



Research Integrity: A primer on research involving animals

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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 is part of a series from the UK Research Integrity Office providing recommendations of best practice within aspects of academic, scientific and medical research. The aim is not to be prescriptive. As with all our publications, it is underpinned by 'lessons learned' from UKRIO's confidential Advisory Service on the conduct of research, which has operated since 2006 and covers all disciplines, from the arts and the humanities to health and biomedicine.

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 research¹ (see Box 1), as well as the Animals (Scientific Procedures) Act 1986² (ASPA) and guidance³ 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 concerns that have underpinned the development of good practice guidelines and standards in this area apply irrespective 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.



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 1986².
- All animal use in bioscience research funded by the BBSRC, DEFRA, EPSRC, MRC, NC3Rs, NERC, Wellcome Trust and other 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 research⁴.
- 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 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 the use of animals for scientific purposes. The current iteration of the Animals (Scientific Procedures) Act 1986² aligns UK legislation with the European Directive governing the use of animals in scientific procedures, EU Directive 2010/63/EU⁵.

The latest available statistics report that in 2017⁶ in Great Britain a total of 3.79 million scientific procedures were carried out involving 3.72 million animals. Around half of these procedures (1.90 million) were for creating or breeding genetically-altered animals and the remaining 1.89 million were for experimental purposes. Of these just over half (1.04 million procedures) were for basic research, another 27% (505,000 procedures) were for regulatory purposes and 322,000 procedures (17%) were for translational or applied studies. In terms of the species used in scientific procedures, the most common were mice (2.78 million), followed by 420,982 zebrafish and 238,538 rats. These numbers contrast sharply with the 18,900 procedures carried out on 'specially protected species'. This category includes cats, dogs, non-human primates and equidae 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 ASPA² (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.

In recent years there has been a drive to improve the reporting of and discuss animal use in research to improve public knowledge and understanding. Until recently, surveys to track and analyse trends in public support for animal use in research have reported that the majority (76% seen in the 2010 survey) of the public support animal experimentation as long as it is for medical benefit and there are no valid alternatives⁷. 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. Since the 2010 survey, the level of public support for animal experimentation has dipped slightly to 67% in 2014. Closer analysis reveals that this dip is due to 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.

In response to this dip, the bioscience sector collectively produced a *Concordat on Openness on Animal Research in the UK*⁸. It was launched in 2014, 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 122 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, Wellcome Trust and other AMRC charities) that fund animal use in research. The research funders have also made it 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 the Concordat 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”⁹. 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 are reviewed annually, and that new developments in all aspects of research conduct are 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 Research¹ (see Box 1 for more information).

In addition to the general research conduct guidance that exists, the *Responsibility in the use of animals in bioscience research: Expectations of the major research council and charitable funding bodies*⁴ guidance has been produced by the BBSRC, DEFRA, EPSRC, MRC, NC3Rs, NERC, Wellcome Trust and other AMRC charities. It gives a detailed breakdown of good practice and states that “Implementation of the principles in this guidance is a condition of receiving funds from the funding bodies” (see page 4⁴). Should there be any question over whether or not animal use in research requires licensed approval under ASPA² (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 call the Animals in Science Regulation Unit (ASRU) at the Home Office on 020 7035 0477.

Box 1. UKRIO Code of Practice for Research¹

3.8 Research involving animals

3.8.1 *Organisations and researchers* should make sure that research involving animals adheres to all legal and ethical requirements and other applicable guidelines. They should consider the opportunities for reduction, replacement and refinement of involving animals in research projects and should refer to the relevant guidance.

3.8.2 When conducting, or collaborating in, research in other countries, organisations and researchers based in the UK should comply with the legal and ethical requirements existing in the UK and in the countries where the research is conducted. Similarly, organisations and researchers based abroad who participate in UK hosted research projects should comply with the legal and ethical requirements existing in the UK as well as those of their own country.

3.8.3 *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.

3.8.4 *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.

3.8.5 *Researchers* should submit research projects involving animals for review by all relevant ethics committees and abide by the outcome of that review. They should also ensure that such research projects have been approved by all applicable bodies, ethical, regulatory or otherwise.

3.8.6 If researchers consider that animals involved in research are subject to unreasonable risk or harm, they must report their concerns to their manager or other appropriate person as identified by their organisation, and, where required, to the appropriate regulatory authority.

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.

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

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”.

ASPA does not regulate³:

- *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 2013¹⁰”. 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 ASPA³ 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 1986³” and “Code of practice for the Housing and Care of Animals Bred, Supplied or Used for Scientific Purposes¹¹”

Non-compliance with ASPA

Despite the Home Office issuing *guidance on the operation of the ASPA*³, a code of practice¹¹ and regular advice notes¹², a number of incidents of non-compliance with ASPA² 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*”¹³. 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. The ASRU’s annual report¹⁴ includes statistics on and an overview of non-compliance issues.

The latest available statistics reveal that in 2017 there were 40 cases of legislative non-compliance¹⁴. The latter figure is higher than the 33 cases reported in 2013, but fewer than the figure for the previous three years (63 cases reported in 2014, 55 cases in 2015 and 45 cases in 2016). Of the 40 cases of non-compliance, 27 were at universities, 9 at commercial organisations, and 4 were at government research establishments. The majority (37 cases) were self-reported, with the remaining 3 cases discovered by an Inspector. Most cases involved mice, but the remainder involved rats, chickens, guinea pigs, zebrafish, ferrets, non-human primates, a wild-caught animal and some larger animals. The categorisation of non-compliance cases remains consistent, with the largest cause in 2017 related to procedures conducted without licensed authority (18 of the 40 cases). Another 8 cases were a failure to provide adequate food and/or water, and the remaining 14 cases involved other issues such as failure to regularly check on animals, exceeding the number of animals stated in the licence, poor training, supervision and conduct of regulated procedures, and failure to identify licence authorities were not in place. Again, it must be noted that these statistics reflect solely the regulated use of animals in research and so the situation regarding animal research practices outside of the regulations is unknown.

Implementation of the 3Rs

The 3Rs principles of Replacement, Reduction, Refinement were first described by William Russell & Rex Burch in 1959¹⁵. They have become synonymous with good laboratory animal science and are required to be applied throughout an animal’s life-time experience, from 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 here in the UK, namely the BBSRC, DEFRA, EPSRC, MRC, NC3Rs, NERC, Wellcome Trust and other AMRC charities. In the introduction of the guidance document⁴ 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*”. 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 21⁴). 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 21⁴).

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 experience to be gained and a more reproducible method, model or technique generating data that translates better into the clinical setting to be developed. Thus, it can be helpful to ensure that replacement is not viewed as advocating an ‘all or nothing’ approach and focus more on identifying the weakness of existing approaches and thinking creatively about how to overcome these until progress in alternative models means the absolute replacement of animal use is viable.

Reduction

This principle is concerned with using **the optimum number of animals to achieve a statistically and scientifically significant 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 good practice in the design of animal experiments. Over recent years this point has been the focus of many initiatives. To this end the National Centre for the 3Rs (<http://www.nc3rs.org.uk>) has 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*¹⁶ is authored by the creators of InVivoStat, Simon Bates and Robin Clarke, and secondly, a new addition of *The Design of Animal Experiments*¹⁷ 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. 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*”¹⁸ and “*the refinement loop*”¹⁹.

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 conclusion.

Specific Points to Consider

Why should research organisations care if staff or students are conducting research using animals?

There are many reasons why it is considered good practice for all research organisations to have an awareness of research using animals that is being conducted by staff or students. This is irrespective of whether the animals' use falls within or outside the scope of ASPA², and whether the project is undertaken onsite or at another location (within the UK or abroad).

From a legal perspective, responsibility for the animals used is determined by the three tiers of licensing and falls upon the establishment, project and personal licence holders if regulated under ASPA². If the research is outside the scope of ASPA² then this is more of a legal grey area. Depending on the animal use, both the individual and the host organisation/employer could be held legally responsible if it falls within the scope of other legislation such as the Animal Welfare Act (relevant only from an animal's birth), or relevant farming, veterinary, or wildlife legislation. However, 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 4⁴). 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 10 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”*.

The research councils and charitable funding bodies guidance was first published in 2008 and last updated in April 2017. It contains details of what *“researchers (grant holders and staff), associated veterinary and animal care staff using vertebrates and cephalopods (live animals or animal products) in bioscience research are expected to implement”* (see page 5⁴). 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 10⁴). Thus, research organisations may not be able to support all researchers in fulfilling these expectations if their use of animals in research is unknown.

The guidance is also thought to be useful to *“ethics committees, referees, and Board and Committee members involved in reviewing research proposals”* (see page 5⁴). 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 play 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 10⁴). 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 20⁴). 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.

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 14⁴). 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 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 and pigs to be assessed wherever the work is carried out (visit <http://www.nc3rs.org.uk/use-of-animals-overseas> for more information).

Another consideration for organisations is the ethical and animal welfare concerns that research using animals 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 15⁴). 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 that has not met societal expectations of responsible conduct or has carried out 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 when staff or students are conducting research using animals, 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.

At present it is difficult to gauge how many research organisations have researchers whom they are not aware are conducting research using animals that falls outside the scope of ASPA², or at another licensed location or research establishment. Such work may include: animals brought in solely to be killed and used as a source of biological material (tissues, blood, cells, organs, embryos); below threshold studies on animals 'protected' by ASPA²; projects on invertebrates other than cephalopods, or immature developmental stages of vertebrates; projects conducted overseas, or samples from overseas.

All research organisations that hold establishment licences under ASPA² (160 at the end of 2017¹⁴) will be aware of the regulated use of animals in research that is carried out within their establishment. The majority will also have some direct or indirect contact with researchers whose use of animals in research falls outside the scope of ASPA². This may be because the researchers are also involved in licensed work, or because there is a centralised service, or licensed researchers are 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 ASPA² that is taking place. 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 6⁴).

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”²⁰ 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.

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.)

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 [continued]

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 end-points

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 Bioethics²¹ and more recently The Royal Society (visit <https://royalsociety.org/topics-policy/projects/research-culture/> for more information). This general focus on research culture also coincides with greater emphasis being placed by the ASRU inspectorate¹² and more broadly within the laboratory animal sciences on the importance of having a good culture of care²². This is in part a response to recommendations contained within the Brown Report²³ 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”²³ 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 56²²). “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 57²²). 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 Trust published a symposium report which discussed research culture: *Reproducibility and reliability of biomedical research: improving research practice*²⁴. 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 ten potential strategies to counteract poor practices in relation to these six issues. The strategies are: openly sharing results and underlying data, pre-registration of study protocols, collaborative working between research groups, automation to technically standardise practices and reduce human errors, openly publishing the detail of study methods, post-publication review and reporting guidelines. Progress in these areas is illustrated below.

The PREPARE guidelines²⁵

The PREPARE (*Planning Research and Experimental Procedures on Animals: Recommendations for Excellence*) guidelines²⁵ represent current best practice for laboratory animal science. It is 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 and was published in August 2017. Visit <https://norecopa.no/PREPARE> for more information.

Open data - Concordat on open research data²⁶

The *Concordat on Open Research Data*²⁶ 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 Cancer Research UK, Sheffield Hallam University, the Scottish Funding Council, the Higher Education Funding

Council for Wales (HEFCW) & the University of Glasgow. Contact opendata@rcuk.ac.uk 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 continues 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 reported²⁷.

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 now <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 120 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.

The ARRIVE guidelines²⁸

“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 40²⁴). The UK research funders are unanimous that “researchers should ensure that they report animal-based studies in accordance with the ARRIVE guidelines” (see page 21³). ARRIVE stands for ‘Animal Research Reporting In Vivo Experiments’ and represents best practice guidance for the reporting of animal studies since its publication in 2010²⁸. The guidelines are endorsed by over 1,000 journals and comprise a 20-point checklist covering items that authors should include within the title, abstract, introduction, methods, results and discussion sections. The intention is to improve the reporting of animal research and promote reproducible, transparent and accurately written manuscripts.

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). Since then an ARRIVE checklist has been published to assist manuscript authors and journals in implementing the ARRIVE guidelines. This can also be used as an educational tool and aide memoir alongside the NC3Rs Experimental Design Assistant (see page 7 for more details) when planning experiments to help researchers reduce the risk of bias and improve the robustness of their research. Despite growing levels of endorsement, improvements in the quality of animal study reporting have been slower than anticipated. The NC3Rs are therefore currently revising the ARRIVE guidelines to accelerate improvements. For more information on this visit: <https://www.nc3rs.org.uk/revision-arrive-guidelines>.

Footnote to the First Edition

This document seeks to highlight the abundance of information regarding good practice, responsible conduct and integrity that relates to animal use 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.

This document will be revised periodically to reflect developments in laboratory animal science, new examples of good practice and additional 'lessons learned' from UKRIO's Advisory Service and other work. UKRIO welcomes feedback from researchers, research organisations, editors and publishers to inform the future development of this document. To contact UKRIO or to seek our advice on authorship, publication ethics or other issues of research practice, visit our website <https://ukrio.org/get-advice-from-ukrio/>.

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