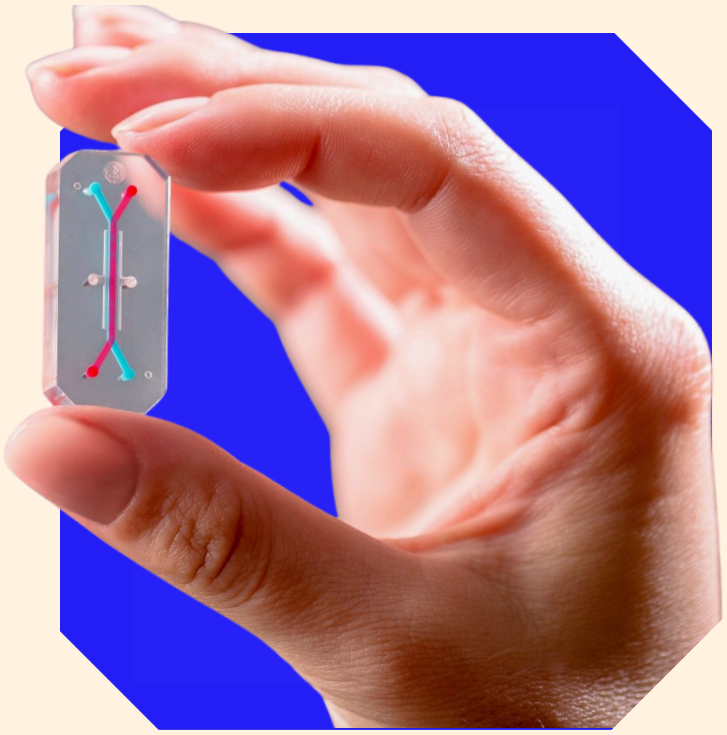
RSPCA
ANIMALS IN SCIENCE

Questions to ask about Replacement

A handy guide for AWERB members



Organ on a chip - Emulate bio

More resources for AWERB members can be found in our AWERB Directory.

Two AWERB tasks have a strong focus on Replacement:

- advise on the application of the 3Rs, and keep staff informed of relevant technical and scientific developments, and

- advise the establishment licence holder whether to support project proposals primarily from a local perspective, bringing local knowledge and expertise to bear on the harms and benefits and practical, scientific and ethical issues.

The issue

AWERB members often think that they all need to have technical expertise in Replacement, or even that the AWERB ought to be able to suggest alternative approaches to protocols using animals when reviewing applications. However, this is not the case. **Within project reviews**, you just need to have an open discussion, in a constructive environment, to satisfy the AWERB that the applicant actively wanted to replace animals and did all they could to achieve this. **When advising on Replacement more broadly**, it is about ensuring that establishment culture will motivate scientists to search for alternatives, and support them if they need training or resources to implement any non-animal methods they find.

How to use this resource?

Here are some examples of questions for you, as an AWERB member, to ask around Replacement, both during review of projects and in more general discussions with scientists. You can ask the applicant to phrase their responses in lay language, and you should be supported if you ask them to explain further.

The aim is to create a helpful, encouraging environment with effective two-way communication between the applicant and the AWERB (see this information sheet on scientist-AWERB engagement for some helpful tips). This 'Care-full story' resource on Talking about Replacement gives examples of constructive, and not-so constructive, conversations around Replacement. If your AWERB would like to use this resource, the instructions are here.

There is a glossary of Replacement-related terms at the end of this sheet.

When reviewing a project licence application, or amendment

Question	Follow-up - what to look for
Could you provide more detail about the steps you took to find non-animal methods? For example, did you consult any other individuals, organisations, or resources including databases? *[This is a good question for any project. It is especially important if there is not much detail around the search for Replacement alternatives, e.g. just a list of a few websites]*	It is positive if the applicant not only has a 'standard' list of resources relating to non-animal technologies and approaches that they use, but also regularly checks for any new sources of information, such as databases, relevant to their field of research. They should be able to give you a summary of the kinds of search techniques and terms they used, and tell you which approaches were most helpful. Consulting more widely also shows that they are motivated to try and replace and avoid animal use. Simply listing some websites, without elaborating further, is not a satisfactory answer and the AWERB is entitled to ask for more information. If the applicant is finding it difficult to access information about potential replacements, training in searching for non-animal methods should be provided. The establishment should recognise that, under the Animals (Scientific Procedures Act 1986 (ASPA), alternatives must be used if they are available, so enabling scientists to find, and use, alternatives is essential for compliance with the Act. Replacing Animal Research has produced a checklist to support researchers in searching for replacements, and AWERBs that are reviewing how the searches were conducted.
What would you say are the main obstacles to replacing animals in this project?	The answer may be that replacement technology has not yet advanced to the point where animals can be partly, or completely, replaced in a specific project. You could ask for more detail on this, including what the main technical problems are and how the applicant is monitoring any efforts to overcome these. Some scientists may be of the belief that funding bodies, and/or journal editors, will require data from animals before they will fund or publish research. Current work on replacement in academia has shown that this should not be the case, and you can ask for evidence (e.g. funding body guidelines, comments from journal editors or peer reviewers) to substantiate statements you hear like these.

What unique insights does the animal model provide that non-animal methods cannot currently provide? **What essential knowledge gaps would remain if the animal model was not available?** *[It is important to press for more detailed answers if there are generic-sounding statements about needing a whole, living animal, e.g. because a particular organ system is being studied]*	Applicants should be able to explain, at an appropriate technical level, how far they would be able to progress without using animals. For example, complex 3D cell cultures and systems like 'organs-on-chips' can simulate and incorporate an increasing range of physiological responses and processes, and may be feasible for at least part of the project - but any limitations should be explained to you in more detail, if this is not clear from the application. Your AWERB may like to look at some published Non-Technical Summaries (NTSs) and discuss the explanations in these. Are any especially helpful, or dismissive? What follow-up questions would you ask? [Search for 'ASRU non technical summaries' for the most recent, then use the Find and Edit function in your browser to find 'Why do you need to use animals to achieve the aim of your project?'. This will take you to the Replacement section of each NTS.]
Have there been any developments in non-animal technologies (NATs) or new approach methodologies (NAMs) in this research area since your last project application? Has this enabled you to partly, or completely, replace animals in some of the protocols? *[This is a good question for applications that follow on from previous work, using similar animal models]*	An applicant who has supplied adequate detail around their search for alternatives ought to be able to answer this question. If the answer is "no", but they can provide a detailed narrative around their search protocol, then you can be satisfied that there have not been any developments that they could reasonably have been expected to find. You can follow up with the next question, at the top of page 5.

Have you, or others, tried to do this work without using animals? What did you try, and why was it not feasible?	If the answer is "no", you can of course explore why not. The applicant may be able to demonstrate that replacement technology is not yet sufficiently advanced, as above. But a response to the effect that the animal model is the established approach would not be satisfactory. If you have a discussion around why an alternative method or approach was not feasible, you could ask what further developments would be necessary to enable replacement in their project and how the applicant will track these.
How do you plan to check for new replacements that may be feasible, during your project? If you find any, will you be supported (e.g. by the funding body) to introduce and use them? *[A question for all applications]*	The applicant should be able to provide a description of their plan. Reviewers should assess the adequacy of this proposal by considering how frequently checks are planned, the specific approaches and resources that will be used to identify new potential replacements (such as ongoing literature searches, attending relevant conferences, or networking with experts in alternative methods), as well as how potential new opportunities will be assessed and acted upon. If no plan is provided, or the plan is insufficient, this should be rectified. The second part of this question is important, but may not have been thought of when preparing the application. The AWERB has the task of supporting named persons, and other staff dealing with animals, on animal welfare, ethical issues and provision of appropriate training, so you can remind the applicant of this and ask them to tell the AWERB if new replacement opportunities arise.
Is it easy to stay well informed about developments in non-animal approaches in this field? • **How do you do this?** • **If you do not currently feel that you can keep up to speed effectively, what would help you?**	This may be difficult to answer, as many scientists are under considerable pressure to publish in their field, and there may be insufficient liaison between people working on non-animal methods and *in vivo*. Common responses to this question include databases and resources or newsletters from 3Rs organisations, which are good gateways to information on developments in Replacement. However, it is more encouraging if applicants go beyond these 'standard' approaches and can describe more active ways of staying informed, such as networks of colleagues or regular, tailored searches. Asking the question may also prompt them to find out more.

Outside of project review, when discussing Replacement with scientists

For example, you could raise these issues with individuals in one-to-one discussions, ask for an agenda item in which one or more scientists could attend the AWERB for an informal discussion, or ask for a panel discussion at a 3Rs day:

What are the main obstacles to finding and using non-animal methods in your work in general, and is there anything practical that the AWERB could do to help overcome these? *[A number of AWERB tasks relate to this]*

Looking ahead, what potential do you think emerging non-animal methods hold for your research in the short and long term?
Are there ways you or our establishment could contribute to their development? If so, what support would you need and how could the AWERB help?

Do you feel that you receive enough support and encouragement when it comes to searching for non-animal methods, with respect to training in search methods and accessing the databases, resources and contacts you need? What more would you need?

Do you think that this establishment demonstrates a clear commitment to replacing animals in science? If not, what more could be done?

Glossary

Animal - under ASPA, an animal is any living vertebrate (other than humans) and any living cephalopod (e.g. octopuses). Mammal, bird and reptile use is regulated from two-thirds of the way through their gestation or incubation period, and amphibian, fish and cephalopod use from the time they are capable of independent feeding (e.g. 5 days after egg fertilisation for zebrafish). The use of other animals, such as vertebrate developmental forms before the times listed above, and invertebrates apart from cephalopods, is not regulated by ASPA - this is why their use is sometimes thought of as an 'alternative'. We have defined 'animal' according to ASPA in the glossary below, but note that there is debate about the ability of some invertebrates (e.g. insects) and developmental forms (e.g. zebrafish larvae) to experience suffering. The RSPCA believes that an ideal Replacement would apply the 'precautionary principle' and not use any type of animal.

Replacement - methods and approaches in science which avoid animal use, or which completely replace an animal experiment with a humane alternative. These can include cell cultures, or tissues, taken from humans and kept alive *in vitro* - but some of these may require growth media containing serum derived from animals, which can present ethical and animal welfare concerns.

Partial Replacement - replacing the use of live animals, with the use of either:
- species whose use is not regulated as they are currently not considered capable of experiencing suffering (i.e. not sentient) e.g. fruit flies, nematodes;
- life-stages before certain timepoints or stages of development, that are not covered by regulation e.g. embryos or larvae early in development (but see 'animal' above);
- cells and tissues taken from animals who have been humanely killed, without having been used in a regulated scientific procedure.

Non Animal Methods - a general term used to describe any approach that does not involve using, or harming, animals to answer a scientific question or obtain data.

Non Animal Technologies - a procedure, product or technology that enables the use of an animal in scientific research to be replaced by an *in vitro* one that does not involve using or harming animals. These often mimic the structure or function of an organ, or can recreate critical aspects of physiological systems and processes, e.g. organoids and organs-on-chips.

New Approach Methodologies - approaches such as computational models, which avoid, or help to replace, the use of animals for assessing the safety of chemicals (including new medicines). These are particularly associated with regulatory decision-making.