have the skills for doing that sort of thing all the time or, you know, to check them and the passages and details of this stuff that can be useful. So, it's almost like a technique unto itself, for sure, now."
(Participant 06, Professor of Physiology, Late-career)

The need to establish guidelines and Standard Operating Procedures for setting up and using NAMs, in particular organoids, in a reproducible and reliable way was discussed by several participants as a challenge that prevented current uptake.

"I don't think there is very much, in terms of best practice guides for if you're a new lab that's just started trying to grow organoids […] but part of that is just that the whole field of organoid models is so rapidly advancing, that if somebody put the two years of time and effort into really carefully putting that guide together for a particular organoid system, by the time it was available to the community people would be using something else anyway. So, there also does need to be a kind of settling period where we coalesce around a few different core models that are more widely shared."
(Participant 18, Group leader, Genetics, Mid-career)

"The barrier is partly resources, the equipment and the materials that you need, but also the expertise to make things work efficiently, because you want the systems to be reproducible and robust, so you don't necessarily want everybody doing their own thing in a different way, you want some standard operating procedures. Although you can't start to have those maybe, until you've got a really good working system. Or the systems you do have, you want people to be using them in the same way."
(Participant 16, Retired Professor, Genetics, Late-career)

"My vision with the uptake of those [organoids and organotypic slice models] is simply, it's just a lack of expertise, there's just not that many people who know how to do it. Again, say that that time to dedicate to setting it up in a lab for the first time, because I think you are looking at a year or two, that somebody who's dedicated to troubleshoot all of that standardised protocol together."
(Participant 13, Associate Professor, Immunology, Mid-career)

For Participant 18, the rate of change around organoid technologies was perceived as a challenge due to the uncertainty it generates around current investment in training remaining relevant and up-to-date in the long-term, as they elaborate:

"If you're talking about making a huge investment in training somebody to do one specific method, because if you train somebody to work with a mouse, a fish, a fly, whatever, in 10 years' time they're still probably going to be able to do that because things aren't going to have changed that much. There'll be updated best practice, blah, blah, blah, but it might be a one-day course to get them back up to speed, even if they haven't done anything for 10 years. Whereas with organoids you could spend a year training somebody and then a completely new system comes out that actually makes what you've done somewhat redundant, and they need to retrain again from the beginning. That, I would say, is one of the biggest challenges."
(Participant 18, Group leader, Biochemistry, Mid-career)

In this way, the speed at which particular potentially disruptive new non-animal technologies are developing may have both positive effects of improving their relevance and usability, but also mean that **they are viewed by some as 'risky' due to concerns that current investment in them may quickly become outdated or obsolete** - are they here to stay?

1b) Familiarity

Whilst acquiring the methodological and technical skills needed to enable te use of new approaches may be viewed as a current challenge by researchers, **the familiarity of animal models can drive their continued usage**. This can be understood as more than simply due to habit or conservativism around model choice, but as also relating to having been trained in using those models and understanding how they work, having an established set-up in place for their use, and having gained an understanding of the broader aspects around those particular models. For instance, one participant remarked on the ability to calculate project costs when discussing how the complexity of new NAMs could disincentivise their uptake:

> "That would be more the complexity, the fact that you cannot easily pass on the skills from one researcher to another and, of course, because you need to cost it really well. So, you need to have been working for quite some time with them to realise what you need."
> **(Participant 08, Senior Lecturer, Toxicology, Late-career)**

Relating back to concerns around following correct protocol when using NAMs, this mid-career researcher highlighted the challenges that moving away from a familiar model may raise for knowing how to publish work using new approaches, as well as confidence in implementing experimental controls:

> "I think it does get harder the more ingrained you get in with a model, because you're switching potentially all of your techniques and things like that. If you've not got any familiarity of how to publish those new techniques, you know what controls should be done and what sort of quality assurance needs to be done, I think that'd be quite difficult."
> **(Participant 13, Associate Professor, Immunology, Mid-career)**

Finally, familiarity around working with a particular animal model can promote their further use due to the practical expertise gained in areas such as handling and the perceived research benefits offered by such skills, as one PhD student described:

"The choice of model, I don't think it necessarily takes away any career opportunities after this. I think it definitely makes it easier to stay in rodent research, if that was something I wanted to do by the end of this, just because you get used to handling the animals. And the more you've done it, the faster you can make them comfortable with you, and feel comfortable around them. It's a very mutual situation, in that sense."
(Participant 29, First-year PhD student, Neuroscience)

As suggested here, the gaining of these kinds of technical skills (which can also promote the refinement of animal use) can "make it easier" to continue to work with particular animal models. The ease associated with familiarity is not only related to an acceleration of the research process but also may be seen as better for the animals. As the description of gaining experience with certain animal models as a "mutual situation" indicates, the gaining of proficiency in handling and acclimating animals in a study can deepen the researcher's connection to their usage, with the building of particular practical *in vivo* skills making them feel like the best person to be undertaking that work.
The importance of familiarity in driving model choice to use can also be seen in discussions of the value of being able to compare research data against previous work, thus building on an established evidence base. As the following participants suggest:

"There's obviously the fear of the unknown and people feeling comfortable with certain methods or models. I suppose the nature of academia itself - to have that backwards comparison to other studies - yes, the longer you do something, the harder it is to break into something else and still have it count as valid or representative. I certainly see that's definitely an issue."
(Participant 09, Experimental Manager, Agriculture, Early-career)

"If [new models] don't have enough varied data for me to compare, then I will have to re-establish everything from scratch. That's definitely not something you really want when you go to actually push out your research into clinic. You don't really want to take that loophole, because you already have enough loopholes in other paid tasks."
(Participant 04, Senior Postdoctoral Researcher, Oncology, Early-career)

"So, you come up with a new research question based on what you've been doing in the past five or 10 years. If you're going to try and answer that question in a new model, you first need to go back and repeat those key results which led to that question in the first place, in the new model to make sure it's an appropriate system. So, every time you do that, you're generating more work for yourself than if you just stuck with what you were doing before."
(Participant 18, Group leader, Genetics, Mid-career)

As illustrated in the above excerpts, the ability to compare results between the same or similar models is seen as helping with the efficiency of research. There is also a perception of 'safety' when continuing with the same model choice, which can provide confidence in the use and interpretation of the data obtained.

1c) Building skills, status, and research interests around particular animal models

More broadly, **the use of particular models can drive their further usage due to cultivating model-specific skills, status, and research interests**. With significant time pressures often surrounding the generation of results and outputs in academic environments, researchers may perceive advantages to continuing to work with approaches that they have already invested in. As the following excerpt demonstrates:

> "I don't know that it's necessarily people wanting to not move away, as much as it is that people become more comfortable and more expert in one area, and then don't want to have to start from… not scratch, but try and relearn that in another model. And I think, as well, there is a pressure, as well, from supervisors. So, moving from a PhD into a postdoc, I think that that increasing pressure to publish and collect positive data, it's just so much easier to do that without having to learn a bunch of new things."
> **(Participant 29, First-year PhD student, Neuroscience)**

With expectations for producing publications within short-term research contracts, **the time required to train in and employ new methods may disincentivise researchers from moving away from what they already know**. Indeed, as careers develop the flexibility to pick up new methodological skills and expertise and use new models was seen by some researchers as narrowing. As this researcher describes in relation to the prospect of moving from using rodents to Drosophila:

> "It goes back to what we were trained on, and yeah, this can change. If you really want to change it, yes, you will change it, but it will take years, and it will not happen… if you have an epiphany when you're a PhD, you can go and do a postdoc in a Drosophila lab. That's fine, and then you can change it, if you have it early enough. But that means again going back, education and training […] in the UK, people finish their bachelor's with honours when they're 22, 23, and they do a three-year PhD straight up […] unless they have some time to reflect, "Is this what I want to do? Is there another model to go and do a postdoc afterwards?" they would stay in the same thing."
> **(Participant 28, Postdoctoral Fellow, Biochemistry, Early-career)**

As this extract suggests, there may be an early window of greater flexibility to move between different models, however, capacity to reflect on how the use of particular models might shape one's career path may be limited within the short-term contracts common within universities. Related to this early process of methodological specialisation, some researchers, even those early in their career, felt that employers would be less likely to offer them a position using methods they did not have experience with. As the following excerpts highlight:

"'I don't necessarily regret that this is the work that I do, but I've now ended up with this very strong in vivo skill set, and that's kind of what I would be hired on now, as opposed to people that do a lot of in vitro work or electrobiology techniques and stuff like that. I have less of them because so much of my work has been in vitro. So, I do find it strange now that that's my main kind of skill. And I don't think I knew when I was deciding on the PhD project, maybe what it would entail. But for the model for that, again, the PI had already worked with this model before and someone else in the lab trained me on it. I would say I never really had a discussion on like, does it have to be an animal?"
(Participant 22, Postdoctoral Research Assistant, Neuroimmunology, Early-career)

"I think, if you commit a lot of time, the skill set, practically, is just so incredibly different, but it's not that you couldn't move away. But I think, if I had a CV that was entirely animal work and then, kind of, pivoted and was like, "Oh, I don't want to do this anymore, I want to replace animals", I think practically, it's so different that I think… I know, physically, you could be trained to do both. But I think employers… it would be quite a hard pivot to go from one to the other […] I think that's because I mostly know people that have either really done animal [or NAMs]. I don't know anyone that's, kind of, weaved between the two, I think. So that's just the impression that I've got from others is that you go one way or you go the other."
(Participant 27, Final-year PhD student, Biochemistry)

As expressed here, **the ability to "pivot" from animals to non-animal methods is seen to be challenging** and, **even at an early career stage**, a person's methodological background is already perceived as closing down certain opportunities. It is also important to recognise the impact that **a perceived divide between animal and non-animal work** might have upon which research positions are viewed as relevant and attainable. As we will return to later in discussing communication and collaboration between those developing/using NAMs and those using animals, this excerpt highlights that, whether or not there is a degree of flexibility to move between research positions using different models, perceptions that 'you either go one way or you go the other' can inform expectations about career paths.

1d) Success with animal models

A significant driver for the continuing use of animal models are experiences of perceived success in using them. Success here encompasses generating positive or significant results, publishing journal articles based on animal data, establishing beneficial collaborations and networks, obtaining funding for projects involving animal work, and the ability to use new techniques to explore new aspects of a model. Compared with *in vitro* methods, **animal models were often discussed as** generating more data and were therefore, as the following participant described, seen as **'a more productive endeavour'**:

"I think animals intrinsically generate quite a lot of data in comparison to… and a more comprehensive dataset, I believe, in comparison to in vitro models. […] Yeah, I feel that the culture, in research and science and for publications and stuff, animals just tend to be intrinsically a more productive endeavour, also. And I think that's maybe one of the key reasons why we're not moving over and why people would spend more time trying to develop animal models versus spending time, energy and money looking elsewhere, I think. There just isn't a strong pull. There's a definite push to try and get away from animals, but I don't think the pull is strong enough […] So yeah, I think animals are more productive. Whether or not that information is necessarily useful could be challenged [...] I mean, it's all fair and well asking all these questions, but are they relevant? I mean, is it applicable? I don't know."
(Participant 31, Post-doctoral Research Assistant, Cardiovascular science)

Highlighted here is a perceived lack of incentive to move away from animal models due to the amount and variety of data they are able to generate and the subsequent benefits of this for producing publications. However, as the participant also reflects on, the usefulness of data generated from such models, i.e. its physiological relevance and translatability, is separate to its value in terms of productivity. As will be discussed in more detail later around the pressure to publish within academia, **the driving force that productivity in relation to publications plays in shaping research requires serious consideration for stimulating and supporting the uptake of non-animal methods**.

Also related to the association of with animal models with productivity is the way in which further physiological understanding of an animal model and the development of new technologies and techniques can create further avenues for investigation. As the following participant suggests:

"I see the same thing over and over again from lots of different people. And they find a new gene and use the same methodology to look at the function of the new gene, and it goes over and over and endless and endless and on and on, and then new technology or new techniques or epigenetics and then epitranscriptomics and whatever the next thing is. And it's like, "We can do the same thing and use this new technology or this new machine, and it'll be better." And you see that a bit."
(Participant 06, Professor of Physiology, Late-career)

Suggested here, is the way in which the use of an animal model can prompt further research questions and promote the model's continued use, suggesting that the research becomes led by use of the model, rather than use of a particular being a product of the research plan.

Also contributing to this lack of 'pull' for researchers to move away from animal models is the broader normalisation of animal use, as the following excerpts describe:

"Using animal models like mice should truly raise ethical concerns regarding animal welfare and the responsible use of the resources, necessitating careful consideration and justification of their use in research, however in practice this usually do not happen."
(Participant 32, Second-year PhD student, Biomedicine)

"The conferences I've been to, people tend to use very similar animal models, get great success and therefore they don't see a scope for using a non-animal model."
(Participant 25, Third-year PhD student, Microbiology)

"I think it has become a bit of a manufacturer that we do the same thing the same way, so in vitro, in vivo, publish, in vitro, in vivo, publish. So, there are some little things trying to incorporate, but I don't think there is an active flow and exchange between different fields because again, I don't think people consider this to be a major problem the way it's done now."
(Participant 26, Research Assistant, Pathobiology, Early-career)

Implied in these excerpts is how **achieving success using animal models can, to some extent, minimise the urgency of developing and implementing alternative methods**. Being identified by researchers earlier in their careers, this lack of problematisation around animal use indicates particular challenges for shifting established research cultures in which animal use is not seen to be rigorously challenged. As discussed later in Section 2a of this report around access to training on NAMs, this has potential impact upon the capacity for ECRs to consider employing non-animal approaches.

1e) In vivo skills seen as sought after both by academia and industry

Finally, another factor identified as driving animal use was **the view that *in vivo* skills are sought after within both academia and industry**, as well as a sense of a decline in researchers with such skills. As the following excerpts demonstrate:

"So, I can say I know how to do animal work, and it's super easy for me to find another postdoc job anywhere in [location], because there are just not enough people doing it right now. And other kinds, in industry, I think they also run a lot of in vivo work. I know their code tries to push them to do more in vitro, but basically, the lab, because the FDA require those data, they still do in vivo. So, if you have those skills, it's also easier for you to find a job."
(Participant 04, Senior Postdoctoral Researcher, Oncology, Early-career)

"My impression is that if you've done animal work at your PhD, that does make you more employable because there's not that many people out there who have significant in vivo experience, handling mice and interpreting that data."
(Participant 13, Associate Professor, Immunology, Mid-career)

"I have quite a comprehensive background in different models. However, I would say that, probably, it's less common to have a skill set in in vivo techniques […] in the short time that I was applying for jobs, certainly, the greatest interest in my CV was derived from the skill set that I had in animals."
(Participant 31, Post-doctoral Research Assistant, Cardiovascular science)

"I found that once people know that you do in vivo, and it's not just injecting, once they know you can do surgery, you become really employable. […] so, once it gets out there that you can do that, people are like, "Yeah," because people don't want people coming in on a project and then they're going to have to spend six months training."
(Participant 20, Pre-Clinical Manager, Stem cell therapy, Early-career)

As Participant 20 suggests, already having experience using animal models, particularly having surgical skills, may be seen as attractive by employers in terms of speeding up the research process by not having to train an incoming researcher. The other participants here all indicate that *in vivo* skills are particularly valued due to there currently being a limited number of researchers with these. In this way, **having training in and experience using animal models can be again linked to career success** in terms of securing research positions due to the appeal of an *in vivo* skillset.

Theme summary: Discussions around knowledge, expertise, and experience were prominent through the interviews and analysis of this indicated several barriers to the uptake of NAMs. These included a lack of the required skills to use NAMs, with the rate of change around their development raising concerns towards the potential obsolescence of current investment in training; familiarity with animal models driving their continued usage; the development of model-specific skills, status, and research interests; previous success with animal models (including positive results, publications, beneficial collaborations, and funding prospects); and a perceived high value currently placed on having *in vivo* skills within academia and industry.

2 Training in NAMs

In discussing their experiences and thoughts on the training opportunities available around NAMs, two key themes were identified: access to training, and a lack of formalised training programmes around NAMs.

2a) Access to training in NAMs

In discussions of opportunities to access training around different models, **a key theme was the tying of training opportunities to a project grant and its specific aims and objectives**. This may raise particular challenges for ECRs who require their supervisor or PI to authorise their training requests. As the following excerpts discuss, access to training opportunities may therefore be constrained by the remit of the current project:

"I suppose it would be quite difficult for me to say, I just want to learn how to do cell culture, will someone teach me? It would more have to be driven that the research needs that question answered."
(Participant 22, Postdoctoral Research Assistant, Neuroimmunology, Early-career)

"Any new technique that a researcher can put under their belt is a huge advantage. Certainly here, you would have to ensure that that training was relevant to the project, that you are actually going to use that, so there are no resources wasted on a researcher just going, "Oh, I'm interested in learning this. It's not relevant, but I'll take a trainer's time, the institute's money to learn this anyway." [...] I suppose, in terms of funding, that would be good, to have those career-enhancing grants. The opportunities, they may not be tangentially linked to the current project, but they are, as in their name, career progressive. You can build a small study with it, or you can learn a technique."
(Participant 07, Fourth-year PhD student, Immunology)

"Early-career researchers face significant challenges, such as lack of structured training, inconsistent support systems leading to trial-and-error approaches, and limited collaboration opportunities [...] some supervisors are not [sic] receptive to researcher's request for formal training and instead expect them to learn through observation, especially when resources/opportunities for such observation are not readily available."
(Participant 32, Second-year PhD student, Biomedicine)

"I think you are quite limited in the PhD, doing what your supervisor wants you to do [...] I think mine's quite flexible actually and I still feel quite constrained."
(Participant 25, Third-year PhD student, Microbiology)

"I always think of PIs as like friendly dictators a little bit. This idea that you are working in a team, but there is somebody who always has that final decision, that is largely because they're the ones responsible for bringing in the money and deciding how it's going be spent [...] I have big chunks of my current grant which are all for animal work, I can't really just go and start spending that on organoids because I have a student who says, "Actually that's what I want to do instead." Because I have to justify to the funder why I'm doing that, because I've justified why I had to have mouse experiments in the first place."
(Participant 13, Associate Professor, Immunology, Mid-career)

As the above interview excerpts demonstrate, the kinds of training that ECRs can access is often only that which is justified by the specific project aims. This can limit PhD students and Postdocs from accessing training in new models and methods and, with the prevalence of short-term positions in academia, moving from the defined objectives of one project to another may prevent researchers from gaining a breadth of methodological expertise and limit the research positions they are able to competitively apply for.

As Participant 07, a PhD student, suggests above, **the inclusion of methods training within broader career development training programmes may be one way of promoting access to training opportunities outside of the project grant and this could either be built into the grant or provided by the home institution**. Funders could also be expected to promote specific NAMs-oriented training opportunities when funding projects involving animal use.

2b) Lack of formalised training programmes around NAMs

Another barrier related to training in NAMs was discussed as a lack of formalised training opportunities. Several participants described a more informal training arrangement, e.g. shadowing a student or researcher, which is subject to the personal time constraints of the 'trainer' as the following participant describes:

"The training that you get when you're learning to work with animals is taking place in a context of a very professionalised service with people who have been doing it for years and absolutely know what they're doing, whereas the training that you're going to get in organoids might be you go and visit the lab of another researcher for a couple of weeks and you shadow a PhD student who's been doing it for six months, because the postdoc doesn't have time and you don't get really the same level of training. Through nobody's fault, it's just that that infrastructure isn't there."
(Participant 18, Group leader, Biochemistry, Mid-career)

UK law requires anybody performing regulated procedures on an animal to have completed mandatory training modules and have obtained a personal licence granted by the Home Office. As highlighted in the above excerpt, the use of animals is also situated within an established professional infrastructure, with Animal Technicians, Named Persons, and Animal Welfare and Ethical Review Bodies, set up to provide hands-on training and oversight of the research. The distinction drawn here between training around animal use and *in vitro* methods, such as organoids, suggests that **the lack of professional training programmes, with their associated infrastructure and support systems, around the latter may impact on researchers' confidence in being able to properly set up and run the model in their own lab**.

Some participants also discussed how there was currently more focus on information-sharing around NAMs rather than providing access to training, particularly training which is applied to a specific context of use:

"I think [the institution is] limited in what they can really find in terms of training or anything like that, I think that's really down to us. We do have a few researchers who work on organoids, I'm not aware of them teaching specific courses on that though. I mean some of the animal facility staff do teach to master's student level about 3Rs and use of mouse models and that kind of thing, so the teaching is filtering down. But in terms of the replacement side of things… although I think the main thing is, we're just given information about how to access other information that's already out there."
(Participant 13, Associate Professor, Immunology, Mid-career)

"Probably, yeah, there is some information. Maybe it's not the entire information, but probably there is something. I'm not aware about exactly how much… maybe I received more as an encouragement to do this, or reflectory exercises, sometimes, rather than a real solution, like, "There is a model," or, "There is a new technique, just, we want to try."
(Participant 10, Veterinary Neurology, Mid-career)

"So, the last two [academic] meetings we attended, yeah, there is definitely a session that are talking about NAMs for this, that. So, it's definitely happening within the field. Training? Not that much. So, I guess, they all assume that the skill is there, and we have the undergrads to pick that up at PhD, and then we have the Postdoc who know how to do it. But, from the own experience we have here, it's not that easy."
(Participant 08, Senior Lecturer, Toxicology, Late-career)

"If we are thinking completely replacement, then the models need to be complex. So, therefore, I think we need to invest more in that kind of thing, and mobility of scientists that can actually go, and see, and discuss […] We can connect online, you know? But there is an element of training, and a proper workshop where you can actually do it hands-on and see things. I don't want to say the right tricks because it's not like a trick, but I don't know, I always say to my students, it's like, "Oh, it's when you decide the cells are ready." And it's like, "Wow, I don't know. I just look at them in the disk," I tell you. It's like, "I know that you think I'm a nutter, but it's like, they're ready."'
(Participant 14, Associate Professor, Pharmaceutical chemistry)

As these excerpts convey, **NAMs are being discussed across scientific communities, however this appears to be more commonly at the level of general awareness-raising rather than providing access to established training programmes**. As suggested by Participant 14, an Associate Professor, this relates back to building confidence in setting up and using NAMs, enabling researchers to develop the kinds of embodied understandings of when aspects of model usage are right or wrong and allaying concerns that the work will fail due to error. **Information-sharing around NAMs, or on the principle of Replacement more broadly, without also providing access to relevant training programmes may contribute to a construction of Replacement as an abstract concept which cannot be effectively implemented in one's own research practice**.

While information-sharing around NAMs is helpful for ensuring that researchers know which individuals and organisations they can contact to find out more, and to appreciate the broader context in which they are emerging, this alone is insufficient for fostering the practical skills, investment, and confidence needed to implement new non-animal approaches.

Theme summary: the linking of training opportunities to a project grant's specific goals and objective, alongside the broader focus on simply raising general awareness around NAMs rather than providing established and specific training programs, can both limit the building of the skills and confidence required to make use of NAMs.

3 Funding

In discussing funding around research and development of NAMs, two key elements seen were the need for previous experience with NAMs in order to obtain funding, and the length of funding grants.

3a) Need for experience and expertise around NAMs to access funding

A key barrier to accessing funding for research using NAMs raised by participants was funder expectations for researchers to have expertise and status around the model(s) used within a project. Without this, funding bids were perceived as likely to be unsuccessful as the researcher cannot justify why they are the most appropriate person to undertake the work. As the following excerpts describe:

"Grant-awarding bodies won't give you the money because you haven't proved yourself in that area. So, it is a catch-22 in the end. And you would have to include someone else on the grant that can do it, and that's the whole how you do it. So that's definitely a thing."
(Participant 06, Professor of Physiology, Late-career)

"You have to have, I would say, a 10-year plan, co-publish some papers with a collaborator, to be able to support a case for how and why you are the right person to get funding to do research in things that you haven't been doing research before."
(Participant 28, Postdoctoral Fellow, Biochemistry, Early-career)

"In terms of writing of grants and sending it to a research council to actually get that money, they want evidence that the people listed on the grant have the expertise to do the things, which they're saying they're going to do. So, I can't, on my own, say we're going to do this in cerebellar organoids or whatever, unless I have a collaborator lined up who can write a letter saying, I know how to do this and I'm willing to commit the time to train people, which is not necessarily easy and not necessarily a given. So, there are definitely those kinds of structural barriers to uptake of those methods as well."
(Participant 18, Group leader, Genetics, Mid-career)

"One of the barriers I think, is that if you're going to go to a funder and say, "Well I'm going to use this organoid model to do this part of my research", then they'll come back and say, "But you've not published in organoids, so you've got no experience, so how do we know you're going to be able to do that?" It's a much harder sell and then it's really hard to get the money in. Sometimes what they want from you is preliminary data showing that I've already set up an organoid and they say, "Okay, clearly you can do it." But it's like, "Where do I get that money from?" You find yourself in a bit of a catch-22."
(Participant 13, Associate Professor, Immunology, Mid-career)

"You can move into new areas but it gets increasingly difficult because if you have a track record that you get funded on the basis of, if you don't have a track record in a new area, how are you going to get the funding? When I've moved areas, I've done it without the funding. I've done it on the sly basically, by having graduate students do that as part of the project. It's not funded but it's funded from my general lab pocket of money. Then once you've published it you can say, oh wow we can do this. They say, all right we'll give you a grant next time."
(Participant 30, Professor, Cancer Biology, Late-career)

As the above excerpts detail, strategies to get around this lack of experience with a model when applying for funding may involve collaborating with others who have the required expertise or undertaking pilot studies or side projects to generate preliminary data with new models. As Participant 28, a Postdoctoral Fellow, emphasises, because of this need to build up experience and academic profile around a model, acquiring funding to work with new models may require long-term forward planning. This means that **drives to encourage researchers to move from *in vivo* to advanced *in vitro* models, for example, may need to factor in the amount of time and preparation required to make this switch**.

3b) The length of funding grants

Related to the length of time it can take to acquire funding for projects involving the use of new models, several participants also mentioned the length of funding grants as an issue for the uptake of non-animal methods. As the following excerpts suggest, **short-term funding grants can raise barriers for researchers to pick up on new methodological developments** while undertaking their research:

"There's partly the challenges around the way science is funded in the UK, and they tend to be short-term grants. So, you've got a grant to do a specific thing and you can change what you do, but a bit more longer-term funding would allow people to follow as the science develops, so it's less restrictive in what could be done. So, if you're trying to get a grant and you're proposing some system, you might struggle a bit to be able to fund it. Whereas if you had money to spend on that sort of thing alongside other research that you're doing which perhaps is more easier to assess, whether it be successful or not."
(Participant 16, Retired Professor, Genetics)

"Usually it's the specific grant that needs to answer a particular research question. There may be some scope for the postdoc to change the methods, but there usually isn't much at all to change what's the direction of research […] I think part of that comes down to short contracts again, like most of these people are being hired for two or three years to do a specific piece of work on a grant, so there just isn't time to train them in something that their group isn't doing. If they were supported for five years and they had a year and a half to just pick up new skills before they actually started doing anything productive it might be a different question, but there just isn't the time for most people."
(Participant 18, Group Leader, Biochemistry)

"I think if you read a paper about, oh, there's this organoid [...] In like a three-year project, if you were halfway through it, and then you saw that paper, it would probably take at least two years to try and get that up and running. And if you got to the point where you have three more questions you want to answer, you haven't even started that, you've just tried to get a different model up and running, and not published it, because someone else has already published it, so no-one's kind of valuing that work in the system, I think. Where I'd say if a department hired some staff scientists, where it was like, we as a department want to get these organoids up and running, and that's someone's job, I think that would be different. But I suppose none of us are really in... the system doesn't reward you for doing that."
(Participant 22, Postdoctoral Research Associate, Biomedical Science)

As all three researchers point out here, **funding grants often do not enable the flexibility needed to "follow as the science develops" and pick up other skills or use other methods alongside the defined research plan set out in the grant**. As well as having limited time to explore options outside of the funded research plan, there may also be a lack of value placed on setting up a new model if it does not lead to novel outputs and publications, as Participant 22, a Postdoctoral Researcher, quoted above states. In this case, **the constraints and pressures of research contracts may prevent the use of novel methods and models due to an expectation that they will incur delays to outputs and the efforts taken to set them up will be not be sufficiently recognised**. As Participant 16 suggests, allocating funding for side-projects which enable use of new models without significant pressures to produce outputs, may allow researchers to try a NAM and assess its merits, 'whether it be successful or not'.

Theme summary: **Barriers associated with the uptake of NAMs related to funding include funder expectations that researchers have expertise with the models used in their projects, making it difficult for researchers lacking experience NAMs to justify their suitability for the work. To overcome this, researchers might involve others with experience around NAMs as collaborators in their funding applications or conduct pilot studies to gather preliminary data. Additionally, participants noted that the inflexibility and limited duration of funding grants can hinder the adoption of non-animal methods, limiting the acquisition of new skills or the conducting of research outside of their specific project grant. There may also be limited incentive to establish new models if they do not produce novel outputs and publications within short timeframes.**

4 Access to NAMs

Access to non-animal methods covers multiple aspects including material resources as well as expertise and support. Key themes relating to access across the interviews that will be further explored here were perceptions of NAMs as incurring high costs and limited access to the required infrastructure to enable use of NAMs.

4a) Perceptions of cost

The upfront costs of the more advanced non-animal methods were mentioned by several participants as a barrier around their uptake. As the following excerpts demonstrate:

> "Organoid specifically, I have to say, is another extremely expensive thing to do, so it's not for everybody. So, if we want to talk about advancement of science, if we think that advancement of science can go with, I don't know, a handful of labs that have the financial muscle to run these studies, okay. But usually, it doesn't go that way."
> **(Participant 28, Postdoctoral Fellow, Biochemistry, Early-career)**

> "It's tricky because, actually, we submitted recently an application to [a funding body] and we were questioned by one of reviewers because of the in vitro NAM model that we wanted to put. And they were not understanding that it cost more than the animal part of the project, but that's the reality. So, the problem is that it's not only the funder, it's whoever is reviewing for them needs to be aware. And I don't think it's widespread that the cost is very, very high."
> **(Participant 08, Senior Lecturer, Toxicology, Late-career)**

"I think small labs can't do it. The only people that can build models are the big labs with lots of money because they can accommodate it within what they're doing. If you've got 30 people in your lab, you can take a little bit of time or money off everyone to actually set up something. If you're not funded to do it, you're not actually funded in the first place […] the people that get the money, are those that have already got a ton of money because they're successful. […] But you need a lot of people, it's a big operation. You might get big companies […] they screen drugs, they use huge numbers of mouse models for things, but they have the resource to build other models as well. So, companies are really big on save money and save animals if they can because it's cheaper for them."
(Participant 30, Professor, Cancer Biology, Late-career)

The above excerpts reveal that **the costs associated with some NAMs, particularly in comparison to using certain animal models, can raise obstacles both for generating researcher enthusiasm towards their uptake and for obtaining funding**. Cost is likely to be a particular concern for researchers earlier in their career or those working in institutions with lower levels of funding, who might find it challenging to justify the higher initial investment required for NAMs. As highlighted by Participants 28 and 30, the costs associated with advanced NAMs like organoids may mean only certain laboratories with higher levels of funding are able to access them.

Though costs around NAMs may be lower in the long-term than maintaining animal models, the upfront costs of setting up and implementing NAMs can hinder their broader adoption. Additionally, as Participant 08 describes of their experience with reviewers of grant applications, funding bodies may be hesitant to allocate resources to more expensive methods and may need further convincing of the justification around their higher costs in relation to animal models.

4b) Limited access to required infrastructure

Access to the required infrastructure was raised by many participants as a crucial component for supporting researchers to move into using non-animal methods. This involves aspects such as space, equipment, and on-hand expertise and support, as expressed below:

"There is not an easy one kit that you can buy and you get [organoids] in your lab. It's not really the case."
(Participant 08, Senior Lecturer, Toxicology, Late-career)

"But I think they're hard work, the organoids, I think some of them need to be fed every day and that sort of thing. So, you kind of need a team doing that. So, I think that's also part of the problem, it's not like it's easy to just, "Oh, I'll just bash these out on the side and see how it looks alongside my other work." It's quite full on. So, I think is a bit of an issue, unless, again, if there were staff employed to do them and then they hand you the organoid at the end. Then we'd probably all use them more […] I've worked in two very well-funded universities, so even in those settings there's nothing. So, you go to smaller or less research-heavy universities, I presume that's even harder to have in place. So, I think it's big picture issues a lot of the way."
(Participant 22, Postdoctoral Research Assistant, Neuroimmunology, Early-career)

"We don't have the facilities on-site for that kind of… well, it would take a lot of change anyway, I'd say [...] the level and scale of the work we do with these animals requires such a massive amount of infrastructure and equipment that there's a requirement to use it [...] so if we wanted to shift away from using living-animal models to a more lab-based thing, we'd have to really justify why exactly we wanted to do that."
(Participant 09, Experimental Manager, Agriculture, Early-career)

"I think more infrastructure would be really helpful for me, specifically as somebody... I have a very small lab [...] so, if I were to hire somebody to do a project on organoids that would be actually a very big part of what was going on in my lab, just by virtue of it being like 50% of the full-time staff. And that means that it then becomes a huge risk for me if we can't get systems up and running properly, if we can't get the training, all of that kind of stuff. So, I would be much more open to it, and I already am, like, I would like to be using some NAMs for some of our research, but I would say the main thing limiting me is that kind of institutional support that takes away some of the risk."
(Participant 18, Group Leader, Biochemistry, Mid-career)

As the above excerpts illustrate, **compared with the animal models that have already been established within an institution, research facilities may have very limited existing infrastructure to enable researchers to use NAMs in-house**.

As Participant 18 points out, the regulatory framework around animal use has ensured that establishments licensed to use animals have the necessary conditions and support to do so, with such institutions having professionalised services on site to share the responsibility and burden of animal care and ethical review.

Having established infrastructure around animal use, such as on-site animal units, technical and support staff, and training programmes, can drive further use of animal models. Change at the individual researcher level requires an institutional reinvestment to support the use of NAMs:

"There's this huge infrastructure that supports us to do that research [using animal models] well. If we decided to go down the organoid route, that would have been a case of collaborating with another group that were researchers. It's not necessarily their job to train us and make sure that we're doing that stuff properly. I'm sure if there was an equivalent facility at a university level that would say, you just come to us with your research projects, tell us what you need to do, we've got 10 staff, or whatever, who are just going to spend their whole days taking care of all the organoids that we've got growing. That same level of infrastructural investments, I think there would be an increase in uptake of those methods definitely."
(Participant 18, Group leader, Biochemistry, Mid-career)

"Most people use mice and rats because they can have a small animal house everywhere, in every university, and so they just tend to use those. And you can do genomic manipulation and what have you, and that's why everyone… mostly, 95% of animals in laboratory are because they can be housed in constant conditions and control the environment and with due disregard for anything that might make the results of that research being translatable."
(Participant 06, Professor, Physiology, Late-career)

"The thing is, with mice, is that they are the most established ones. They are the easiest ones to create genetically modified lines, genetic lines. Yeah, and the staff in the animal unit have the most experience with these animals. So, I think, in terms of experience, it would be… I don't think I was actually given another choice in terms of other animals."
(Participant 17, First-year PhD student, Genetics)

As Participant 06 and 17 point out, some animal models are easier to accommodate on-site than others, with certain species such as mice having long-established global histories of use. Given the length of time they have been bred and used in research, mouse models are perceived as being associated with a high-level of standardisation and ease of use across research environments, with researchers and technical personnel having cultivated expertise around both their husbandry and scientific use. As is also reflected on in these excerpts, however, **the establishment of infrastructure around certain animal models does not necessarily mean these are the most appropriate for research, particularly in terms of translatability, but rather it represents their embedded status**.

Theme summary: The perceived initial high costs of implementing some NAMs compared to using animal models can deter both researchers and funding bodies', particularly early-career researchers or those in lower-funded institutions. As well as this, existing infrastructure and resources around animal models can further promote their continued usage, with the widespread establishment of technical and professional services around animal use across institutions and the broader histories of standardisation across laboratories reinforcing their uptake.

5 Career progression

The role that model choice can play in terms of career progression emerged throughout interviews, involving discussions of what kinds of outputs are valued most in assessments of academic performance, how pressures to publish can drive use of familiar and established models, and wider pressure to validate NAM data against *in vivo* data.

5a) Pressure to publish

Many participants discussed how **the pressure to publish can drive use of familiar models**, due to the additional time associated with learning how to use, setting up, and producing results from a new model, as shown below:

> "I would say that's probably the biggest driver because there's such a high pressure to publish, and publish in good journals, and get the next grant. That makes more risky work, like using a brand-new model to do something, much, much harder to get people to uptake that, because they can't afford the risk effectively."
> **(Participant 13, Associate Professor, Immunology, Mid-career)**

> "I think a big issue with all of it is that within academia, people are working short contracts, I'm sure that comes up a lot. But I think it's the lack of kind of progression within the career that I think leads to a lot of its problems. If people are needing to get papers published in order for their careers to progress. So, I think there may be less space for a real discussion of like, could we move away from animal, could we try something else? Because there's this constant cycle of like, "If I want to progress here, I really need to publish this. So, I'm just going to keep going with the model that we know works and try and generate results that way". So, I think that's a real fundamental issue that's difficult for anybody individually to change."
> **(Participant 22, Postdoctoral Research Assistant, Neuroimmunology, Early-career)**

As these participants express, the use of new non-animal approaches can be linked with slower research, with researchers needing more time to learn new techniques and set up a new model, causing potential time delays for publishing results. Given the pressures around publishing that exist in academia, with publications, particularly in journals with a high 'impact factor', continuing to play a significant role in securing academic positions, research funding, and promotions, perceptions that the use of new non-animal approaches may impact upon the ability to publish quickly or in journals with prestige are crucial to meaningfully address.

5b) Pressure to validate NAM data against in vivo

As well as being as associated with slowing down the publication process, **the use of non-animal methods was also linked with expectations that any results would have to be validated in animal models in order to be accepted for publication**. As the following excerpts demonstrate:

"When we work on purely in vitro models and claim it was as good as in vivo, the reviewer definitely said, "Oh, then, do you have the equivalent in vivo data to prove it?" And a lot of times, because in vitro model, we can actually study more physiological factors than in vivo. So, you won't be able to find any relevant in vivo data […] I think if you actually go to those high-impact factor journals right now, I think most of the medical research work, you will definitely have in vitro, and then you definitely do in vivo."
(Participant 04, Senior Postdoctoral Researcher, Oncology, Early-career)

"So, I think it's almost like you can't claim too much from a piece of research if you don't have the ultimate proof that this could be validated with an in vivo model. So, then the choice is always, "I'm settling not to use in vivo model, but I need to resign on publishing in a smaller journal," for example, where maybe it is more accepted […] So, therefore, you're almost feeling you are downgrading your research if you haven't got that."
(Participant 14, Associate Professor, Pharmaceutical chemistry, interview 14)

"I don't particularly enjoy doing [animal studies], but you want to do them as little as I can, but if we find something in vitro, we want to prove it in vivo to be able to publish it and to get it out there. Because publishing in vitro data alone, I mean we could do it but it's not robust enough I don't think."
(Participant 25, Third-year PhD student, Microbiology)

"There has been a huge effort to try and replace [a particular] gland, basically. Very interesting, very worthwhile and definitely worth doing, but for all this beautiful work that [a former PhD student] did, he never got the high-profile papers because it was never done in a mouse. That's always the balance I think, at the moment."
(Participant 30, Professor, Cancer Biology, Late-career)

"I think because there is such a huge pressure on publishing, you have to take it in vivo, otherwise you're not going to get published."
(Participant 26, Research Assistant, Immunology, Early-career)

As suggested here, expectations of and experience with reviewers requesting that *in vitro* data is validated against *in vivo* data can lead to researchers conducting animal studies in order to publish, rather than being driven by scientific need. **Even if**, as Participant 04 points out, **the *in vitro* model is arguably more physiologically relevant than the *in vivo* models, researchers may still experience demands for the inclusion of animal data**.

This phenomenon is what Krebs et al. (2023) have referred to as '*animal-methods bias'*, a particular type of publication bias which involves *'a reliance on or preference for animal-based methods despite the availability of potentially suitable non-animal-based methods*'. As both Participants 14 and 30 convey, expectations that papers without animal data will not be accepted for publication in high-impact factor journals can therefore raise broader concerns around career progression and lend to further characterisations of NAMs as 'risky'. Therefore, as Krebs et al. argue, *'[e]limination of this type of bias may help reduce unnecessary animal experiments and will ultimately improve the fairness of the peer review process by removing unwarranted barriers for researchers*' (ibid).

Theme summary: Pressures around publishing in academia, the so-called 'publish or perish' principle, can promote the use of familiar models as they avoid delays to publication caused by learning and setting up new models. Relatedly, expectations that journal reviewers and editors will request validation of non-animal data against data derived from animal studies also raise concerns around moves away from animal use, with jeopardisation of the ability to publish, particularly in high-impact journals, posing a significant risk for researchers in the academic system.

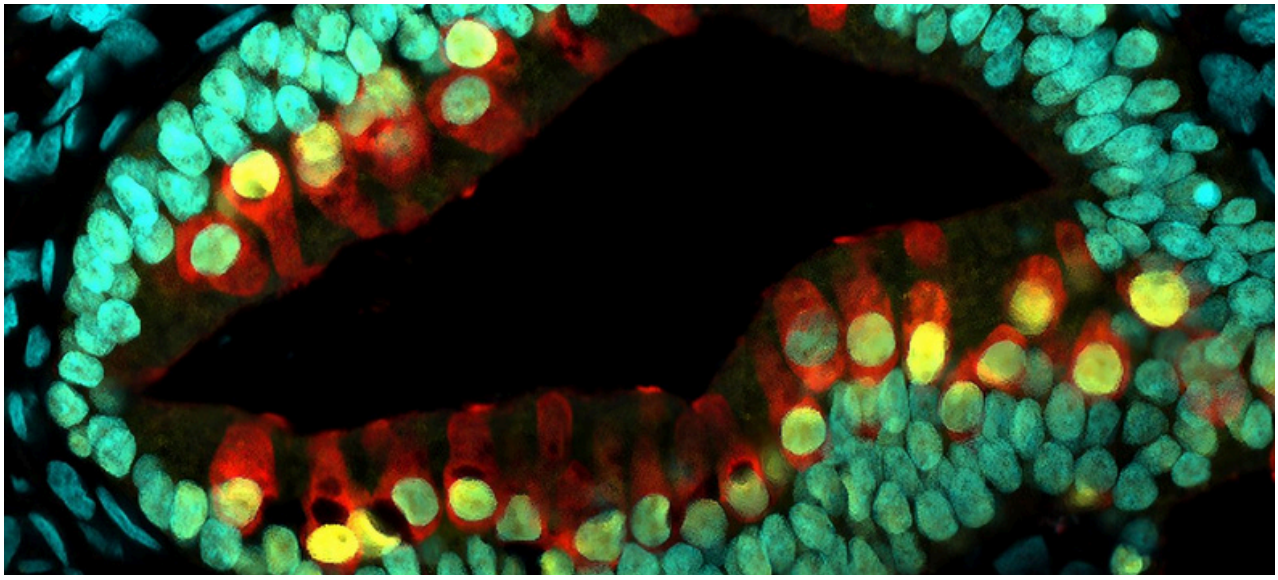


Image: Cross section of an inner ear 'organoid' created by human stem cells - BSIP SA / Alamy Stock Photo

6 Communication and collaboration between those developing/using NAMs and those using animals

Communication between those using animal models and those using non-animal approaches is a highly important aspect of supporting Replacement efforts. Fostering knowledge-exchange around methodological needs, limitations and strengths, as well as collaborations where NAMs can be developed, optimised, validated, and adopted in experiments. On this topic, key barriers identified from the interviews were a lack of communication across research fields and between those using NAMs and those using animals, and arguments that the development of alternatives needs to be informed by the *in vivo* context.

6a) Lack of communication across fields and between those using NAMs/animals

Many participants described **limited communication between users of animals and those using NAMs**. As the following participants discuss:

> "Because we are all in silos in our own building, we are not really talking with each other. And even when we have the institute where all these people are somehow working on different floors, it's not always really happening. Like, I'm sure cancer people are not even aware of what is happening in tissue engineering at the moment and that, eventually, someone may have a model that can prevent them from using animals."
> **(Participant 08, Senior Lecturer, Toxicology, Late-career)**

> "I work in a multi-school building […] And we have these weekly, monthly seminars, and you will always hear people presenting about an animal-free model […] but I don't think I've ever seen anyone openly acknowledge that they're going to talk about animal work […] I think people really want to shy away from what they've done […] it's almost like this very self-contained thing."
> **(Participant 27, Final-year PhD student, Biochemistry)**

> "I don't think there is an active flow and exchange between different fields because again, I don't think people consider this to be a major problem the way it's done now."
> **(Participant 26, Research Assistant, Immunology, Early-career)**

As the excerpts above indicate, some researchers may feel that active exchange between their field and fields where non-animal models are being developed or more commonly used can be limited. Participants often discussed engagement with research communities who develop non-animal models as needing to be driven by the individual researcher and their interests, with them being required to go outside of their typical communities. This means that unless individual researchers are interested and actively looking to establish connections and collaborations around non-animal methods, they may be unlikely to come across these in their usual networks. This is problematic if, as Participant 26 suggests, many researchers do not feel that their current use of animals requires change. Indeed, as another participant discussed:

> "I think the thing is when I was talking to people around, I think if people are interested, they will talk to you, but if they are not interested, they won't even show up in the meeting. Even if we put the 3Rs in all the regulations, I don't think… I mean, if you don't specifically ask people to do it, then people, well, especially a lot of medical researchers are really, really busy. They might also have clinical duties or something else. They will just say, "Oh, I don't have time. I'll just stick to my mice work, because I know it will give me results.""
> **(Participant 04, Senior Postdoctoral Researcher, Oncology, Early-career)**

As a PhD student who works with both researchers involved in animal studies and researchers working with NAMs, Participant 27 discusses silos between the two, with them functioning as two separate groups. Interestingly, despite being part of a "multi-school building" in which there is active discussion around NAMs, they describe a situation in which there is little discussion of both non-animal methods and animal models. Gesturing to a sense of taboo around discussing animal use at the school level, they go on to describe their experience of being "pigeonholed" by animal use:

> "In my network, it's very much a group of animal people, a group of non-animal people […] it is easier for me to go and talk to animal people about replacing an animal than it is to go and talk to replacement people about an animal. Even though I morally and ethically agree with animal replacement, I think the second you say, "Oh, well, I've done animal work," people assume that you are just very okay with it, almost. But, I guess, to some extent, I clearly am okay with it, else I wouldn't have done it. But I think you almost get this false sense of people hear you do animal work and think you're just… I don't know what the right word is. But I think they, kind of, pigeonhole you into a type of person rather than acknowledging that I can do animal work but also agree with animal replacement and work with people that are actively replacing animals."
> **(Participant 27, Final-year PhD student, Biochemistry)**

As discussed above, feeling characterised as "okay with" animal use, this PhD student states that they would find it easier to talk to "to animal people about replacing an animal" than "talk to replacement people about an animal". The situation described here demonstrates **the importance of making conversations around NAMs inclusive and accessible to those currently using animals, bringing them into the fold without definitively categorising them as 'animal users'**. Allowing those who use animal models to share their research across departments can provide opportunities for those working with other methods to share information, suggest potential alternatives methods or approaches, and build collaborations. This would also help to develop cross-departmental understandings of the methodological needs of researchers who work with animal models and what requirements they might have for an alternative method. In this way, clear-cut characterisations of researchers as 'animal users' or 'animal-free' can at times be unhelpful, reinforcing silos and limiting the potential of such knowledge-sharing events to attract those who currently work with animals.

On the other side of this, many participants discussed the ways in which established connections and collaborations around animal models can discourage moves into new areas. **Establishing connections within others in a particular field or around particular models, histories of collaborating with others exploring aspects of the same models, and being successful in working together and securing funding, can all support further use of the same models**. As the following excerpts illustrate:

> "There's a lot of inertia, particularly if you have a group, and let's say three or four research groups in one department who were all focusing on slightly different aspects of something and have a long history of working together, then you do get that, almost kind of peer pressure. There's just a lot of momentum there for one group to say, "Actually, we're going to stop using this mouse and we're going to start using something else," because then that almost cuts them off from their support network that they've built for themselves […] So, there's like an activation energy almost, there's a cost for switching to a new model that is definitely front and centre in people's minds when they're thinking about what projects they want to do. And especially when you combine that with the pressure to publish, switching models is going to be another year or two before you can actually get that paper out of the door, because you're having to do all of that groundwork again. But all of that stuff is not things that actually makes the science any better at the end of the day."
> **(Participant 18, Group leader, Biochemistry, Mid-career)**

> "'the networks of PIs, like a PI that's going to hire you might know your current PI, but then you end up probably staying in a similar field."
> **(Participant 22, Postdoctoral Research Assistant, Neuroimmunology, Early-career)**

As described here, **once collaborations have been built around particular model usage with an established history of successfully working together, securing funding and publishing, there is likely a momentum to keep going and conversely a "cost" associated with moving to new models**. Researchers also gain status within particular networks from being attached to certain people, which, as Postdoctoral Researcher Participant 22 describes, can promote the continuity of certain lines of research.

6b) Development of alternatives needs to be informed by the in vivo context

As part of supporting communication and collaboration between researchers using animal models and those using or developing NAMs, the need to ensure that the development of NAMs is informed by or relevant to the *in vivo* context was discussed by several participants. **Without** this level of **communication and understanding of the *in vivo* context, some participants implied that** such **non-animal models will never become a 'replacement' or 'alternative' for those currently using animals**. As the following excerpts illustrate:

"When I was training as a bioengineer, because we're more training to engineer, so most of the thinking, we're trying to solve a problem, especially like tissue engineer, our angle is actually to build, for example, an organ, a heart, and myocardial tissues. But, the problem is a lot of those people never do animal work, and they never see how an actual physiological system is working in vivo. So, even if right now sometimes I go to those in vitro model-focused conferences, I can feel like people are trying to build something quite similar. But, because they never know how animal work was done, and they never worked with animals, they never worked with human beings sometimes, so the model they build is still really far from facts [...] So, if you don't actually work on both fields at the same time, you don't know what you are building. You are just building something similar, but the other guy is not going to be interested, because that's not what he's looking at"
(Participant 04, Senior Postdoctoral Researcher, Oncology, Early-career)

"I think if there was more communication between the two worlds then I think there would be more refinement and 2D scientists would think, how can I make this more applicable to in vivo research down the line? So, it's very easy to just stay very focused within my lab and my research and not really be aware or as interested in research of... yeah, someone's using your research to then base their 3D in vivo model."
(Participant 21, Second-year PhD student, Cancer Biology)

"You can't develop a model if you don't know what the question is you're going to ask. You can't just say here is a model, you have to say what questions do you want to ask and then we'll develop the model, if you see what I mean. So, it's not just a case of saying here's an organoid."
(Participant 30, Professor, Cancer Biology, Late-career)

"These alternatives cannot be developed in a vacuum because you need to… well, either way, you've got two facets. You've got to make sure that your alternatives are relevant to the first steps for translation and for patient-driven research. And, in order to do that, you need to understand what it's trying to replicate and that a lot of that knowledge is in animal research. […] I think they've got to move forward in lockstep, so there's got to be a… one side may put what we know forward. It could be either side. But everyone's got to speak to each other. Everyone's got to move forward together to ensure that all of our models are most relevant to humans, most relevant to patients."
(Participant 07, Fourth-year PhD student, Immunology)

As shown here, for researchers currently using animal models it is important that the **development of new non-animal models is embedded within specific contexts of use to ensure their applicability and uptake**. To achieve this, as Participant 21 puts it, there is a need for "more communication between the two worlds". However, in regards to developing NAMs that are applicable for answering research questions that currently involve animal use, there are also questions around which parameters are most important to replicate, i.e. a NAM may be more relevant to the human physiological context rather than a mouse model, for example.

In this way, the development of NAMs is not always aiming to reproduce an animal model, but, in studies aimed primarily at advancing human health, produce something closer to the intended target group of humans. Nevertheless, these insights suggest that communication between those developing NAMs and those using animals is crucial not only to practically inform the development of new models, but also to instil confidence in and understanding of their purpose and application.

Finally, Participant 04 also discusses the unintended barriers that can be caused by funding opportunities that are targeted specifically on Replacement:

"A lot of funding agencies, when they want to try to promote the in vitro model, they only focus on the in vitro model. They forget about those guys doing in vivo. But, I believe that's probably not something we should do. Yeah, and when I say those funding agencies, they even, sometimes, because I also wrote some grants […] and they do have specific sections, like, "How many animals you can actually replace." It's, like, yeah, but then, my things, our messaging is always that, "Yes, I want to replace, but at the same time, I want to first prove it's replaceable. I want to first prove this is actually equivalent to the in vivo model." But then, they won't fund you, because you're not replacing […] Long term is, like, you definitely want to replace, but before that, you need to prove it can be replaced."
(Participant 04, Senior Postdoctoral Researcher, Oncology, Early-career)

Again, the need to maintain open channels between NAMs and *in vivo* research is underscored here, with this postdoctoral researcher describing wanting to develop a replacement model whilst also needing to undertake animal studies to "first prove it's replaceable". This example shows a potential pitfall of Replacement-only oriented funding opportunities that don't allow use of animal models, thus limiting the capacity for researchers currently using animal models to develop and prove their NAMs.

Theme summary: Active exchange between fields where NAMs are being developed and used, and those where the use of animal models remains common, is essential. To support further cross-communication and collaboration, this analysis indicates that enabling those already acquainted with and invested in NAMs to share their work with those using animal models may be more productive than encouraging researchers using animal models to look outside of their established networks and communities. It has also signalled that labelling researchers strictly as 'animal users' or 'animal-free' can sometimes be counterproductive, reinforcing divisions and reducing the likelihood of knowledge-sharing events drawing in researchers across all methods and approaches. Finally, the development of NAMs must be informed by the in vivo context in order to ensure that NAMs are applicable and relevant, as well as to build researcher confidence and understanding around their adoption.

7 Awareness of NAMs

Awareness around NAMs is of course an important factor on its own, however within the interviews, participants discussed how awareness should also be linked to opportunities, such as funding and collaborations. Another important theme identified in discussions around awareness of NAMs was a perceived imbalance in the promotion of 3Rs information, with Replacement often seen as featuring less, and being more difficult to implement, than Refinement and Reduction.

7a) Need for better communication of the benefits of and opportunities around NAMs

Discussions of awareness illustrated that awareness involves more than simply knowing about NAMs, with many participants emphasising the importance of advertising specific NAMs and **how they can be accessed, highlighting relevant funding opportunities, addressing the practicalities involved in using them, and their scientific benefits**:

"Maybe we can invest some time in looking at alternatives in a more systematic... and putting that into some format that could be used more generally. Organoid models that you could be applying; this is what it's been used for, this is what it might be used for, this is where you can get training."
(Participant 16, Retired Professor, Genetics, Late-career)

"If you don't force them to go [to Replacement-focused webinars and workshops], only the ones who will be interested will go, and then probably a lot of them will figure out, "This is not a model I'm looking for." Probably just 1% or 3% will actually try to use the new model. But, on the other hand, if we're trying to say, "We have a specific funding call, I want to use this," for example, "I want definitely this funding call, is the purpose to use the zebrafish to treat cancer," and then people will say, "Hey, there's money there, so maybe I should do something.""
(Participant 04, Senior Postdoctoral Researcher, Oncology, Early-career)

"My understanding of replacement models isn't very good at all, and I don't feel like visualisation of that or accessibility of that has been something that's been advertised during my research career, for sure. I'm aware that these exist out there somewhere, but I don't know where they are or how much they cost or where they might be beneficial over and above that. So yeah, I think, probably, enhanced visibility would support a move"
(Participant 31, Post-doctoral Research Assistant, Cardiovascular science)

These excerpts reinforce the importance of linking awareness-raising and community-building around NAMs to tangible opportunities for uptake. In this way, **awareness-raising around NAMs is seen as most valuable if it communicates the purposes they can serve, the benefits they can offer, and the opportunities surrounding them**. Situating the promotion of NAMs in the worlds of researchers, conveying the specific scientific and career benefits of training in and using them, as well as the ethical imperative to move away from animal use and the broader methodological pressures to use more 'physiologically relevant' models, is therefore likely to better incentivise researchers to seek out and engage with information around them.

As well as this, Participant 31 discussed the importance of where and who information on NAMs comes from. For them, information-sharing via researchers was seen as more valuable as this was linked with further research and career opportunities, e.g. for working together and collaborating on papers:

"For me, personally, I would find that information coming from us more valuable because I would say, "Oh, well I can get in with them and we could work together. Whereas, I think biological services are proposing these replacement models and, while informative, you're like, "Well, at the very most you're giving me technical support for that. You're not necessarily helping me to work with that model. You're not helping me in my pursuit of generating data." Whereas, if researchers were to be more forthcoming about these models and say, "Look. I have this new model. Look what I can do, and look what I can answer. Come and work with us," I think that would just be much more attractive. Without a second thought, that would be much more attractive because it moves from being pretty much purely informational, for informational purposes, to an opportunity and opportunities of generating data for publications, etc."
(Participant 31, Post-doctoral Research Assistant, Cardiovascular science)

Highlighted again here is the need for promotions of NAMs to be connected to the structural drivers and constraints of academia. Although staff within the Biological Service Unit might be able to share information around the benefits posed by training in or use of a particular NAM, this researcher emphasises that it is the opportunities for collaboration that may come with researcher-led information-sharing around NAMs that would be seen as most attractive, moving the situation from "being pretty much purely informational, for informational purposes, to an opportunity".

Returning back to the need for community-building around NAMs, Participant 10, a clinician working in veterinary research, points out the need to facilitate dialogue and cultivate networks as well as sharing information around Replacement:

"I think, probably, the knowledge is there. I know there are people that I can contact, I guess, and I think the knowledge that was passed to me is very good. Maybe, I don't feel like a network. I feel like a process, rather than a network […] maybe information, or some kind of presentation, or speaking, or sometimes they send a newsletter about information, information, information. But, I don't feel active, or participating in this [interview], as for example now, today, that is why I accept that is like, maybe I can help, but just one to… I mean, help, I'm not going to chase nothing, but just have this information, you are open to hear that point of view. That is what I feel, yeah, and in the past, I never feel that someone was interested to hear opinions, or new ideas, or something like that. We had information to do this, that is a must, but that's all."
(Participant 10, Clinician, Veterinary Neurology, Mid-career)

This researcher describes the **need for two-way communication around NAMs and Replacement, with their current experience being of one-way information-sharing**, feeling more "like a process, rather than a network". As they point out, participating in the interview for this current study was of interest because it provided an opportunity to share their point of view and opinions.

This emphasises the importance of creating spaces for researchers to dialogue around NAMs, enabling them to communicate their needs and concerns in a way that is valued. Given the challenges that many researchers may associate with transitioning away from animal use, **creating communities in which researchers can share their perspectives on Replacement with stakeholders is essential for building trust and ensuring an understanding of the contexts, constraints, and needs of researchers currently using animals**.

As these insights show, awareness around NAMs must expand beyond simply knowing about their existence. A comprehensive approach to raising awareness around NAMs that includes advertising their availability, explaining access routes, detailing funding opportunities, addressing practical usage concerns, and emphasising their scientific benefits is crucial for encouraging their uptake.

7b) Imbalance in the promotion and implementation of the 3Rs

Several participants also suggested an imbalance in the sharing and promotion of information and resources related to the 3Rs, with Replacement seen to feature less than Refinement or Reduction.

> "Replacement doesn't really seem like… me, as just an everyday researcher, replacement doesn't really seem like a tangible thing that I can really implement. Again, without having the information, I would have to make a proactive effort to go and deviate from what I'm doing in day-to-day research and go and search for that and invest a good amount of energy into it. Whereas, reduction and refinement are things that I can just look at in my day-to-day processes and say, "Oh, well, I think that would be really good for the animals," or, "I think that might make the regulatory procedure slightly more comfortable. Let's do that." And you can do it the next day. You can start there and then. Whereas, replacement, it seems like this wee thing that we tack on the end of the 3Rs that I don't think anybody necessarily thinks about seriously or spends a good amount of time thinking about. They're just aware that we should be striving towards it, and we should."
> **(Participant 31, Post-doctoral Research Assistant, Cardiovascular science)**

> "University wise, they do circulate, if there's any specific webinar about animal models. But, I feel like most of those are just generic 3Rs, and a lot of times, it's more about just refinements, not really replacement. Enhancing the in vitro model part, it's always, when they have that sort of information, it's really niche, and most people go to those conferences, are not doing animal work, for example."
> **(Participant 04, Senior Postdoctoral Researcher, Oncology, Early-career)**

"I always see people doing refinements and reductions, but there's never… I never see replacement. And I think that is something I think we should push for because I don't believe that replacements are advertised and made as aware as... because it's so much harder to replace."
(Participant 15, Research Assistant, Immunology, Mid-career)

"I've always said it's called the three Rs, there's three of them, they should carry equal weight between them all and we should be taught exactly about them. In my licence, it doesn't say you know 'standard condition one you should aim to follow refinement' it says 'refinement, replacement, reduction', it says all three. So therefore, I should treat all three of them with respect in order to be compliant with the Home Office regulations. However, how can I do that when I've only got access to one and one and a half if you like?"
(Participant 01, Animal Technician)

As discussed here, Replacement can seem to be given less focus in general 3Rs communications and be **perceived as something abstract and difficult for researchers to implement in their current practice**. This may be particularly challenging for Animal Technicians who, as Participant 01, describes, are obliged to implement the 3Rs with equal weighting, yet may feel as though they only have "access to one and one and a half". Participant 31 elaborates on the distinction between implementing Replacement by describing it as "disturbing" animal use, while the other Rs are seen as either optimising it or having only a 'neutral' impact:

"You can deal with these other Rs and you can help uphold them without disturbing the flow of science and the flow of the research and the flow of the group. Whereas replacement, I don't think it's possible to integrate that without disturbing the flow […] Even if it doesn't optimise it for us, it's still an overall net neutral. If it can improve animal welfare, then great. If the effect on us is positive or neutral, then that's fab. Let's do it. Whereas, I feel like a replacement model, looking at integrating one of them, a replacement model would probably be, "Well, what's the net impact on me, as the researcher?""
(Participant 31, Post-doctoral Research Assistant, Cardiovascular science)

With Replacement seen as necessitating moves away from current ways of working, which may be viewed to be providing success, this participant indicates that **researchers may have little drive towards moving away from animal use**. As discussed earlier, information-sharing around Replacement must demonstrate the practical and scientific benefits of NAMs, displaying an understanding of the structural pressures that researchers face in academia and the ways these may promote continuing animal use and discourage transitions away. Animal technicians may also require further support so they feel able to support researchers in considering and implementing Replacement.

Theme summary: This analysis has indicated that in order to increase their uptake, awareness-raising around NAMs must also provide information about the scientific benefits of specific NAMs, how to access and use them, as well as highlighting opportunities surrounding their use, such as funding and collaborations. This section also pointed to a perceived imbalance in the sharing of information around and implementation of the 3Rs, with Replacement seen as often deprioritised and being more difficult to put into practice, particularly as it may be associated with disrupting the established research process.

8 Institutional commitment to replacing animals

Near the end of each interview, participants were asked about to what extent they perceived their institution as having commitments and ambitions around Replacement, and whether they were aware of, or involved in, an institutional strategy aimed at replacing the use of animals at their establishment. Responses were mixed across the interviews, with some participants feeling there to be a good institutional level of commitment around Replacement, some being unsure whether there were any specific commitments or strategies, and others perceiving this to be limited. Key themes within these discussions were **perceptions of a continuing institutional investment in maintaining animal facilities, and of institutional 3Rs implementation being tokenistic**.

8a) Continuing investment in animal facilities

In explaining why they perceived there to be a limited institutional commitment around Replacement, some participants discussed **a lack of visible financial investment in the infrastructure needed to stimulate and support uptake of NAMs**:

> "I think if you talk to senior people, they would say that they were committed, but I don't see on the ground the investment. Money talks, I guess that's what I'm saying. I don't see that there's the level of investments that would be happening from an institution that was really genuinely ambitious about reducing animal use […] If you were thinking about this from a revolutionary point of view, like, let's try and have 50% reduction in animal use over the next 10 years, you would be seeing really concrete changes in the way that research was being done in a university. And I'm not necessarily saying that that isn't achievable or a realistic target, but if that was their target then they would be doing things differently […] Yeah, and just de-risk it for the individual researchers. It's not that I have to hire somebody who's going to have to be trained in this, and they may not have the aptitude for it, and then if they can't grow these things that whole project just goes down the pan. It's "we're going to really help and make sure that this research project that you want to start is not going to fall over just at the basic technological level"."
>
> **(Participant 18, Group leader, Biochemistry, Mid-career)**

"Not at all […] I think they helped provide facilities that were needed but you'd pay to use those facilities on your grant. So, they'd charge your grant £60 an hour to use the microscope or whatever. But the university would fund the animal facilities […] The university itself isn't going to say, we don't like animal research, we will build an organoid facility. That's not the driver, the driver would come from the researchers who want grant funding and the grant-awarding bodies saying you need to have a core facility, so the university has to provide that, then we will give you the money to then use that facility. That's the way it works. I'm not aware of any university that would have a body that would think about what do we need to do and we will drive it. It comes from the researchers, always."
(Participant 30, Professor, Cancer Biology, Late-career)

As Participant 30 describes, their university had an established investment in animal units and facilities which were internally funded, whereas use of equipment needed for non-animal approaches incurred extra costs to the researchers. However, they explain that the university's set up is responsive to researcher needs and interests, with the acquisition of funding grants then directing the university's spending around research facilities and resources. On the other hand, Participant 18 expresses that universities could take a more top-down approach to their research infrastructure to better support transitions to NAMs, a move they believe would help to "de-risk" the use of these new approaches for researchers.

Similar to Participant 30, other participants felt that transitions towards NAMs was being, or should be, driven by researchers and shifts within their field of study, not their institution:

"That's what I hear, that of all the funding that's happening, the new projects are definitely really NAM-focused. So, for me, it's happening. At the institutional level, I'm not even sure I've heard that much about it […] But yeah, I wouldn't say that there is a promotion of NAMs at the institutional level."
(Participant 08, Senior Lecturer, Toxicology, Late-career)

"Because obviously, I'm so around… I'm just around in vivo people. I'm with them […] So, for me I would that's very beyond me knowing. Maybe on the upper management and the boards or whatever, I don't know how it works, they're probably thinking like that. But I think as a medical school that I think this does… I think we need to continue the animal work unless there is a proven 100% replacement. And often there's going to be people that don't use animals, which we have. All manner of research happens at the university. Not everything is animals, and some people are strictly in vitro, in vivo, but to see an in vivo group go to in vitro because the university is pushing for it, I just don't see that happening, right?"
(Participant 15, Research Assistant, Immunology, Mid-career)

That researchers are unsure about a broader institutional commitment around Replacement or feel this to be limited or lacking conviction is important to acknowledge. Although there will be differing speeds at which the range of research areas that employ animal models will be able to move away from their use, **overarching institutional aims and strategies to replace animals will help to focus attention to what is needed locally within an establishment to support and accelerate this shift**. **Although the uptake of NAMs may be seen as most appropriate if researcher-led, it is necessary for research institutions to understand the needs of researchers in accessing, setting up, and using NAMs in their home institution**. An overarching ambition around Replacement may direct architectural, infrastructural, and internal funding decisions to encourage and support the use of new non-animal technologies. It may also influence curricula as well as helping to shape a broader culture in which current animal use is situated within a trajectory towards Replacement.

8b) Implementation and engagement with 3Rs perceived as tokenistic

In discussing the lack of a broad institutional commitment or ambition around Replacement, some participants also expressed feelings that the 3Rs in general are often engaged with in a tokenistic way at both the institutional and researcher level:

"What I felt is that it's a tick box exercise to be completely honest. Like you know about the 3Rs, you receive the emails, you're like, "Oh, we need to justify just the numbers that that calculation fill in the licence. So, we need to do some sort of analysis just to prove that." So, it's all like a tick box and basically being able to say in the licence for why that can't be replaced and let me say my research is super important, which it isn't necessarily."
(Participant 24, Final year PhD student, Psychology and Biosciences)

"I do think that universities and institutions and departments are all aware of the pressure to... being cynical, it's not to actually reduce animal use than at least look like you are trying to [...] I think probably they would be more open to hiring and promoting people who are doing innovative stuff with organoids because they are aware of that broader pressure to be supporting that work."
(Participant 18, Group leader, Biochemistry, Mid-career)

"I don't think anyone is really interested in the 3Rs, to be quite honest. Unless it's mandated from on high, it's something we have to do and I would always certainly reduce suffering, reduce the number, it's money... there's lots of reasons for paying attention to the 3Rs. I know on the science it says, it's all driven by the 3Rs. No. I'm very cynical about commitment to that, to be honest."
(Participant 30, Professor, Cancer Biology, Late-career)

As suggested here, **some researchers find that, in practice, implementation of the 3Rs often becomes a "tick box exercise" and more concerned with "looking like you are trying".** Such insights raise questions towards the power the 3Rs and the current oversight of their application for driving transitions away from animal use. As Participant 30 describes, reducing suffering (Refinement) and reducing the number of animals used in experiments (Reduction) may be carried out without issue. Yet, as discussed in the previous section, given the ways that implementation of Replacement may disturb usual research practices, current researcher relations with and obligations towards the 3Rs may not be enough to encourage a shift from animal to non-animal methods.

Theme summary: Institutional commitment to, and strategy around, Replacement may be seen as limited by some researchers, with a perceived lack of financial and infrastructural investment in NAMs and a continuing investment in animal facilities. Although this analysis has also highlighted that some researchers may feel that Replacement should be primarily researcher-led, institutional commitment to Replacement remains important for providing direction locally and ensuring that universities have the required resources for researchers to employ NAMs. This section also illustrated that some researchers find that the 3Rs are engaged with in a tokenistic manner by both researchers and institutions. Again, this underscores the importance of overarching strategies around Replacement which feature specific plans and actions to ensure that the use of animals is avoided where currently possible and which work to create the conditions for their future full Replacement.

9 Use of NAMs in conjunction with animal models

Across the interviews, many participants discussed the use of NAMs as accompaniments to animal use, being used before, after, or alongside *in vivo* models. Though not necessarily a barrier to the uptake of NAMs, current positioning of NAMs as conjunctives to animal models, with an *in vivo* component often reinforced as an essential step in the research process, is important to address to understand how NAMs are currently positioned and whether or not they are conceived or used as 'replacements' or 'alternatives' for animal use.

9a) Use of NAMs seen as refining and/or reducing, rather than replacing animal use

Throughout many of the interviews, NAMs were discussed as currently helping to direct more precise *in vivo* investigations and reduce or refine rather than replace the use of animal models. As the following excerpts show:

"I'm not sure they are robust enough to be a replacement at the moment. I think it's definitely kind of, "Okay, you develop a concept using these techniques in vitro, test it in vivo and then go from there." Unfortunately, I don't think they're robust to stand alone […] I think they definitely give us a direction to go in with the in vivo model, so we're not just taking a stab in the dark […] it definitely gives us a bit of a guideline as to what to look for, because you don't really want to be just going in blind to an in vivo model because that's just… it's a mess."
(Participant 25, Third-year PhD student, Microbiology)

"Maybe, if we had three real animals do it and the computer do it, and they all did the same thing, then that would really contribute to reduction, if not replacement, which is I think what most people are going for."
(Participant 29, 1st year PhD student, Neuroscience)

"I think in vitro systems is a lot more targeted questions that we would use to ask, whereas I think in vivo systems could be more broad."
(Participant 13, Associate Professor, Immunology, Mid-career)

"When you go into that animal, having done your in vitro work, depending on how you've done it, you can and very often will, get a completely different response is the truth. So, we do need to get things… we need to, sort of, design these models so that we can ask the discrete questions, the genetic questions, the receptor questions that you shouldn't be doing those in a mouse."
(Participant 12, Professor, Cancer Biology, Late-career)

"I mean, genuinely, it can lead to novel insights that you may then choose to ultimately chase up in the actual animal, and therefore, you've restricted the use of loads of animals to get to that point […] So, there's definitely, as an addendum way of refining things, for sure."
(Participant 06, Professor, Physiology, Late-career)

As the above excerpts suggest, NAMs are often used before or alongside animal use, enabling researchers to develop "more targeted questions" to investigate *in vivo*. In this way, **NAMs are currently conceptualised as impacting on the reduction of numbers of animal used rather than stimulating a move away from animal use**.

They may also be seen as another way of answering a scientific question, but not necessarily animal replacement-focused. In this way, NAMs may be currently conceptualised as impacting on the reduction of numbers of animal used rather than stimulating a move away from animal use. Whilst not necessarily a barrier to the uptake of NAMs, their usage alongside or in parallel with animal models means that their uptake may not be easily understood as contributing towards the Replacement of animals in science. The concomitant use of NAMs and animal models may represent current stages of progression towards Replacement, reducing animal use where possible until it may be eventually replaced. However, there are also possibilities that NAMs will propagate further streams of research that will exist separate to animal studies or will inform traditional animal use.

9b) Lack of confidence in the feasibility of full replacement

Alongside discussions of parallel or accompanying use of NAMs and animal models, many participants articulated or a lack of confidence in the feasibility of the total replacement of animal use in science:

> "In my field we can use the cell cultures or in vitro models instead of animal living and undergoing the experimental process for days and weeks, like surgeries, it's just sacrificed and then cut open essentially parts of its brain is collected. This happens in parallel but unfortunately it just can't answer many questions. It's just a scientific fact."
> **(Participant 05, Associate Professor, Neuroscience, Mid-career)**

> "I don't think anyone could ever invent a way to replace an animal. You might get an AI, you might get an algorithm that you can get close but how on earth are you ever going to replace a living, breathing creature with a culture model? You can't. It's not possible, it's never going to happen."
> **(Participant 30, Professor, Cancer Biology, Late-career)**

> "For us, with our particular products, we have to show efficacy. So, we have to show that, basically, we get neurons growing. We put these cells and we get neurons growing. And we do do that a lot in vitro. You know, I'm growing some right now, for long term, to see how long I can make the neurons, that sort of thing. But, there are things that I don't think… I just don't know how you would be able to replace in vitro […] I don't think we will ever go to full replacement. We can get rid of as much as we can, but with the current methodologies, I don't see how that would work."
> **(Participant 20, Pre-Clinical Manager, Stem cell therapy, Early-career)**

"I think it really depends. I can't imagine replacing in vivo altogether or possibly not in the near future. And I'm not completely against it per se. I think it is very important […] I actually do think that the ex vivo should replace the in vitro rather than the in vivo, but massively, massively reduce the in vivo […] I think that in in vitro we generate so much stuff that moves into the animals and that just does not work, and I think that's incredibly wasteful. So, I think that's how I see it. And then ideally that replacing the animals altogether in the end with possibly human ex vivo stuff is possible."
(Participant 26, Research Assistant, Immunology, Early-career)

In stating their view that animal models could not be fully replaced, participants discussed the need to use a whole, living organism at some stage in many biomedical research projects. As Participants 05 and 26 describe, Replacement may be configured as using ex vivo tissue, meaning that the use of living animals is replaced by use of their tissues collected after death (or of ethically sourced human tissue). Lack of researcher confidence in the viability of full Replacement is important to address to ensure that the trajectory of NAMs uptake impacts upon the eventual phasing out of animal use rather than simply expanding in parallel. Such doubts around the possibility of fully replacing the use of animals in scientific research, particularly that which is concerned with understanding fundamental physiological mechanisms, or requiring a fully functioning immune system, for instance, are not trivial for researchers. However, **instead of constructing Replacement as a dichotomy of that which is possible or impossible, buy-in can be generated for replacing animals where currently possible, whilst also being open to the technological advances that may occur in the future**. Given the speed at which NAMs are advancing, with complex technologies such as organoids and organ-on-chips now creating new new possibilities for research without animal use, it will be crucial to promote the positioning of NAMs as potential replacements for animal use rather than complementary models.

Theme summary: NAMs may currently be used as accompaniments to, rather than replacements of, animal models. NAMs were often described as tools that can help to guide more precise in vivo investigations, lending more to aims of reducing or refining, rather than replacing, animal use. Alongside this, some researchers expressed a lack of confidence in the feasibility of fully replacing animal use in scientific research. This report argues the importance of recognising the current scientific challenges around recapitulating complex physiological systems, and the varying rate at which different fields may be able to move away from animal use, whilst also fostering investment in the uptake of NAMs and the replacement of animals whenever and wherever possible.

10 Perceived technoscientific limitations of NAMs

Although focusing on the social and cultural aspects of barriers and opportunities around the acceptance and uptake NAMs in academia, perceptions of current the technoscientific limitations of NAMs were often discussed by participants across the interviews. One key limitation articulated was the level of complexity that current NAMs could provide.

10a) Complexity of NAMs

A key component seen to be missing from current NAMs was complexity in terms of representing the physiological characteristics of a whole living animal body and its ability to capture off-target effects. As the following excerpts illustrate, many participants expressed doubts around the capacity for NAMs to fully and reliably replicate the complexity of living organisms:

"It's hard to see in the medium term maybe, how you would replace the in vivo model all together, because the in vitro systems aren't there yet for the complex physiology. That doesn't mean that it won't get there, but I guess there are barriers to achieving that sort of system. There needs to be some concerted development work, research and development around trying to make these models more physiologically relevant, and then to address the question of how you might get tissue interactions in a sort of microfluidic type systems. But they start to become low throughput and [need] a high level of expertise and a lot of equipment and a lot of resources. And that they're adequate models as well, so you want them to reflect the situation in human, I guess, at the end of the day."
(Participant 16, Retired Professor, Genetics, Late-career)

"In a sense, as a physiologist speaking, you would say, in actual fact, some of the underappreciated things are simply your blood pressure or your rate of blood flow, how it responds to general anaesthetics. And so, when you're thinking systemically, whole-body, then inevitably, you're thinking of the whole animal. And, if that's not a consideration, then fine. But, quite often, it is, and it can explain why… a variability between different animals and how they respond and all sorts of things."
(Participant 06, Professor, Physiology, Late-career)

"I don't see any model showing biodistribution ability."
(Participant 08, Senior Lecturer, Toxicology, Late-career)

"Because of the number of variables involved in so much of this work, I get the impression it's generally accepted that live animals is more realistic rather than any lab-based methods currently […] It's definitely accepted that it's useful for the pilot stage of a study […] I think that is accepted as a viable option, but not necessarily proof in itself."
(Participant 09, Experimental Manager, Agriculture, Early-career)

Theme summary: There are perceptions that the use of NAMs are, and could even always be, limited in comparison to animal models due to a relative lack of complexity, for instance, with a perceived limited capacity to account for variability in response to compounds, or to enable capture of biodistribution across the system. To provide confidence on these systematic levels, use of an animal model was thus often claimed to be a required step. Relatedly, some participants argued that there is a need for further fundamental physiological understandings of animal models in order to inform and enable the development of relevant, accurate and more complex NAMs.

11 The established nature of (particular) animal models

The 'established nature' of particular animal models across institutions and research disciplines was discussed across the interviews and can be identified as a key driver for their continued use. As well as animal use being well supported via the widespread creation and maintenance of critical infrastructure (as detailed earlier in this report), the establishment of animal models also involves their long histories of use and status as 'gold standard' across research communities.

11a) History of use and characterisation

Relating to, but expanding on the previously discussed role of familiarity in influencing decisions to use particular models, the historical establishment of certain animal models was another factor influencing their further uptake. As the excerpts below show:

> "I know labs that are doing both, like they have *in vitro* non-animal systems that they use for some things and animals that they use for other things. Actually, they definitely could be using the non-animal models for a lot more. The part of it is that the data that you build up over a long career is in one particular model, let's say a mouse, and you want to compare new results to what you've done before, then you either have to redo everything in the non-animal system or you just do this one experiment in a mouse and you can compare back. That provides one barrier to doing more."
> **(Participant 18, Group leader, Biochemistry, Mid-career)**

> "I think another reason we're using mice is, so far, I think this is the species who has most of the molecular and genomic information. So, whatever we've found, we can easily just go online to see what other people have done and whether that's relevant to our current research. So, they've definitely got more background information compared to other species."
> **(Participant 04, Senior Postdoctoral Researcher, Oncology, Early-career)**

"We wanted something mammalian, for sure, and then the mouse, I don't know, it, kind of, gets selected by default for a lot of these things, just because of how well genotyped mice are, how well studied the mouse brain is in particular for us. Yeah, and the mice being studied that much makes selection easy from that point, when I want to do surgeries and target very specific areas."
(Participant 29, 1st year PhD student, Neuroscience)

"The mouse models of these […] infections are really well established, been used for decades. I think some of the models are more established than others, so for the […] infection models for example, those are really all standardised across the world, in different labs, everyone uses the same sort of strains, same mouse backgrounds, things like that."
(Participant 13, Associate Professor, Immunology, Mid-career)

As these excerpts demonstrate, **that certain animal models have been used for long periods of time comprises multiple aspects which contribute to their continued use**. This can mean that certain animal models have been well-characterised i.e. via mapping of their genetic profile and analysing the phenotypic expressions of their particular genotype, have an extensive body of literature built around their use which researchers can build upon, and may be standardised across laboratories nationally and internationally. It also means that individual researchers may have amassed expertise, status, and data around certain models which, as discussed earlier in this report around the role of familiarity in decision-making around models, allows for backwards comparison, enabling researchers to contextualise new findings within an established framework.

11b) Gold standard' status and status quo of animal models

More broadly, some participants gestured to a continuing sense that certain animal models remain the 'gold standard' in their area, with influence on the ability to publish, on research directions within academic fields, and investment in research funding and infrastructure:

"There's definitely a large degree to which it's simply that it's a new technology that's rapidly developing and hasn't had time to accumulate that infrastructural support. But equally there's a huge amount of inertia and cache with animal methods. People who are embedded within research communities are going to conferences where everybody is talking about their mouse or rat model or blah, blah, blah, and I think we can't discount that as influencing the decisions that people are making about what research they're going to do over the next five or 10 years."
(Participant 18, Group leader, Biochemistry, Mid-career)

"I think because I've trained in them, and I've become really… I understand the model really well, which means I can interpret the data much better and easier. I think also because a lot of the bigger labs in my field have also been using them for many years and that's now become a gold standard, so to publish, the expectation is that you would use those models."
(Participant 13, Associate Professor, Immunology, Mid-career)

"People are still building massive animal facilities for research, it's like the gold standard."
(Participant 30, Professor, Cancer Biology, Late-career)

As these excerpts show, the historical status of (certain) animal models as "gold standard" remains salient across research communities and is likely to raise challenges for transitions away from animal use. **The persistence of this positioning of animal models as the standard by which other models are judged may drive the continuing use of animals due to perceptions of how this "gold standard" informs publication success and the allocation of funding and resources**. Given the pressures around publishing and securing funding across academia, biases towards animal methods for success in either of these, whether perceived or actual, is likely to raise substantial barriers to the adoption of NAMs.

Theme summary: Particular animal models have become established via their histories of use, with their widespread usage, associated historical data-sets, and standardised protocols around their use promoting their continued uptake. Interrelatedly, some animal models remain perceived as the 'gold standard' in certain research areas and thus their use is seen as impacting upon academic success and status.

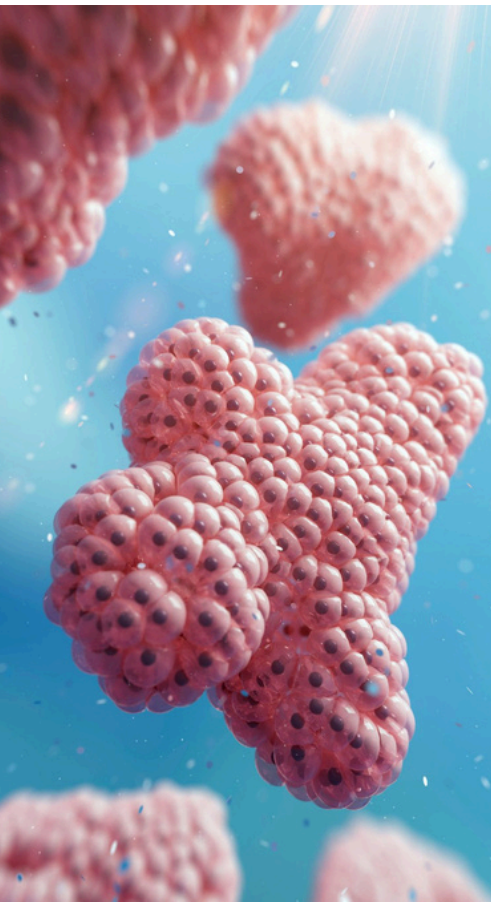
Implications and conclusions

This study identified a range of barriers to the acceptance and uptake of NAMs in academia, as well their links to key drivers of animal use.

This analysis has shown that current positionings of NAMs in academic research may not always be linked to 'replacements' or 'alternatives' for animal models, but rather NAMs may be understood as complementary models which may allow researchers to ask different questions, alongside animal studies, or help to inform their *in vivo* investigations. This suggests that, **for many researchers, the ambition of transitioning away from animal use is unlikely to be the prominent driver behind the consideration and uptake of NAMs**. However, in order that NAMs do not become detached from the ultimate goal of replacing animal use across science, it is important that the ethical imperative of Replacement is maintained as a central part of the conversations surrounding their implementation. Therefore, this analysis suggests that pushes for the acceptance and uptake of NAMs would be most effective if situated within both a broad 3Rs and ethical narrative which connects them to the phasing out of animal models, and also within specific scientific conversations and spaces which assess and demonstrate their scientific value, acknowledging the current position of NAMs as being part of a 'toolkit' of methodologies, rather than necessarily being ready to act as complete replacements for all animal use.

Although the 3Rs are an established framework for good scientific practice, as some researchers interviewed in this study have asserted, they are not a prominent motivator for all researchers and there will be a diversity of familiarity and engagement with 3Rs networks and organisations.

Image: Mice - Andrew Forsyth/RSPCA Photolibrary



As this study has indicated, there may be particular barriers to engaging with Replacement, as this R often involves the building of new skillsets, new collaborations, and can be seen as disrupting established research directions which involve animal use. Rather than signalling that individual researchers simply do not care enough about the 3Rs, this analysis argues that given the structures of academia and the significant pressures researchers face from short-term contracts and demands to produce research outputs, including publications in high-impact journals, and secure funding, researchers may feel currently unable to prioritise Replacement and the efforts required to implement it. This can be particularly challenging for researchers earlier in their careers, with varying levels of agency and flexibility available to ECRs, many of whose research directions and training plans will be under the discretion of a supervisor or PI.

In order to reach those researchers who are not embedded within typical 3Rs spaces or for whom the 3Rs is not, or currently cannot be, a driving force for decision-making in research, **the push for NAMs must also occur across routine science spaces and communities and align with the established academic reward system**. Crucially, this means ensuring that researchers can generate reliable results within short-term research contracts and publish NAMs data in prestige journals. Use of NAMs should also not pose any additional obstacles to gaining funding. Overall, to succeed, **the uptake of NAMs cannot have negative impacts upon career progression and plans to support the transition from animal use to NAMs across academia must seek to address or work within current structural confines and pressures faced by researchers**.

Returning back to how the range of sociocultural barriers identified in this study might shape researchers' awareness of, confidence in, and enthusiasm towards NAMs:

Image: Illustration of an organoid - Science Photo Library / Alamy Stock Photo

Awareness

Researchers need to know what kinds of NAMs are available, be informed about their advantages and limitations, and understand their specific purposes and applications. Information-sharing around NAMs should be connected to **opportunities for accessing training, building networks and collaborations, and funding pots**. Communication and collaborations across research areas and models may be limited and research groups were described as organising around particular interests and models which, if successful, can prevent moves away from animal use. Such silos are important to address, particularly as several researchers emphasised the need for the *in vivo* context to inform the development of NAMs in order that they are applicable and have the potential to function as a replacement of an animal model.

Confidence

To boost researcher confidence in the uptake of NAMs, this analysis suggests that further support should be given to training researchers in the set-up, use of, and analysis of data from, NAMs. As discussed within the interviews, the quality of training provided is important to address for the way it may be compared with the formalised training programmes around animal use. That training opportunities around NAMs may often be the result of informal requests to shadow another researcher also means that such training relies on researcher interest, connections, and capacity to make time for this. **Working to increase the confidence of researchers in using NAMs not only means providing access to relevant training but also providing access to dedicated support to facilitate their use, help with troubleshooting, and offer guidance on wider aspects, such as how to cost projects involving NAMs or how to publish papers with data from NAMs**. In practice, this might be delivered through in-house technical staff or external expert hubs, but will ultimately provide training, support, and reassurance for researchers in implementing NAMs.

Given the current rate of change and innovation occurring around NAMs, efforts to build confidence around the uptake of NAMs **should also account for concerns around their long-term viability and stability**. As this analysis has shown, there may need to be a settling period in which NAMs development and innovation stabilises and Standard Operating Procedures are established to promote confidence towards investing in NAMs and using them in reliable and reproducible ways. **Ensuring and promoting the feasibility of career paths that do not involve animal use will help to increase researcher confidence in investing in NAMs** and the wider shift away from animal research.

Enthusiasm

To generate enthusiasm towards NAMs, **it is crucial that initiatives aimed at their development and uptake play into established systems of reward and recognition within academia**. This is to say, that the implementation of NAMs should not pose additional barriers to publishing papers in journals with high-impact factors and securing funding bids. Disruptions associated with the uptake of NAMs, such as additional time being required to access, learn how to use, and set up new models, are important to mitigate for researchers. Even if these may be short-term and can be balanced out by long-term benefits, the prevalence of short-term contracts and pressures to publish quickly in academia mean that disruptions to research are not trivial.

The productivity of a model can be a key consideration for researchers, with widespread pressures to produce positive results and publications meaning that models able to generate large amounts of varied data are likely to be attractive. In this regard, NAMs are sometimes seen as more suited to answering targeted research questions, producing a comparatively limited dataset to animal models. As well as this, the initial implementation of NAMs may require additional time and therefore slow down the generation of results and publications. To ease some of the pressures around producing outputs from the use of NAMs, funding bodies should provide support for ancillary pilot projects which enable researchers to trial NAMs without significant demands for this to translate into traditional academic outputs. This would allow researchers to see how NAMs could fit into their research plans, work out what questions they might be used to answer, and gain a level of familiarity and experience with using them.

To generate enthusiasm towards NAMs amongst researchers currently using animal models, it is important that their promotion is linked to further research opportunities, such as collaborations with other academics which may lead to co-authored publications or future collaborative funding applications. The development and use of NAMs must be recognised within the established reward systems in academia in order to incentivise their uptake. Though significant for informing decisions on internal funding schemes, investment in infrastructure, and shaping local cultures around animal use, institutional commitment and strategy around NAMs alone is unlikely to be enough to drive the uptake of NAMs amongst researchers. The value of NAMs also needs to be promoted by funding bodies and learned societies, who can provide incentives towards their use and embed their uptake within and between relevant research fields. Importantly, this analysis has suggested that **greater communication is needed between those developing NAMs and those using animal models.** In supporting this, it may be

more effective to support those developing and working with NAMs to showcase their work to *in vivo* researchers and communities, rather than encouraging *in vivo* researchers to seek out information and connections around NAMs. This way, those already invested in NAMs can share their knowledge, connections, and enthusiasm with those currently working with animal models, while also gaining further understanding of the needs of *in vivo* researchers.

Final remarks

Overall, this report has provided insights into key barriers around the acceptance and uptake of NAMs for researchers working with animal models in academia. By focusing to the sociocultural aspects of the transition to NAMs in biomedical research, this study has shown how **although there are still scientific and technological barriers to be addressed in the implementation of NAMs, there are also significant social and cultural** ('how science is done') **issues that require equal attention**.

This is crucial for ensuring that the necessary environment is in place that will optimally stimulate and support researchers to use NAMs as and when they are available. As this analysis has demonstrated, these issues go beyond simply being aware of the existence of NAMs and also entail factors relating to confidence and enthusiasm. **Researchers must be aware of which NAMs are specifically relevant to their work and must see their value. They must be able to confidently make use of them, with the necessary infrastructure and support on hand, and the use of NAMs must play into the established structures of reward and recognition in academia, with researchers able to publish data from NAMs in high-impact journals and access funding**.

Image: 3D bioprinting - Alamy Stock Photo

Key challenges and next steps

This study has highlighted a number of factors, issues, concerns and barriers which impact on the perception and consideration of NAMs by researchers in academia, and on their acceptance and future uptake. These include:

- **The use of a particular model can cultivate specific skills, professional status and research interests, which can then be hard to move away from**
- **Familiarity with an animal model can drive their continued use**
- **The pressure to publish can drive use of familiar models**
- **There are expectations that results using NAMs would have to be validated in animal models to be accepted for publication**
- **There is often insufficient challenge of whether and how animals are used**
- **With concerns that only lip-service may be paid to implementing the 3Rs**
- **Where considerations of replacement are particularly neglected**
- **Achieving success using animal models may minimise the perceived urgency of developing and implementing alternative methods**
- **Many researchers think employers value *in vivo* experience**
- **And, that employers are less likely to offer them a job using methods they did not have experience with**
- **NAMs may be viewed as 'risky' due to concerns that current investment in them may quickly become outdated or obsolete**
- **Training opportunities are usually tied to a project grant and its specific aims and objectives**
- **The lack of professional training programmes, with their associated infrastructure and support systems, may impact on researchers' confidence in being able to properly set up and run NAMs in their lab**
- **Information-sharing around NAMs, or on the principle of Replacement more broadly, without also providing access to relevant training programmes, may contribute to a construction of Replacement as an abstract concept which cannot be effectively implemented in one's own research practice**
- **Awareness-raising around NAMs is most valuable if it communicates the purposes they can serve, the benefits they can offer, and the opportunities surrounding them**

- **Funding grants usually don't enable the flexibility needed to pick up other skills, or use other methods alongside the defined research plan**
- **In particular, short-term funding grants can raise barriers for researchers to pick up on new methodological developments**
- **Communication between users of animals and those using NAMs is limited**
- **Conversations around NAMs have to be inclusive and accessible to those currently using animals, bringing them into the fold without definitively categorising them as 'animal users'**
- **Without greater communication and [further] understanding of the *in vivo* context, some people currently using animals feel that non-animal models will never become a 'replacement' or 'alternative' in their research area**
- **NAMs aren't yet as 'established' as animal models**
- **NAMs are often conceptualised as reducing or supporting, rather than replacing, animal use**
- **With concerns around what NAMs are currently capable of and reflection that more work is needed**
- **There are perceptions and concerns about the upfront costs associated with some of the more advanced non-animal methods**
- **As well as a comparative lack of infrastructure to support the use of NAMs**
- **There is currently a lack of visible financial investment in the infrastructure needed to stimulate and support the uptake of NAMs**
- **Universities are seen as being responsive to researcher needs and interests, and do not themselves drive how the research should be done**
- **But universities may be able to take steps to help 'de-risk' researchers changing practice**

We will be re-convening the stakeholder group assembled at the beginning of this initiative, to discuss the findings raised in this report. The aim will be to share expertise, insights, knowledge and experience to provide further clear ideas and recommendations for helping to overcome the barriers highlighted by researchers to the greater and faster development, acceptance and uptake of non-animal methods within academia. These ideas and recommendations will be targeted at academic institutions, funders, professional bodies (e.g. learned societies), publishers, governments, and other people in relevant different roles (e.g. AWBs, scientists).

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Contact us

This report has been produced as part of the RSPCA's ongoing initiative aimed at helping to accelerate the transition away from the use of animals in research and testing - unlocking the significant scientific, economic, ethical and animal welfare opportuntiies and benefits this can bring.

If you would like to contact us about this initiative, or our work related to animals in science more generally, you can use the links below.

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