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Research integrity: A primer on research involving animals

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Overview

Aim

Animals, and/or biological materials (tissues, blood, organs, cells) derived from them, remain a common research model within Life Science research disciplines. This note gives an overview of contemporary good practice in the responsible use of animals in research, and the issues that can arise.

Introduction

This document focuses on responsible conduct, good governance, and ethical oversight of animal use in research. It complements existing UKRIO guidance referencing animal use in research[1] , as well as the Animals (Scientific Procedures) Act 1986[2] (ASPA) and guidance[3] regulating the use of animals in scientific procedures. It is intended to provide research ethics committees, research staff, and research support or integrity/governance post-holders with an overview of issues that need to be considered to facilitate a robust approach to good practice in the context of research involving animals.

The document is relevant to all research involving the use of live animals, biological materials derived from animals, or animal-derived data. This is because the scientific, ethical, and welfare considerations that underpin good practice guidelines and standards remain relevant regardless of legislative requirements.

Research organisations may use this document as a reference tool to aid the review of how best to support the responsible use of animals in research, revise specific policies on animal use in research, develop training material, and/or consider how to manage or resolve potentially controversial aspects associated with research involving animals.

Footnote to the Third Edition

This is the third iteration of this document, which aims to highlight the wealth of information on good practice, responsible conduct, and integrity relating to the use of animals in research. General awareness of these across the Life Science research community is highly variable. However, many of the documents referenced here offer useful tools to assist in the review of training, support and/or mentoring to equip students and staff with the necessary knowledge and skills that they will need to achieve, or work towards achieving, the expectations described above.

Animal use in research in the UK

Overview

- Animals are used in Life Science research to advance our understanding of human development, health, disease and treatment, as well as animal health and welfare.
- Alternative (non-animal) research models, methods and techniques are available, and their use is increasing in accordance with legal requirements as the technology develops and the quality of the data produced is reported.
- The Animals in Science Regulation Unit (ASRU) within the Home Office regulates the use of animals in research under the Animals (Scientific Procedures) Act 1986[2].
- All animal use in bioscience research funded by the DEFRA, MRC, NC3Rs, NERC, Royal Society, UKRI, Wellcome and other Association of Medical Research Charities
- (AMRC) charities is expected to implement the 3Rs principles of Replacement, Reduction and Refinement; and demonstrate high standards in the design and conduct of animal research[4].
- Animal use in research is an aspect of Life Science research that gives rise to societal and institutional concerns because of ethical and welfare issues arising from the potential to cause pain, suffering, distress or lasting harm to animals.

Background

Animals have been used in scholarly research for over 400 years. This activity became more commonplace when the use of human bodies for scholarly study was forbidden in the 17th century. At this time, animals were thought to be incapable of suffering. Since then, our knowledge and understanding of animals has increased and informed developments in animal welfare legislation. From 1849 onwards, such legislation has included provisions to regulate and refine the use of animals for scientific purposes. The current iteration of the Animals (Scientific Procedures) Act 1986[2] aligns UK legislation with the European Directive governing the use of animals in scientific procedures, EU Directive 2010/63/EU[5].

As an example, the latest available statistics report states that in 2024[6] in Great Britain, a total of 2.64 million scientific procedures were carried out involving 2.55 million animals. Nearly half of these procedures (1.2 million) were for creating or breeding genetically altered animals, whilst 1.35 million were for experimental purposes. Of these, over half, 28% (741,555 procedures), were for basic research, another 12% (315,290 procedures) were for regulatory purposes, and 339,673 procedures (13%) were for translational or applied studies. In terms of the species used in scientific procedures, the most common was the mouse (1.8 million),

followed by 380,318 fish (mainly zebrafish), 149,571 rats, and 153,445 birds. These numbers contrast sharply with the 12440 procedures carried out on 'specially protected species' and involved 3,224 animals. This category includes cats, dogs, non-human primates, and horses and represents those species whose use in scientific procedures causes the greatest societal concern. These statistics do not report the total number of animals used for scientific research in Great Britain because not all animal use in research requires approval under ASPA[2] (see Box 2 for more information). Some research establishments do publish their own statistics on the total number of animals used for both regulated and unregulated research, but there is at present no legal requirement to do so.

Surveys to track and analyse trends in public support for animal use in research had, until 2010, reported that the majority (76%) of the public support animal experimentation as long as it is for medical benefit and there are no valid alternatives[7]. These caveats reflect concerns relating to the ethics of using animals as research models, and the potential for animals to experience poor welfare, pain, suffering, distress, or lasting harm. By 2019, the percentage of the public agreeing that scientists should be able to carry out research with animals, if this can lead to improvements in human health, fell to 56%[8]. Some analysis[9] suggests that this dip correlates with a rise in the number of 'don't know' responses recorded rather than an increase in responses opposed to animal use in research. This may reflect changes in public understanding of animal use in research, a reduced confidence in how well animal research is conducted and regulated, or concerns regarding the validity and translatability of animal data for human benefit. However, a more recent survey conducted during the UK national lockdown due to the Covid-19 virus provides some evidence that public support for the use of animals for medical research may be increasing back up to pre-2010 levels[10]. It is thought that this resurgence of support may be due to increased awareness that animals are used in medical research and the perception that this work is important. That said, this survey also indicates that the public remains concerned about animal welfare and wants to see more alternatives to using animals in research[10].

Since 2010, there has been a drive to improve the reporting of animal research and to encourage discussion in order to improve public knowledge and understanding of animal use in research. This drive resulted in the publication of a *Concordat on Openness on Animal Research in the UK*[11] by the bioscience sector in 2014. It was launched as a voluntary code of practice, to help "*organisations develop more transparent communication processes surrounding the use of animal in research*". To date, the Concordat has been signed by more than 130 organisations, including universities, commercial companies, learned societies, umbrella bodies, and all UK medical research councils and charitable funding bodies (i.e., BBSRC, DEFRA, EPSRC, MRC, NC3Rs, NERC, Royal Society, Wellcome, and other AMRC charities) that fund and/or permit animal use in research. The research funders have also made compliance with the Concordat part of the terms and conditions of their funding awards, such that those in receipt of funding are expected to fulfil, or work towards fulfilling, the four commitments that it contains. One of the many benefits felt by signatories of this Concordat has been a "(*perceived) reduction in the number of Freedom of Information (FOI) requests received by publicly-funded research organisations such as universities*"[12]. Thus, there is some evidence that proactively sharing information relating to the use of animals in research can help reduce the

potential for reputational risk that individuals or organisations can face if they are perceived as being secretive or having something to hide.

The framework for animal use in research in the UK

Most research organisations have their own policy, or will be aware of published recommendations for guidance, on responsible research conduct or good research practices. It is recommended that these policies be reviewed annually and that new developments in all aspects of research conduct be incorporated. Over recent years, this process has resulted in a growing number of policies being updated to include specific sections relating to research involving animals, including UKRIO's Code of Practice for Research[1] (see Box 1 for more information).

Box 1. UKRIO Code of Practice for Research[1]

3.7 Research involving Animals and Animal Materials

3.7.1 Organisations and researchers should make sure that research involving animals adheres to all legal and ethical requirements and other applicable guidelines. They should also ensure responsible use of animal-derived materials (where possible).

3.7.2 They should meet the legal requirements of the **3Rs** for reduction, replacement, and refinement of research involving animals and refer to relevant guidance:

- *Home Office – Research and testing using animals: licences and compliance;*
- *Animals in Science Committee (ASC);*
- *Laboratory Animal Science Association (LASA);* and
- *UKRIO – A primer on research involving animals.*

3.7.3 Organisations and researchers should ensure that they continue to address the 3Rs with help from the National Centre for the Replacement, Refinement & Reduction of Animals in Research (NC3Rs).

3.7.4 Organisations should set up systems to ensure the ethical, regulatory, and peer review of research projects involving animals. The systems should include mechanisms to make sure that such research projects have been approved by all applicable bodies, ethical, regulatory, or otherwise. Organisations should have an institutional **Animal Welfare and Ethical Review Body** (**AWERB**) and follow appropriate guidance (e.g., LASA/RSPCA).

Box 1. UKRIO Code of Practice for Research[1] (continued)

3.7.5 Organisations should ensure that their researchers are trained in all procedures necessary to conduct the research.

3.7.6 Organisations should make sure that their researchers are aware of the above systems and have access to all relevant guidance and legal and ethical frameworks.

3.7.8 Researchers should submit a draft project licence application for research projects involving animals for review by their local AWERB and amend their application in accordance with the recommendations of that review. They must have the necessary procedure training and maintain accurate record keeping. They should also ensure that such research projects have been approved by all applicable bodies, ethical, regulatory, or otherwise before starting the research.

3.7.9 If researchers consider that animals involved in research are subject to unreasonable risk, harm or licence infringement (either or both project and personal Home Office animal licences), they must suspend the activity that is deemed harmful and then report their concerns to their manager or other appropriate person(s) as identified by their organisation, and, where required, to the appropriate regulatory authority (e.g., Home Office).

3.7.10 Researchers should comply with appropriate standards by following the *PREPARE* checklist when planning animal research, in conjunction with the *ARRIVE* guidelines for transparent reporting and dissemination of outputs from research involving animals and/or animal material.

Should there be any question over whether or not animal use in research requires licensed approval under ASPA[2] (see Box 2 for more information), then an enquiry should be sent at the earliest opportunity to ASPA.London@homeoffice.gov.uk, or you can contact the Animals in Science Regulation Unit (ASRU) at the Home Office via emailing asc.secretariat@homeoffice. gsi.gov.uk. Or call 020 7035 0477.

Box 2. Animals (Scientific Procedures) Act 1986 (ASPA)[2]

ASPA governs the use of protected animals in scientific procedures.

Under ASPA "*protected animals*" are defined as:

- "*any living vertebrate, other than man, and any living cephalopod*"
- "*embryonic and fetal forms of mammals, birds and reptiles are protected once they have reached the last third of their gestation or incubation period*"
- *"larval forms of fish and amphibians are protected once they are capable of feeding independently*"
- *"Cephalopods are protected from the point when they hatch"*.

NOTE - If research involves the use of "protected animals" prior to the developmental time points set out in the legislation, but the animals are allowed to continue developing past the point at which their use becomes regulated under ASPA then the early developmental work might also require licensed approval.

Within the legislation "*scientific procedures*" are defined as:

- "*procedures that are carried out on 'protected animals' for scientific or educational purposes that may cause pain, suffering, distress or lasting harm*"
- "*the methods used to kill protected animals*"
- "*the breeding and supply of certain species of animals for use in regulated procedures, or for the scientific use of their organs and tissues*".

NOTE - The last point may be relevant to some *in vitro* studies depending on how the biological material to be cultured or studied *in vitro* is collected. For example, if biological material is collected from an animal whilst it is under general anaesthesia then this is a scientific procedure regulated under ASPA. If biological material is collected from an animal after it has been humanely killed, then this is not regulated.

ASPA states that a "*regulated procedure*" can be acts of:

- "*commission, for example an action such as dosing or sampling"*
- or of *"deliberate omission, for example withholding food or water"*
- or of *"permission, for example the natural breeding of animals with harmful genetic defects, modifying the genes of a protected animal;* procedures *performed under anaesthesia or analgesia; administering an anaesthetic, an analgesic or other measure to sedate or dull the perception of pain; humane killing of a protected animal; the removal of organs, blood or other tissue under general anaesthetic"*.

Box 2. Animals (Scientific Procedures) Act 1986 (ASPA)[2] (continued)

ASPA does not regulate[3]:

- *non-experimental clinical veterinary practices* – this "*is generally considered to be non-experimental clinical veterinary practices when it involves an intervention which is of direct benefit to the animal or its immediate peer group*". You should consult the Royal Veterinary College of Surgeons if you have any questions on this
- *veterinary clinical trials* – these are "*required to be carried out for marketing authorisations of veterinary medicinal products and are a requirement of the Veterinary Medicines Regulations 2013*[13]". You should consult the Veterinary Medicines Directorate if you have any questions on this
- *non-experimental agricultural practices and practices undertaken for the purpose of recognised animal husbandry* – these "*must comply with other animal welfare legislation and regulations and are being applied to manage or conserve animals*"
- *identifying animals* – this means "*ringing, tagging or marking an animal primarily to identify it as a specific individual, or using any other humane way to do so, are not regulated procedures if they cause no more than momentary pain and not lasting harm*"
- *humane killing of animals* – this applies only to "*an appropriate humane method listed in Schedule 1 of ASPA, or by a method specified in the establishment's licence*" (see Guidance on the operation of ASPA[3] for more information on this).

To support implementation of ASPA, the Home Office has issued a number of useful documents including "*Guidance on the Operation of the Animals (Scientific Procedures) Act 1986*[3]" and "*Code of practice for the Housing and Care of Animals Bred, Supplied or Used for Scientific Purposes*[14]"

Non-compliance with ASPA

Despite the Home Office issuing *guidance on the operation of the ASPA*[3], a code of practice[12], and regular advice notes[13], a number of incidents of non-compliance with ASPA[2] are reported each year. ASRU published a new Compliance Policy in 2017 to "*explain how ASRU identifies and investigates potential incidents of non-compliance and decides on appropriate and proportionate measures and sanctions aimed to minimise the risk of recurrence*"[14]. The scale and severity of such incidences varies greatly, and there is rarely evidence of deliberate misconduct, but it is still helpful to be aware of common compliance issues [15]. The ASRU compliance policy described how ASRU identifies and investigates potential incidents of non-compliance and decides on appropriate and proportionate measures and sanctions aimed to minimise the risk of recurrence[16].

The ASRU's annual report[17] includes statistics on and an overview of non-compliance issues. They include self-reported legislative non-compliance, reports from whistle-blowers, or cases identified by Inspectors. Cases typically relate to procedures conducted without licensed authority; however, others include cases where there has been a failure to provide appropriate care (food, water, and/or facilities).

Implementation of the 3Rs

The **3Rs** principles of **Replacement, Reduction, and Refinement** were first described by William Russell and Rex Burch in 1959[18]. Since then, the 3Rs have become synonymous with good laboratory animal science and are required to be applied throughout an animal's life-time experience, from the point of sentience (the developmental time-point for this is still a topic of debate for many species) until they are humanely killed. Implementation of these principles is something that is taken seriously by the main funders of research involving the use of vertebrate animals in the UK, namely the BBSRC, DEFRA, EPSRC, MRC, NC3Rs, NERC, Royal Society, Wellcome, and other AMRC charities.

In the introduction of the guidance document[4] issued by these funders, it states, "*High standards in the design and conduct of animal research and full implementation of the 3Rs are important for ethical reasons and to obtain the best possible scientific results* (see page 4[4])". To this end, the guidance also states that "*the funding bodies will recognise the publishing of significant and original contributions to the development of the 3Rs in reviews of establishments and in reports on grants*" (see page 21[4]). Thus, the expectation is clear, "*researchers should ensure that any new procedures or improvements in techniques that avoid or replace animal use, reduce the number of animals needed for research, testing or diagnosis, or reduce the suffering arising from scientific procedures or husbandry and care are communicated to other researchers and to veterinary and animal care staff, as appropriate*" (see page 21[4]).

Replacement

This principle is about either:

- avoiding animal use through the '*absolute*' replacement of methods, models or techniques involving live animal use with a non-animal alternative; or
- '*relative*' replacement of live animal use with research involving materials derived from animals.

In practice, replacement is often considered the most difficult of the three principles to apply and is commonly most successful when viewed as part of a structured approach. For example, many researchers start by replacing one procedure or an individual experiment within a programme of work. This enables researchers to gain experience and to develop a more reproducible method, model, or technique generating data that translates better into the clinical setting. Thus, it can be helpful to ensure that replacement is not viewed as advocating an 'all or nothing' approach and to focus more on identifying the weakness of existing approaches and thinking creatively about how to overcome these, whilst progress in the development of alternative models continues. Institutions can support this approach by improving awareness of the non-animal alternatives being developed, validated, and implemented within their own and other Biomedical research and testing facilities.

The journals Alternatives to Animal Experimentation (ALTEX https://www.altex.org/index.php/altex) and Alternatives To Laboratory Animals (ATLA https://journals.sagepub.com/home/atl) are another source of such information. As are the information networks and search tools provided by organisations such as the

European Union Reference Laboratory for alternatives to animal testing (EURL ECVAM https://ec.europa.eu/jrc/en/eurl/ecvam) and John Hopkins Center for Alternatives to Animal Testing (CAAT https://caat.jhsph.edu/).

Reduction

This principle is concerned with **using the optimum number of animals to achieve a statistically and scientifically meaningful result**.

This is relevant to the breeding of animals for use in experimental procedures, as well as those used in experiments. It is the principle most pertinent to issues of research quality, reproducibility, and reliability, and relates to contemporary standards of good practice in the design of animal experiments. In practice this means that all animal experiments should: include measures to minimise risk of bias (using appropriate measures such as randomisation and blinding); be adequately powered by using a predetermined number of animals and controlling variation (by randomly allocating animals to control and treatment groups and minimising confounding factors); have a range of applicability (possible using factorial experimental designs); indicate a measure of variability or range of uncertainty.

This point has been the focus of many individual efforts resulting in freely available resources such as those produced by Dr Michael Festing (https://norecopa.no/more-resources/experimental-design-and-reporting/michael-festing) and *Statistical Experiment Design for Animal Research,* an e-book by Dr Carlos Sorzano and Dr Michael Parkinson[19]. The National Centre for the 3Rs (http://www.nc3rs.org.uk) has also developed an Experimental Design Assistant tool (EDA https://eda.nc3rs.org.uk/) to help researchers improve the design of experiments. InVivoStat (http://invivostat.co.uk/) is another freely available software package specifically designed for the analysis of data from animal experiments.

For those who prefer a reference book to assist them, there are two worth considering. Firstly, *the design and statistical analysis of animal experiments*[20] is authored by the creators of InVivoStat, Simon Bates and Robin Clarke, and secondly, a new addition of *The Design of Animal Experiments*[21] has been published.

Refinement

This principle is about **developing methods associated with breeding, accommodation, care, and use of animals, to minimise or eliminate the potential for animals to experience pain, suffering, distress, or lasting harm, and maximise their welfare**. Historically, the focus of this principle has been on providing laboratory animals with a life worth living by minimising negative experiences. As our understanding of animal sentience, health, and welfare has improved, the focus has progressed to achieving a good life for laboratory animals that includes positive and rewarding experiences. This shift in focus is synonymous with concepts such as "*marginal gains*"[22] and "*the refinement loop*"[23].

It is worth noting that there can be a perceived conflict between reduction and refinement. For example, is it better to conduct procedures that cause moderate or severe suffering on fewer animals, or milder procedures on more animals if both result in equivalent knowledge gains? Of course, there is no definitive answer to this question, which would be considered as part of the harm-benefit analysis when a

project licence is applied for. The answer will also vary between institutions and depend on the specific research project, but it is generally accepted that the experience of the individual is what matters, so using more animals with less overall suffering is usually the preferred conclusion. However, to support institutions in such decision-making, the Animals in Science Committee (ASC), in their Review of Harm-Benefit Analysis in the use of Animals summary for AWERBs[24] recommend that establishments use retrospective severity assessments detailing the actual harms experienced by animals to inform the harm-benefit analysis conducted for future experiments using the same or similar procedures (see page 5). In so doing, areas requiring refinement to reduce suffering can be identified and prioritised at a local level.

The ASC report also encourages the use of freely available tools such as the Animal Welfare Assessment Grid (AWAG https://github.com/PublicHealthEngland/animal-welfare-assessment-grid/wiki) jointly developed by Public Health England (PHE) and Surrey University Veterinary School to assist in project planning and support refinement through the assessment of animals' lifetime experiences. For such a tool to be most effective, institutions should ensure that scientists planning animal experiments are aware of the importance of close collaboration with the animal facility and its staff from the earliest possible stage. This will aid the implementation of all three Rs and the identification of all the practical issues that need to be addressed if a study is to be successful.

Scientists are often unaware of the complexity of animal facility management and the multitude of factors that can influence research animals and thereby the validity of data obtained from them. Thus, institutions can support researchers to consider all the topics that may influence the outcome of their studies and aid collaboration by promoting the PREPARE guidelines published in 2017[25] (see https://norecopa.no/PREPARE), a good practice checklist for use when planning experimental procedures on animals.

Specific points to consider

Why should research organisations care if staff or students are conducting research using animals, or animal-derived material?

There are many reasons why it is considered good practice for all research organisations to have an awareness of research using animals, or animal-derived material, that is being conducted by staff or students. This is irrespective of whether the animal use falls within or outside the scope of ASPA[2], and whether the project is undertaken onsite or at another location (within the UK or abroad).

Not all use of animals, or animal-derived material, is regulated under ASPA[2]

From a legal perspective, not all use of animals, animal-derived material, or animal-derived data for research purposes is regulated under ASPA[2]. Responsibility for protected animals used in scientific procedures and within the scope of ASPA[2] is determined by the three tiers of licensing and falls upon the establishment, project, and personal licence holders. The assignment of responsibility for research that is outside the scope of ASPA[2] is more of a legal grey area and depends upon many factors. Both the individual and the host organisation/employer could be held legally responsible if the animal use falls within the scope of other legislation, such as the Animal Welfare Act (relevant only from an animal's birth or hatch), or relevant farming, veterinary, or wildlife legislation. There is also a provision under the Animal By-Products (Enforcement) (England) Regulations 2013[26], for animal by-products not intended for human consumption to be used in research. Under this regulation, the site where animal by-products are used must be approved or registered with the Animal and Plant Health Authority (APHA). Further guidance on the use of animal by-products can be found here https://www.gov.uk/guidance/animal-by-product-categories-site-approval-hygiene-and-disposal.

Research funders' expectations apply irrespective of whether the research is regulated under ASPA[2] or not

Irrespective of legal requirements, the research councils and charitable funding bodies are quite clear. They are "*committed to introducing and implementing standards which reflect contemporary good practice, including when these exceed the minimum requirements of legislation and codes of practice,* ***for all research using animals, not just that regulated under ASPA***" (see page 4[4]). In 2024, UK Research and Innovation (UKRI) published a Policy on Research and Innovation Involving Animals, which includes clear responsibilities for research and innovation involving or impacting animals that are not regulated under A(SP)A. This includes the use of animal materials such as tissues and primary cells[27].

In terms of who is responsible for ensuring research is conducted according to the terms and conditions of the research funding, then according to page 6 of the guidance "*the funding bodies only support work involving the use of animals on the basis that* ***researchers and those administering the funding*** *comply with legal provisions, plus any related codes of conduct or guidance issued by government departments and the specific conditions of licenses*".

Research funders expect host organisations to support individuals to apply the principles in their guidance

The research councils and charitable funding bodies' guidance was first published in 2008 and last updated in April 2019. It contains details of what "*researchers, associated veterinary and animal care staff using vertebrates and cephalopods (live animals or animal products) in bioscience research are expected to implement*" (see page 5[4]). This guidance states that "*in addition to fulfilling any legal responsibilities, they (researchers and associated veterinary and animal care staff) are primarily responsible for applying the principles in this guidance,* ***with support from their host establishments***" (see page 10[4]). Thus, research organisations may not be able to support all researchers in fulfilling these expectations if they are unaware of their use of animals or animal-derived material in research.

Research funders recommend that an establishment's research ethics committee ensure the implementation of their guidance

The guidance is also thought to be useful to "*ethics committees, referees, and Board and Committee members involved in reviewing research proposals*" (see page 5[4]). Topics covered within the guidance include: *the design of research and the 3Rs; ethical review; research or collaborations outside the UK; studies of free-living animals; the breeding and supply of animals; surgical procedures; husbandry and transport of animals; housing and care; capture, handling, restraint and training of animals; dosing and sampling; animal health and welfare; humane endpoints; staff training; communication of advances in the 3Rs*; and, *the reporting of animal based studies"*. With respect to research governance and staff training the guidance states that "*ethics committees are responsible for reviewing animal use at a local level and addressing situations where there is a risk that the use of animals may be in conflict with the best welfare interests of the animals involved. They have a key role in ensuring high standards.* ***It is therefore recommended that the research establishment's ethics committee****, whether the AWERB established under the ASPA or otherwise,* ***should be central to ensuring implementation of this guidance***" (see page 10[4]). The guidance also states that "*there should be an appropriately resourced programme of continuing professional development for staff at all levels. All staff should be actively encouraged to extend their knowledge and experience and to spread good practice by visiting other establishments and attending courses, meetings, and symposia*" (see page 20[4]). It is clear, therefore, that research organisations could easily fall short of fulfilling funders' expectations if they are not aware that they are applicable to the organisation.

Research funders' guidance applies to the researcher and host establishment, irrespective of where the research is undertaken

It is worth noting that the funders' guidance applies irrespective of where the researcher is based and/or research is undertaken. "***When collaborating with other laboratories, or where animal facilities are provided by third parties, researchers and the local ethics committee in the UK should satisfy themselves that welfare standards consistent with the principles of UK legislation and set out in this guidance are applied and maintained.*** *Where there are significant deviations, prior approval from the funding body should be sought and agreed.*

International research should also be compliant with all relevant national and local regulatory systems in the host country where the research is to be conducted" (see page 14[4]). This expectation reflects societal concerns highlighted in the general press that the research activities of UK residents may receive less scrutiny when the use of animals, or the collection of animal-derived materials, takes place overseas. To assist with the assessment of welfare standards outside of the UK, the NC3Rs has produced a series of checklists to enable the welfare standards of rodents, rabbits, sheep, goats, pigs, cattle, and xenopus to be assessed wherever the work is carried out (visit http://www.nc3rs.org.uk/use-of-animals-overseas for more information).

Ensuring oversight of all research involving animals or animal-derived material

Another consideration for organisations is the ethical and animal welfare concerns that research using animals or animal-derived material can give rise to. For example, **it is important to consider even research that falls outside the scope of regulation but has the potential to cause pain, suffering, and distress (however mild)**. The research may also involve **killing animals,** which **is an ethical issue even if done humanely**. "*Studies of free-living animals in their natural habitats can cause disruption, particularly if feeding, capture, marking, or scientific procedures are involved*" (see page 15[4]). Other individuals, species, or habitats may also be affected indirectly and so must be considered. **With all these concerns, there is an element of reputational risk to organisations** if it transpires that a researcher has conducted research using animals or animal-derived material that has not met societal expectations of responsible conduct or has carried out/requested others carryout work overseas that would not be permitted in the UK. Thus, it is recommended that research establishments have policies or procedures in place to identify and request notification whenever staff or students are conducting research using animals or animal-derived material. These should apply irrespective of whether the research is being undertaken onsite, elsewhere within the UK, or abroad. Such an approach facilitates local discussions and, if appropriate, the development of management or oversight measures to support all research staff and/or students in the implementation of good practice and to help them meet expectations in terms of the responsible use of animals in research.

There are many non-ASPA-regulated uses of animals and animal-derived material in research

At present, it is difficult to gauge how many research organisations are unaware of researchers who are conducting research using animals or animal-derived material that falls outside the scope of ASPA[2], or at another licensed location or research establishment. Such work may include:

- projects conducted by UK researchers or their collaborators on their behalf overseas
- animals brought into the organisation solely to be killed and used as a source of biological material (tissues, blood, cells, organs, embryos)
- animal-derived samples collected from overseas sources specifically for use in UK-based research projects

- samples of animal-derived materials purchased from, or donated by external sources, including biobanks, commercial sources, abattoirs, veterinary diagnostic services, existing sample collections (from zoos, museums, nature reserves, wildlife projects, other organisations or members of the public)
- the use of purchased or donated research reagents produced using animals, for example, monoclonal and polyclonal antibodies, supplements for in vitro cultures such as fetal calf serum (also known as fetal bovine serum), hormones to superovulate animals, such as pregnant mare serum
- below threshold studies on animals 'protected' by ASPA[2], projects on invertebrates other than cephalopods, or immature developmental stages of vertebrates.

The ethical and animal welfare considerations relating to each of these points are largely the same as relates to research involving the use of animals and animal-derived materials under ASPA. However, specific ethical concerns have been raised over recent years relating to the production of animal-derived antibodies and fetal calf serum. In relation to the production of animal-derived antibodies, the NC3Rs and Research Councils UK issued a joint statement on the "Animal welfare standards expected of suppliers of antibodies to Research Council establishments"[28]. In relation to fetal calf serum, The Netherland National Committee for the Protection of Animals Used in Scientific Procedures has created a short video[29] outlining the concerns relating to the production of fetal calf serum and points to be aware of when purchasing for use in research. Concerns have also been raised relating to the reproducibility of data generated by experiments using animal-derived antibodies[30]. The European Reference Laboratory for alternatives to animal testing (EURL-ECVAM) has therefore recently published recommendations on the use of non-animal derived antibodies[31].

In 2025, the Animal Materials Working Group, a UK-wide initiative, published an Ethical Framework for Obtaining Materials from Sentient Animals to support research organisations and other stakeholders in their ethical decision-making when obtaining materials from sentient animals. Although it does not remove the need for ethical review where this is specified in relevant regulations, it is designed for use when materials have been obtained from a wide range of settings, including:

- research laboratories
- historical collections
- zoos, farms, and veterinary contexts
- owned animals and animals in the wild
- retail procurement.

Those administering the funding are jointly responsible for ensuring compliance with the guidance as part of the terms and conditions of accepting research funding

All research organisations that hold an establishment licence under ASPA[2] (160 at the end of 2019[6]) will be aware of the regulated use of animals in research that is carried out within their organisation. The majority will also have some direct or

indirect contact with researchers whose use of animals in research falls outside the scope of ASPA[2]. This may be because the researchers are also involved in licensed work, or because there is a centralised service. Licensed researchers may also be known to be supplying embryos of the required developmental stage or other biological material for research purposes to an unlicensed collaborator. Hence, it is likely that licensed establishments will have some knowledge or awareness of the scale of animal use outside the scope of ASPA[2]. However, this does not mean that a licensed establishment will have any involvement in the oversight or management of such unlicensed research. Nor does it mean that they will have knowledge of how well the research is planned or conducted. However, "*the **funding bodies only support work involving the use of animals on the basis that researchers and those administering the funding comply** with legal provisions, plus any related codes of conduct or guidance issued by government departments and the specific conditions of licences*" (see page 6[4]).

It is therefore recommended that all research organisations should consider how best they can assess the scale of unregulated animal use in research being undertaken either on site, or by their staff and students at other locations, as well as regulated animal use undertaken at other locations, especially if this is outside of the EU. Please see Box 3 for an example policy for "*research using animals carried out overseas*"[32] and form for the purpose of "*registration, reporting and oversight arrangements for work conducted at non-UK premises*" provided by University College London.

Box 3. Example policy for 'research using animals carried out overseas' and form for the 'registration, reporting and oversight arrangements for work conducted at non-UK premises'

POLICY

Staff must notify their local AWERB, before the works starts, of any research they intend to carry out that involves the use of animals in a laboratory overseas.

Procedures that use non-human primates, or which would be assessed as severe under A(SP)A, must receive formal AWERB approval for the work.

AWERBs, at their discretion, might also require formal appraisal and approval, by an AWERB panel, of procedures using other species.

These requirements apply to:

- import of animal tissues (e.g., blood samples and antibodies)
- export of live animals
- collaborative studies, any aspect of which uses animals in a laboratory outside the UK.

Box 3. Example policy for 'research using animals carried out overseas' and form for the 'registration, reporting and oversight arrangements for work conducted at non-UK premises' (continued)

FORM

Study personnel and institutions

- Applicant name
- Department
- Contact email and phone number
- Name and contact details of lead investigator at non-UK site
- Local investigator's research institution (University etc.)

Study compliance with AWERB requirements

- Project title
- Funder
- Has the funding body been informed of the planned work to be conducted at non-UK premises?

  Yes □ No □ If 'No', indicate why this is not necessary
- Duration of study overseas

  Start date: _____ End date:_____
- Location of research sites (laboratories or other research sites)
- Is this work subject to a confidentiality (non-disclosure) agreement?

  Yes □ No □
- Is this work subject to a material transfer agreement (MTA)?

  Yes □ No □

  If the answer is 'Yes' to either question above, please include agreement(s) as an appendix

Please summarize (300 words max) the local arrangements (e.g. AWERB equivalent) for ethical approval and oversight of animal studies

Please reference here, and attach, relevant local approval documents (with English translations if necessary)

Please reference here, and attach, a work plan for the proposed studies showing the experimental groups to be studied, the species, the numbers expected to be used (with statistical justification), and the planned humane endpoints.

Box 3. Example policy for 'research using animals carried out overseas' and form for the 'registration, reporting and oversight arrangements for work conducted at non-UK premises' (continued)

Please justify the proposed work and explain why it is to be carried out in a non-UK institution (300 words max)

Please explain how the 3Rs principles are addressed in the project plan. If endangered species are involved, how has this been addressed? (300 words max)

Research monitoring arrangements

How will the progress of the work and compliance with protocols be monitored (300 words max)?

Availability of veterinary support and qualified animal facility staff. Please describe local arrangements (100 words max)

Please describe what arrangements are made for animal disposal or rehoming at study completion or in the event of early termination (300 words max)

Health and safety

Has an appropriate risk assessment been approved?

Yes □ No □

If 'Yes', please provide the reference number.

The culture of research and a culture of care

Over recent years, there has been much general interest in the culture of scientific research here in the UK. This has been led by the work of the Nuffield Council on Bioethics[33] and more recently The Royal Society (visit https://royalsociety.org/topics-policy/projects/research-culture/ for more information), Wellcome (visit https://wellcome.org/what-we-do/our-work/research-culture) and UKRI (visit https://www.ukri.org/our-work/supporting-healthy-research-and-innovation-culture/research-and-innovation-culture/). This general focus on research culture also coincides with greater emphasis on promoting a good culture of care[34] being placed by the ASRU inspectorate[15] and other organisations working within the laboratory animal sciences. New resources include the NC3Rs 'Research culture and the 3Rs' resource hub (see https://www.nc3rs.org.uk/research-culture-and-3rs), and Norecopa hosted the International Culture of Care Network (visit https://norecopa.no/coc).

This is in part a response to recommendations contained within the Brown Report[34] published in 2013, following an independent investigation into animal research at a licensed establishment. The report highlights the fact that "*responsibility for high standards in animal research lies with a number of individuals at any institution*"[35] or, as this guidance seeks to emphasize, there may also be a shared responsibility across institutions. "A *healthy culture of care requires a shift away from merely responding to externally imposed standards, to one in which leaders and frontline staff actively commit to improving 3Rs, animal welfare and research and working together to do so*" (see page 56[35]).

"*Mechanisms to ensure that standards at animal suppliers, contracted organisations, and research partners overseas are consistent with the good practice that is implemented in-house*" is also considered a feature of a good culture of care (see page 57[35]). Therefore, identifying the extent of animal use in research by an organisation's staff or students is a critical step in the development of both a good culture of care and a good research culture.

The Academy of Medical Science, BBSRC, MRC, and Wellcome have also published a symposium report discussing research culture: *Reproducibility and reliability of biomedical research: improving research practice*[36]. This report documents six main issues that are thought to be the cause of irreproducible results within biomedical research disciplines: data dredging, omitting null results, underpowered studies, technical errors, underspecified methods, and weak experimental design.

The report then goes on to identify seven potential strategies to counteract poor practices in relation to these six issues. These seven strategies are: 1) openly sharing results and underlying data, 2) pre-registration of study protocols, 3) collaborative working between research groups, 4) automation to technically standardise practices and reduce human errors, 5) openly publishing the details of study methods, 6) post-publication review, and 7) reporting guidelines. Some examples of progress in these areas are illustrated on the following pages.

The ARRIVE 2.0 guidelines

"*At present, publications describing animal studies pay insufficient attention to the reporting of measures (e.g., randomisation, blinding) to reduce the risk of biases…*" (see page 40[36]). The UK research funders are unanimous that "*researchers should ensure that they report animal-based studies in accordance with the ARRIVE guidelines*" (see page 21[4]).

ARRIVE stands for '*Animal Research Reporting In Vivo Experiments*' and has presented best practice guidance for the reporting of animal studies since its publication in 2010[37]. In 2012, the chief executives of the BBSRC, MRC, and Wellcome Trust wrote to the Vice-Chancellors, Principals of universities, and Heads of research institutes, urging them to support their researchers to report animal studies in accordance with ARRIVE (visit https://www.nc3rs.org.uk/news/open-letter-uk-funding-bodies for more information). An ARRIVE checklist is intended to assist manuscript authors and journals in implementing the ARRIVE guidelines. In addition, the checklist makes a useful educational tool to help researchers identify potential sources of bias and other flaws in the experimental design of published research and inform their opinion on the robustness, rigour, and reproducibility of the results.

Despite growing levels of endorsement (including over 1,000 journals), improvements in the quality of animal study reporting have been slower than anticipated. The NC3Rs therefore undertook a project to revise the ARRIVE guidelines to accelerate improvements. This resulted in the creation of a dedicated website https://arriveguidelines.org/ that hosts the revised ARRIVE2.0 guidelines published in 2020 and a collection of useful resources.

ARRIVE 2.0 comprises two lists: the 'ARRIVE essential 10' (considered minimum information reporting requirements) and a 'recommended set'. Together, these lists cover all the information that authors should include within the title, abstract, introduction, methods, results, and discussion sections to report in accordance with best practice.

Open data – Concordat on open research data[37]

The *Concordat on Open Research Data*[38] was published in July 2016 by HEFCE, Research Councils UK, Universities UK, and the Wellcome Trust. It sets out ten principles that may take time for organisations to fulfil but will ensure that research data are "*openly available for use by others in a manner consistent with relevant legal, ethical, disciplinary and regulatory frameworks and norms, and with due regard to the cost involved*."

The four original signatories have since been joined by several other organisations, including the Natural History Museum, Cancer Research UK, Sheffield Hallam University, the Scottish Funding Council, the Higher Education Funding Council for Wales (HEFCW) & the University of Glasgow. Contact openresearch@ukri.org for more information.

Openly sharing results and underlying data generated by animal studies will help address the significant impact of publication bias. This source of bias is the result of the unknown volumes of research data that, for various reasons has in the past and

continue to go unpublished. Efforts to assess the impact of publication bias are ongoing in relation to pre-clinical animal studies. For example, one study reviewing the efficacy of drugs reported in animal stroke studies suggested that an additional 14% of studies may have been conducted but never reported[39]. Over recent years, there have been a number of different initiatives seeking to address the issue of unpublished data, including BioRxiv (https://www.biorxiv.org/), a free online archive for unpublished preprints in the life sciences. Some research funders have also gone a step further by establishing their own free publication services for grant holders. For example, the NC3Rs has, together with F1000Research, established its own gateway to publish the 3Rs research it funds (https://f1000research.com/nc3rs).

The PREPARE guidelines[25]

The PREPARE (*Planning Research and Experimental Procedures on Animals: Recommendations for Excellence*) guidelines[25] represent current best practice for laboratory animal science. PREPARE consists of a checklist containing 15 specific points relating to: *1. the formulation of the study; 2. the dialogue between scientists and the animal care staff; 3. quality control of the components in the study*. The checklist is a useful aide-memoire for scientists and is supported by a dedicated website, which includes references to the latest quality-controlled resources for each topic. Visit https://norecopa.no/PREPARE for more information.

Pre-registration of study protocols

https://www.preclinicaltrials.eu/ is an international online register of protocols for preclinical animal studies. The idea is comparable to the protocol registries for human-based clinical trials, and exists to "increase transparency, help avoid duplication, and reduce the risk of reporting bias by enabling comparison of the completed study with what was planned in the protocol".

There is also http://www.animalstudyregistry.org for the registration of all scientific studies involving animals conducted around the world. The aim of this registry is to encourage transparency, enhance reproducibility, and promote animal welfare by assigning entries a DOI (digital object identifier) number to protect the intellectual property that can be referenced to discourage selective reporting when results are published.

Registered reports

This format for publishing research was first introduced by the journal Cortex in 2013 and has since been adopted by over 200 other journals (for a list of participating journals, visit https://cos.io/rr/). Registered reports are submitted prior to the study being undertaken, and the peer review process evaluates the importance of the research question and the quality of the proposed methodology. If the study protocol and methodology pass peer review, then the study authors are offered an in-principle acceptance for the study's publication, irrespective of the study findings.

This format is a good way of obtaining an independent assessment of the quality of the study methodology as it relates to the specific hypothesis being tested. It also incentivises researchers and students to implement good practice in relation to their own experimental design, and in time could help reduce the impact of publication bias. This is a big problem generally, but also raises ethical issues when the

unpublished data was generated by research involving animals or animal-derived material.

ReproducibiliTEA

ReproducibiliTea (https://reproducibilitea.org/) is a volunteer-run journal club initiative that started in Oxford in 2018. The purpose is to create local open science journal clubs for early career researchers to discuss research papers, ideas about improving science, reproducibility, and the concept of 'open science' more generally. ReproducibiliTea journal clubs are now active in over 85 research institutions in more than 20 different countries. The initiative is currently sponsored by the UK Reproducibility Network (see page 20 for more details), with a starter pack and any resources required to set up new local clubs freely available from the website. To register a new ReproducibiliTea journal club and become connected to other journal clubs around the world, email reproducibilitea@gmail.com.

RIOT Science Club

The RIOT Science Club (http://riotscience.co.uk/) is a seminar series that started at King's College London in 2018. The purpose is to raise awareness of and provide training in Reproducible, Interpretable, Open & Transparent science practices. This initiative, led entirely by early-career researchers and in partnership with the UK Reproducibility Network, has now expanded to a growing number of other sites. All presentation slides can be accessed via the RIOT Science Club Open Science Framework page (https://osf.io/8y7h2/), and recordings can be found on the RIOT Science Club YouTube channel, available at (https://www.youtube.com/c/RIOTScienceClub/featured). To join their event mailing list, email riotscienceclub@kcl.ac.uk .

The UK Reproducibility Network

The UK Reproducibility Network (www.ukrn.org) is a grassroots, peer-led organisation that was formed with small grants from the UK Research Integrity Office, Universities UK, Wellcome, UKRI, MRC, Nature, PLoS, JISC, and others in early 2019. The network aims to investigate the factors that contribute to robust research, promote training activities, disseminate best practice, and work with stakeholders (researchers, institutions, publishers, and funders) to coordinate efforts across the biomedical sciences and other research disciplines to promote robust and rigorous research practices.

Afterword

Ultimately, for research organisations to be able to deliver research involving the use of animals, or animal-derived material, in accordance with expectations of good research practice requires a collective effort.

Individuals need awareness, knowledge, skills, and support:

- **awareness** of the expectations that exist
- **knowledge** and understanding to recognise what these expectations mean in terms of how research is planned, conducted, and communicated
- **skills and support** to be able to translate the theory into practice.

Research organisations need awareness, knowledge, and understanding:

- **awareness** of external expectations, plus the tools and resources that exist to support best practice
- **knowledge and understanding** of the research activities undertaken by staff and/or students, plus the training and support that these individuals need to deliver best practice.

This document seeks to contribute to this collective effort, and the links contained within it provide further sources of information and support. If you require any additional advice from UKRIO, please contact us via our website: https://ukrio.org/get-advice-from-ukrio/.

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