National Centre
for the Replacement
Refinement & Reduction
of Animals in Research

Choosing contractors for animal research: expectations of the major UK public funders

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Pioneering Better Science

Aims of this presentation

- This presentation is aimed at researchers proposing to use animals overseas in applications for funding to any of the organisations below, all of which use the NC3Rs peer review and advice service:

- It has been produced to help applicants understand the requirements of the funding bodies with regard to standards of animal welfare and study design, including for preclinical studies at contract research organisations.

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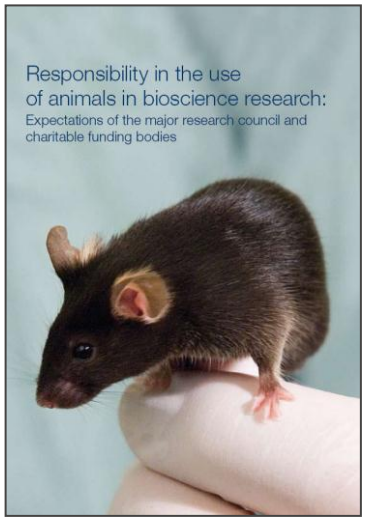
Expected animal welfare standards

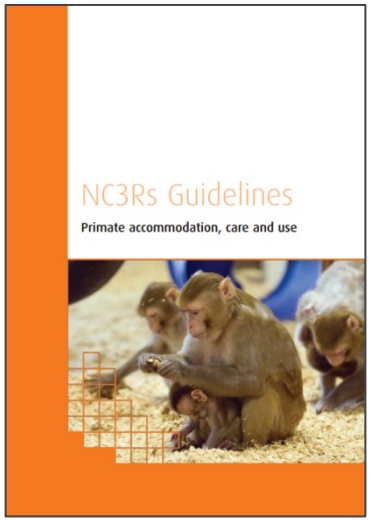
- Applicants aiming to conduct animal research outside of the UK should be aware that compliance with local regulations (e.g. USA Animal Welfare Act and ILAR Guide), and accreditation from organisations such as AAALAC, do not substitute for compliance with the guidelines adopted by the UK funding bodies, namely:

  Responsibility in the Use of Animals in Bioscience Research

  NC3Rs Guidelines: Primate Accommodation, Care and Use

- A key principle of these guidelines is that animal welfare standards consistent with those provided under UK legislation (e.g. UK ASPA) must be applied and maintained, wherever the work is conducted.





Enclosure sizes and space allocations

- This means that enclosure sizes and space allocations should be at least equivalent to those in Annex III to Directive 2010/63/EU* (and preferably meet those in the UK Home Office Code of practice for the housing and care of animals bred, supplied or used for scientific purposes). Note in the case of macaques and dogs, and depending on the circumstances, this can mean minimum space allocations 5 to 12 times larger than those in the ILAR Guide.

Dogs

Directive 2010/63/EU			ILAR Guide	
Weight, kg	Minimum enclosure size, m^2 (ft^2)	Minimum floor area for 1-2 animals, m^2 (ft^2)	Weight, kg	Floor area per animal, m^2 (ft^2)
≤20	4.0	4.0	<15	0.74 (8.0)
>20	8.0	8.0	≤30	1.2 (12.0)

Macaques

Directive 2010/63/EU				
Age, years	Minimum floor area, m^2 (ft^2)	Minimum height, m	Minimum enclosure volume, m^3 (ft^3)	Minimum volume per animal, m^3 (ft^3)
<3	2.0	1.8	3.6	1.0
≥3	2.0	1.8	3.6	1.8
ILAR Guide				
Weight, kg	Minimum floor area per animal, m2 (ft2)	Minimum height, m (ft)	-	Minimum volume per animal, m3 (ft3)
≤3	0.28 (3.0)	0.76 (3.0)	-	0.21 (9.0)
≤10	0.4 (4.3)	0.76 (3.0)	-	0.30 (12.9)

* Transposed from Appendix A of Convention ETS 123

Other housing and husbandry requirements

- There are many other principles that must be met. For example, environments for the animals must be properly enriched to allow for performance of a wide range of natural (species-specific) behaviour; single housing and grid floors are not permitted (save for exceptional reasons); and higher mammals must be well habituated to humans and trained for voluntary co-operation with scientific and husbandry procedures using positive reinforcement techniques.

- UK experience demonstrates that animal welfare provisions such as these rarely conflict with the demands of the science. Hence, exemptions that have been granted by the local IACUC can and will be challenged.

Your responsibilities

- Compliance against the required standards will be assessed by the NC3Rs as part of our input into the peer review processes of the funding bodies. **Failure to meet the standards could lead to your application being declined or delays in receiving any grant award.**

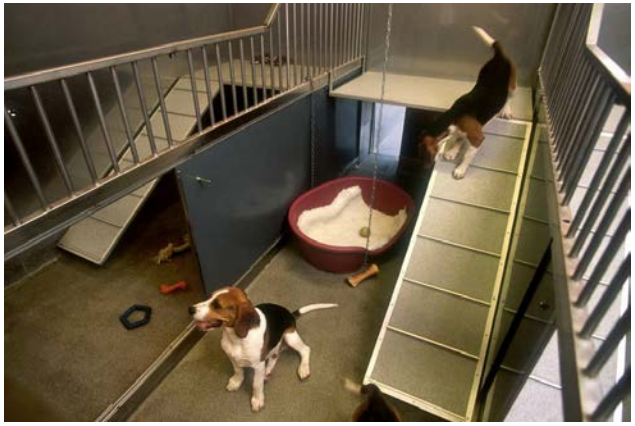
➢ Please ensure you read and satisfy the guidelines before submitting your application.

➢ Where you are contracting research to others, compliance with the required welfare standards is your responsibility and should be a factor in your choice of contractor.

➢ Please ensure you give full answers to all of the animal use questions in the funders' application form.

- Examples of the types of housing and husbandry for dogs and macaques that are acceptable (and those that are not) are given on the following slides.

Dogs – acceptable



Pens designed to meet the behavioural needs of the dog. Note the pair housing, pen space, raised platform, bed with fleecy bedding, chews and toys, visual barriers and access to outdoors.

Dogs should receive at least 20 minutes per day socialisation and exercise out of the pen with larger groups of dogs, preferably in a dedicated and enriched play area, under staff supervision. Such areas increase environmental stimulation and choice for the dogs and should be used in preference to leaving dogs in their pens.

For further information and guidance on appropriate conditions for dogs, see Prescott et al. 2004, Scullion-Hall et al. 2016, and the NC3Rs website

Dogs – not acceptable

It is not acceptable to house dogs in small, metal cages. Grid floors are not allowed without strong scientific justification. This cage also lacks environmental enrichment.

Single housing is not acceptable. Most safety assessment studies can be completed with pair/group housed dogs, with only short periods of temporary separation (maximum 4 hours) for feeding and post-dose observation of clinical signs. For cardiovascular studies, telemetered dogs (and NHPs) can be housed with naïve companions, or else newer systems used that permit group housing by transmitting data on different frequencies.

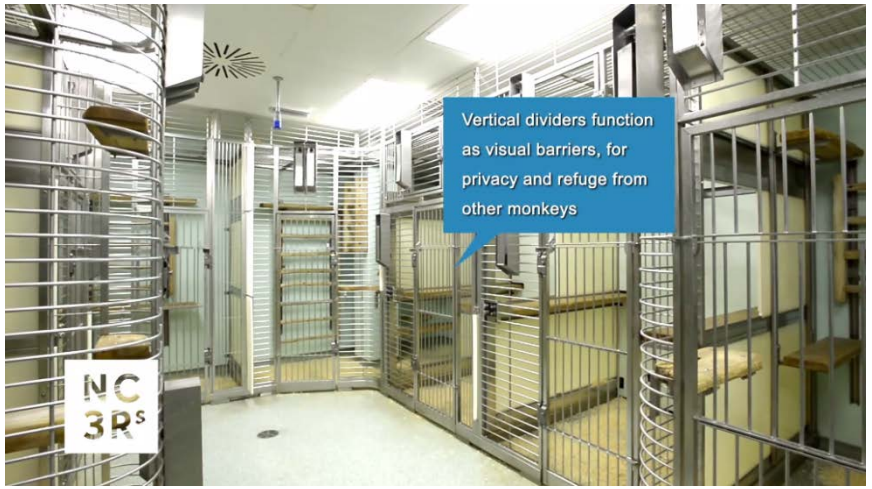
For further information and guidance on appropriate conditions for dogs, see Prescott et al. 2004, Scullion-Hall et al. 2016, and the NC3Rs website

Macaques – acceptable

Gang housing system for macaques on toxicology studies, with sufficient space and complexity to permit a range of natural, species-specific behaviours and social housing in stable groups. The pens are floor-to-ceiling high with elevated verandas for resting above human eye level. Note also the catching box on the left. Macaques are less aggressive and more cooperative in such caging.

Floors should be solid, and covered with substrate such as wood shavings into which fine food items can be scattered, to promote natural foraging behaviour for psychological wellbeing.

For further information on best practice for indoor caging of macaques, including perceived problems with EU style pen housing and how to overcome them, see: www.nc3rs.org.uk/macaques/captive-management/housing/



Features of a high quality caging system

For further guidance on appropriate conditions for macaques and other non-human primates, see Jennings & Prescott 2009, Chapman et al. 2015, and the NC3Rs Macaque Website resource.

Macaques – not acceptable

It is not acceptable to house macaques in small, double-tiered caging with grid floors. Single housing is also usually not acceptable; toxicology and safety studies are routinely conducted with group housed macaques in the EU and elsewhere. Individual food consumption data are usually not needed; for biologics, urinalysis is a largely irrelevant end point and has been omitted from studies without comment from EU regulators. A mirror, kong toy and perch is not sufficient environmental enrichment.

Improvement case studies

Additional space and complexity can be provided by adjoining a purpose-built play area to a bank of caging, like the one on the left constructed cheaply of sturdy wood and thick mesh.

In some cases, it is possible to customise existing housing and husbandry in order to provide an acceptable standard of welfare. For example, in the case of conventional metal caging, by combining adjacent cage units to increase the space to the EU minimum, converting the grid floor to a solid one and using floor substrate for foraging, providing additional structural enrichment (e.g. verandas, panels, perches, swings) and destructible materials, such as wood and cardboard.

Use of rodents

- Occasionally applications involving the use of rodents overseas will be referred to the NC3Rs for review.
- We take a pragmatic approach requiring completion of a checklist, which balances the burden on applicant and the NC3Rs with the desire of the funders for scrutiny of the planned animal use.
- Again, standards equivalent to the UK ASPA are required.

Additional questions on the use of rodents overseas

The expectations of the major UK public funding bodies for the use animals in bioscience research are set out in the document 'Responsibility in the Use of Animals in Bioscience Research'. Compliance with the principles in this document is a condition of receiving funds for animal research. Welfare standards consistent with the principles of UK legislation must be applied and maintained, wherever the work is conducted.

Please confirm the following: (Y/N)

1. The enclosure sizes and space allocations meet or exceed those in Annex VII to Directive 2010/63/EU (Tables 1.1 to 1.5)	
2. Rodents are provided with: a) substrate/bedding on a solid floor; b) a shelter and/or nesting material for refuge and to help regulate body temperature and light exposure; c) chew blocks or other gnawing material.	
3. Rodents are housed socially. Exceptions to this must be justified below.	
4. Appropriate, contemporary anaesthesia and/or analgesia is provided to minimise pain and distress. Any withholding of pain relief during painful procedures must be justified below.	
5. Surgery is performed using aseptic technique, the least invasive surgical approaches, and appropriate perioperative care (pre-operative medications, hypothermic prevention, ophthalmic protection, nursing care where required).	
6. Toe clipping and/or tail biopsy are not used for identification or genotyping purposes.	
7. Where genotypes are known to be harmful, animals of that type are not produced unless required scientifically (e.g. if homozygous null is harmful and heterozygotes are desired, then heterozygous is crossed with wild type, not another heterozygous animal).	
8. Where new GA strains are being generated, best knowledge will be applied to predict potential harmful outcomes and the animals will be monitored closely for emerging phenotypes.	
9. Animals are monitored with a frequency appropriate to keep pain and distress to a minimum, using appropriate, tailored welfare indicators and score sheets.	
10. Humane endpoints have been established for each experiment with the potential to cause moderate or severe harm, after consultation with the veterinarian and animal care staff, and implementation of these is recorded during the experiment. (Note the humane endpoint criteria may be requested by the Wellcome Trust).	
11. The methods of humane killing are those recommended by the AVMA (2013) or permitted under Directive 2010/63/EU.	

Where there are deviations from the above, please explain below:

Design of preclinical studies

- Although regulatory guidelines require toxicology data in two species before first-time-in-man studies, the guidelines are not prescriptive about how the studies are done and there is much scope for implementing the 3Rs.
- The NC3Rs plays a leading role in identifying such 3Rs opportunities, as part of its collaborative data sharing projects with the pharmaceutical industry and regulators internationally.
- As part of the NC3Rs review of your application, you will be asked about meeting the recommendations from relevant NC3Rs-industry projects.

Example

Typical mAb safety evaluation programme using 144 NHPs

Dose group	Low	Medium	High	Control
Number of animals	4♂ + 4♀	4♂ + 4♀	4♂ + 4♀	4♂ + 4♀
Number of recovery animals	2♂ + 2♀	2♂ + 2♀	2♂ + 2♀	2♂ + 2♀
Total for one study				48
Total per programme (three studies)				144

New paradigm from NC3Rs that reduces NHP use without compromising the programme

Dose group	Low	Medium	High	Control
Number of animals	3♂ + 3♀	3♂ + 3♀	3♂ + 3♀	3♂ + 3♀
Number of recovery animals			2♂ + 2♀	2♂ + 2♀
Total for one study				32
Total per programme (two studies)				64

Chapman et al. 2012

Recommendations from NC3Rs-industry projects

- There are many opportunities to apply the 3Rs in safety assessment studies without compromising the drug development process, regulatory requirements or human safety.
- Be sure to read the papers at: www.nc3rs.org.uk/animals-drug-discovery-and-development

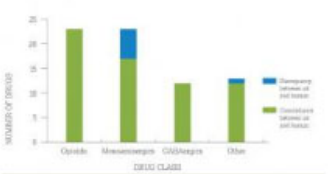
Monoclonal antibody development

Reducing the use of non-human primates in the development of biotherapeutics

Reducing the use of recovery animals

Strategies to minimise the use of recovery animals

Abuse potential studies

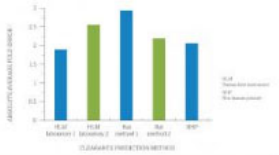


Avoiding the use of non-human primates.

Refining MTD studies

Recommendations for maximum body weight loss limits for the rat,dog and non-human primates

Pharmacokinetics in candidate selection

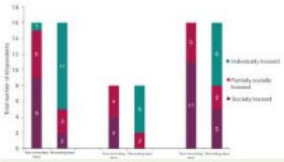


Replacing and reducing animal use for pharmacokinetic analysis of hepatically and renally cleared compounds

Microsampling

Guidance on microsampling

Social-housing during non-rodent telemetry recordings



Guidance on best practice and recommendations for telemetry recordings from socially-housed non-rodents.

Gathering the required information

- Speak to the scientists and veterinarians/animal welfare officers who will oversee your research at the contract research organisation. They are more likely to have the required information and to be up-to-date with 3Rs advances than are initial contacts within the marketing/business development team. Use the questions in the funder's application form to guide your discussion.
- Ensure that the potential contractor understands and can deliver what is required, especially if there are language difficulties. Where improvements are necessary, do they have the appropriate knowledge and skills to deliver them.
- Request up-to-date photos of the enclosures and areas that will be used for the animals on your study. Most companies will share this information with prospective clients.
- Consider visiting the animal facilities – this is the most robust way of ensuring the funders' requirements can be met.
- Since the funders expect animal welfare standards consistent with those provided under UK and EU legislation, UK and EU contract research organisations are the most likely to be able to meet the required standard.

Checklist

- ✓ Have you read and applied the guidelines adopted by the funding bodies as a condition of research funding, namely ‘Responsibility in the Use of Animals in Bioscience Research’?
- ✓ If your application involves use of non-human primates, have you read and applied the ‘NC3Rs Guidelines: Primate Accommodation, Care and Use’?
- ✓ If you are contracting animal studies to a contract research organisation (CRO), does the chosen CRO meet the requirements of the funding body?
- ✓ Are the animal welfare standards equivalent to those provided in the UK? Are you able to justify any exceptions?
- ✓ Are you, and the CRO on your behalf, implementing the recommendations of the NC3Rs-pharmaceutical industry projects? (where relevant)
- ✓ Have you given appropriate answers to all of the animal use questions in the funder’s application form?

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Questions: enquiries@nc3rs.org.uk