



Research Integrity: A primer on research involving animals

Version 2.0

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Competing interests

NO is the founding director of Responsible Research in Practice Ltd and is in receipt of payment for the provision of specialist training and consultancy services to UK universities and bioscience research organisations on research integrity and ethical issues in relation animal research practices. Prior to this **NO** worked for 10 years in the Research Animals Department of the RSPCA during which time contacts were established and subsequently maintained with many of the organisations whose resources are referenced within this document. **NO** is a UKRIO volunteer advisor on animal research issues and in receipt of travel reimbursement as an independent lay member of the 3Rs committee and central AWERB at UCL.

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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 is part of a series from [the UK Research Integrity Office \(UKRIO\)](#) 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 of research.

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.

Footnote to the Second 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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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, Royal Society, 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 and refine 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 2019⁶ in Great Britain a total of 3.4 million scientific procedures were carried out involving 3.32 million animals. Nearly half of these procedures (1.67 million) were for creating or breeding genetically altered animals, whilst 1.76 million were for experimental purposes. Of these over half (984,000 procedures) were for basic research, another 25% (437,000 procedures) were for regulatory purposes and 277,000 procedures (16%) were for translational or applied studies. In terms of the species used in scientific procedures, the most common was the mouse (1.0 million), followed by 278,860 fish (mainly zebrafish), 162,699 rats and 130,682 birds. These numbers contrast sharply with the 17,720 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).

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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 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. 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 analysis⁹ 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 animal use for medical research may be increasing back up to pre-2010 levels¹⁰. 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 remain concerned about animal welfare and want to see more alternatives to using animals in research¹⁰.

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 120 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 Trust 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 are reviewed annually, and that new developments in all aspects of research conduct are incorporated. Over recent years this

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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, Royal Society, 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 5⁴).

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.

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.

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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*”.

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

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 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 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 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 practice¹² and regular advice notes¹³, 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*”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. The ASRU’s annual report¹⁵ includes statistics on, and an overview of, non-compliance issues.

The latest available annual report reveals that in 2018 there were 28 cases (detailing 33 separate incidences) of legislative non-compliance¹⁷. This figure continues the downward trend in incidences over previous years (63 cases reported in 2014, 55 cases in 2015, 45 cases in 2016, and 40 cases in 2017). The 28 cases of non-

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compliance occurred in 20 different establishments, of which 17 were at universities and 3 were at commercial organisations. The majority (26 cases) were self-reported, with 1 case reported by a whistle-blower and 1 case identified by an Inspector. In 24 cases 2,680 animals were involved – 1,631 fish, 483 birds, 376 mice, 170 rats and 20 pigs. Of these animals, 588 suffered an adverse welfare outcome and 100 resulted in death. It was not possible to determine the number of animals involved in the remaining 4 cases, but it is thought that there were no adverse welfare outcomes for the animals involved. The categorisation of non-compliance cases remains consistent, with the largest cause in 2018 relating to procedures conducted without licensed authority, most commonly exceeding the licensed approval (16 of the 28 cases). The remaining 12 cases were a failure to provide appropriate care (food, water and/or facilities). 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 and Rex Burch in 1959¹⁸. 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 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 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 (see page 4⁴)*". 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 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

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<https://ec.europa.eu/jrc/en/eurl/ecvam>) and the 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 Parkinson¹⁹. 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,

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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 AWERBs²⁴ 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 implementation of all three Rs, and 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 which can influence research animals and thereby the validity of data obtained from them. Thus, institutions can support researchers to consider all the topics which may influence the outcome of their studies and aid collaboration by promoting the PREPARE guidelines published in 2017²⁵ (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 ASPA², 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 ASPA²

From a legal perspective, not all use of animals, animal-derived material or animal-derived data for research purposes is regulated under ASPA². Responsibility for protected animals used in scientific procedures and within the scope of ASPA², 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 ASPA² 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 provision under the Animal By-Products (Enforcement) (England) Regulations 2013²⁶, 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 funder's expectations apply irrespective of whether the research is regulated under ASPA², 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 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 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*”.

Specific points to consider

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 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 there 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 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 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 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.

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***

Specific points to consider

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, or 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 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 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-ASPAs 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 ASPA², 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);

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- 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 zoo's, museum's, 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 super ovulate animals such as pregnant mare serum.;
- below threshold studies on animals 'protected' by ASPA²; projects on invertebrates other than cephalopods, or immature developmental stages of vertebrates.

The ethical and animal welfare considerations relating to each of these points is 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”²⁷. In relation to fetal calf serum, The Netherland National committee for the protection of animals used in scientific procedures has created a short video²⁸ 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 antibodies²⁹. The European Reference Laboratory for alternatives to animal testing (EURL-ECVAM) has therefore recently published recommendations on the use of non-animal derived antibodies³⁰.

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 ASPA² (160 at the end of 2019⁶) 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 ASPA². 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 ASPA². 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).

Specific points to consider

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*”³¹ 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.)

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

Specific points to consider

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]

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 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)

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.

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 Bioethics³² and more recently The Royal Society (visit <https://royalsociety.org/topics-policy/projects/research-culture/> for more information), the Wellcome Trust (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 care³³ being placed by the ASRU inspectorate¹⁵ 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 International Culture of Care Network (visit <https://norecopa.no/coc>).

This is in part a response to recommendations contained within the Brown Report³⁴ 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*”³⁴ 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 56³⁴).

“*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 57³⁴). 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 has also published a symposium report discussing research culture: *Reproducibility and reliability of biomedical research: improving research practice*³⁵. 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 detail of study methods, 6) post-publication review and 7) reporting guidelines. Some examples of progress in these areas are illustrated on the following pages.

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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 40³⁵). The UK research funders are unanimous that “researchers should ensure that they report animal-based studies in accordance with the ARRIVE guidelines” (see page 21⁴).

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 2010³⁶⁹. 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 data³⁷⁶

The *Concordat on Open Research Data*³⁷⁶ 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

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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 reported³⁷⁸. 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 guidelines²⁵

The PREPARE (*Planning Research and Experimental Procedures on Animals: Recommendations for Excellence*) guidelines²⁵ 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

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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 Kings 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 grass roots, peer-led organisation that was formed with small grants from the UK Research Integrity Office, Universities UK, the Wellcome Trust, 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 means 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/>.

References

- 1. Section 3.8 Research involving animals - Code of Practice for Research** UKRIO
<http://ukrio.org/publications/code-of-practice-for-research/3-0-standards-for-organisations-and-researchers/3-8-research-involving-animals/>
- 2. Animals (Scientific Procedures) Act 1986** (2012) Home Office
<http://www.legislation.gov.uk/ukpga/1986/14/contents>
- 3. Guidance on the Operation of the Animals (Scientific Procedures) Act 1986** (2014) Home Office
https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/662364/Guidance_on_the_Operation_of_ASPA.pdf
- 4. Responsibility in the use of animal in bioscience research: Expectations of the major research council and charitable funding bodies** (2019) NC3Rs
<https://www.nc3rs.org.uk/responsibility-use-animals-bioscience-research>
- 5. Directive 2010/63** (2010) Council of the European Parliament <https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A32010L0063>
- 6. Annual Statistics of Scientific Procedures on Living Animals Great Britain 2019** (2020) Home Office
<https://www.gov.uk/government/statistics/statistics-of-scientific-procedures-on-living-animals-great-britain-2019>
- 7. Attitudes to Animal Research – a long-term study of public views 1999-2014** (2014) IPSOS MORI Social Research Institute
https://www.ipsos.com/sites/default/files/migrations/enuk/files/Assets/Docs/Polls/sri_BISanimalresearch_TRENDreport.pdf
- 8. Public Attitudes to Science 2019** (2020) Department for Business, Energy and Industrial Strategy
https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/905466/public-attitudes-to-science-2019.pdf
- 9. Public Attitudes to Animal Research in 2016** (2016) IPSOS MORI Social Research Institute
<https://www.ipsos.com/sites/default/files/publication/1970-01/sri-public-attitudes-to-animal-research-2016.pdf>
- 10. Public attitudes to animal research under COVID-19** (2020) Understanding Animal Research
https://www.understandinganimalresearch.org.uk/files/3315/8687/3612/attitudes_to_animal_research_under_covid-19_final.pdf
- 11. Concordat on Openness on Animal Research in the UK** (2014) Understanding Animal Research
<http://concordatopenness.org.uk/wp-content/uploads/2017/04/Concordat-Final-Digital.pdf>
- 12. Concordat on Openness on Animal Research in the UK Annual Report 2017** (2017) Understanding Animal Research
<http://concordatopenness.org.uk/wp-content/uploads/2017/12/Concordat-Report-2017.pdf>
- 13. Veterinary Medicines Regulation** (2013)
<http://www.legislation.gov.uk/uksi/2013/2033/contents>
- 14. Code of practice for the Housing and Care of Animals Bred, Supplied or Used for Scientific AWERB Purposes** (2014) Home Office
<https://www.gov.uk/government/publications/code-of-practice-for-the-housing-and-care-of-animals-bred-supplied-or-used-for-scientific-purposes>

References

15. **Identification and management of patterns of low-level concerns at licensed establishments** (2015) Home Office
https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/512098/Patterns_low-level_concerns.pdf
16. **Animals in Science Regulation Unit Compliance Policy** (2017) Home Office
https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/670174/ASRU_Compliance_Policy_December_Final.pdf
17. **Animals in Science Regulation Unit Annual Report 2018** (2020) Home Office
https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/887289/Animals_in_Science_Regulation_Unit_annual_report_2018.pdf
18. **The principles of humane experimental technique** (1959) W. M. S. Russell & R. L. Burch
http://altweb.jhsph.edu/pubs/books/humane_experiment-to-c
19. **Statistical Experiment Design for Animal Research** (2019) C. O. S. Sorzano & M. Parkinson
<http://i2pc.es/coss/Articulos/Sorzano2018d.pdf>
20. **The design and statistical analysis of animal experiments** (2014) S. T. Bate & R. A. Clarke. Cambridge University Press
<https://doi.org/10.1017/CBO9781139344319>
21. **The Design of Animal Experiments** (2016) Sage Publishing <https://uk.sagepub.com/en-gb/eur/the-design-of-animal-experiments/book252408>
22. **Refinement: lessons from the 2012 Olympics** (2013) E. Lilley & M. Jennings. *Perspectives in Laboratory Animal Sciences* (paywall)
<https://doi.org/10.1177/026119291304100309>
23. **Refinement: promoting the Three Rs in practice** (2008) M. H. Lloyd, B. W. Foden & S. E. Wolfensohn. *Laboratory Animals* 42 (3) 284-293
<http://journals.sagepub.com/doi/pdf/10.1258/la.2007.007045>
24. **Review of harm-benefit analysis in the use of animals in research, Summary of recommendations for AWERBs** (2020) Animals in Science Committee Harm-Benefit Analysis Sub-Group
<https://www.gov.uk/government/publications/harm-benefit-analysis-review-animals-in-science-committee-report>
25. **PREPARE: guidelines for planning animal research and testing** (2017) A. J. Smith, R. E. Clutton, E. Lilley, K. E. A. Hansen, & T. Brattelid. *Laboratory Animals* 52(2) 135-141
<https://doi.org/10.1177%2F0023677217724823>
26. **Animal By-Products (Enforcement) (England) Regulations (2013)** Home Office
<https://www.legislation.gov.uk/ukxi/2013/2952/contents>
27. **Animal welfare standards expected of suppliers of antibodies to Research Council establishments.** NC3Rs and Research Councils UK
<https://www.nc3rs.org.uk/sites/default/files/documents/Funding/Antibody%20supplier%20policy%20-%20will%20be%20updated.pdf>
28. **Careful use of fetal calf serum, for reliable research results and taking into account.. video (2020)** Netherland National committee for the protection of animals used in scientific procedures
<https://english.ncadierproevenbeleid.nl/latest/news/2020/6/1/1>

References

29. **Animal-derived-antibody generation faces strict reform in accordance with European Union policy on animal use** (2020) Gray, A.C., Bradbury, A.R.M., Knappik, A. et al *Nat Methods* 17, 755–756 <https://doi.org/10.1038/s41592-020-0906-9>
30. **EURL-ECVAM Recommendations on the use of non-animal derived antibodies (2020)** EURL-ECVAM <https://op.europa.eu/en/publication-detail/-/publication/3f74f5ea-94c1-11ea-aac4-01aa75ed71a1/language-en>
31. **UCL policy for research using animals carried out overseas**
<https://www.ucl.ac.uk/research/integrity/research-ethics/outside-the-uk>
32. **The culture of scientific research in the UK** (2014) Nuffield Council on Bioethics
http://nuffieldbioethics.org/wp-content/uploads/Nuffield_research_culture_full_report_web.pdf
33. **Promoting a culture of care: Resource for AWERB Members** (2020) RSPCA
<https://science.rspca.org.uk/documents/1494935/0/PromotingACultureOfCare.pdf/a71b9544-95e7-a3b1-5bee-54ae3019dc66?t=1600448337263>
34. **Independent Investigation into Animal Research at Imperial College London** (2013) S. Brown, P. Flecknell, I. Jackson, M. Leggett, V. Robinson & N. Yates <http://brownreport.info>
35. **Reproducibility and reliability of biomedical research: improving research practice symposium report** (2015) Academy of Medical Sciences, BBSRC, MRC & Wellcome Trust
<https://acmedsci.ac.uk/policy/policy-projects/reproducibility-and-reliability-of-biomedical-research>
36. **Improving Bioscience Research Reporting: The ARRIVE Guidelines for Reporting Animal Research** (2010) C. Kilkenny, W. J. Browne, I. C. Cuthill, M. Emerson, & D. G. Altman. *PLoS Biol* 8(6):e1000412.
<https://doi.org/10.1371/journal.pbio.1000412>
37. **Concordat on Open Research Data** (2016)
<https://www.ukri.org/wp-content/uploads/2020/10/UKRI-020920-ConcordatonOpenResearchData.pdf>
38. **Publication bias in reports of animal stroke studies leads to major over statement of efficacy** (2010) E. S. Sena, H. B. van der Worp, P. M. W. Bath, D. W. Howells & M. R. Macleod. *PLoS Biol.* 8(3):e1000344.
<https://journals.plos.org/plosbiology/article?id=10.1371/journal.pbio.1000344>



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