



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

Experiences from the UK 3Rs Centre – the NC3Rs

Dr Ian Ragan

NC3Rs Board member

Overview

- Background to the NC3Rs and its strategy
- CRACK IT
- Experimental design and reporting
- Institutional activities

NC3Rs – the headlines

- Established in 2004 by the UK Government
- Research funder plus in-house programmes
- Works across biosciences with industry, academia, regulators & funders
- 24 staff based in London
- Budget ~ £10 million p.a.



Last ten years: big changes in how the 3Rs are perceived in the UK

- Many scientists at all levels involved across the biosciences
- Active engagement from most of key organisations in public and private sectors
- Increased investment in the 3Rs
- New collaborations, cross-sector and cross-discipline
- UK seen as a world leader
- Delivering measurable 3Rs impacts and also supporting new scientific discoveries, technological advances and commercial opportunities

The 3Rs are relevant to today's needs

Pharmaceutical industry

- High attrition rates, often late in development
- Relative lack of new drugs, increasing costs
- Animal models cited as bottlenecks for efficacy & safety

Chemicals industry

- Conflicting legislation (e.g. cosmetics & REACH) & geographical requirements
- Utility of current testing paradigm controversial, little change in 40 yrs
- Need for high through-put screens not possible *in vivo*

Publicly funded research

- Emphasis on translation & exploitation (need appropriate models)
- Need to improve conduct of *in vivo* research

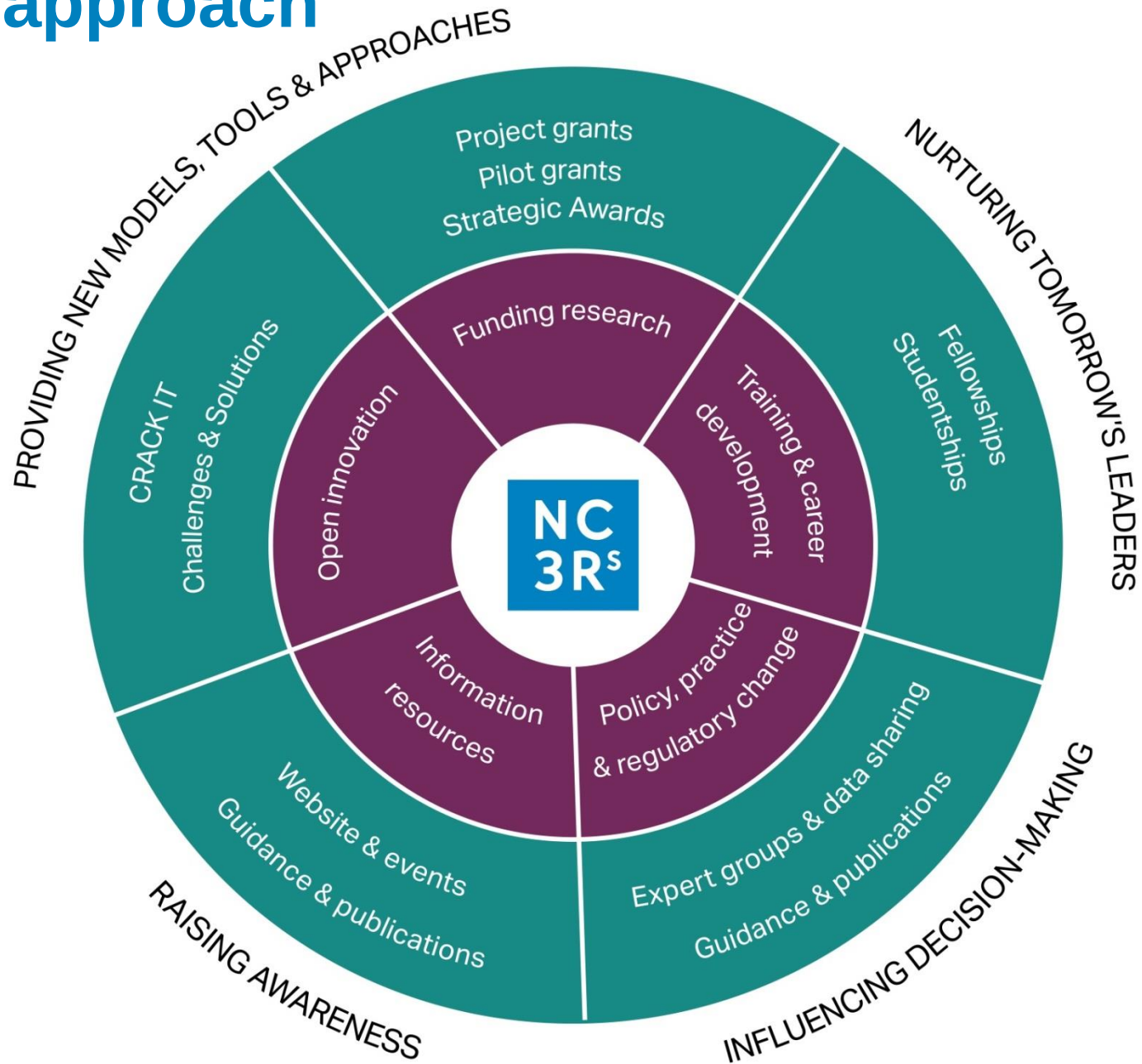
Political & societal concern

- Opportunities to address concerns & gain support

Challenges for the 3Rs

- Historically little scientific support or interest in the 3Rs
- Anti-vivisection groups 'owned' the 3Rs agenda
- Regulation controlling animal use can be used as 'screen' to hide behind
- Scientific process - intrinsically supports continued animal use, even where animal models are 'poor'
- Finding alternatives is not trivial
- Regulatory conservatism on risk assessment
- Operating in international arena - attitudes to animal use vary

Our approach



Role as research funder

Hypothesis-driven basic research	Early career development	Infrastructure
Project Grants	Studentships	Infrastructure for impact
Pilot Grants	David Sainsbury Fellowships	
Strategic Awards		



Research funding headlines

Sept 2004 – November 2015

236 major
awards

totalling
>£50 million

>450
investigators

>60 research
organisations

93% to
universities

85 students
and fellows

Does not include CRACK IT awards

The scientists we fund



"We now have a model that avoids paralysis in our mice and has also led to the development of a new clinical trial design."

DAVID COOPER
Professor in Neurotechnology
Imperial College London

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and Reduction of Animals in Research



"Our *in vitro* model challenges the traditional dogma that animal studies of spinal cord injury can never be replaced."

DRY GARDNER
Professor in Cellular Neuroscience
University of Glasgow

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and Reduction of Animals in Research

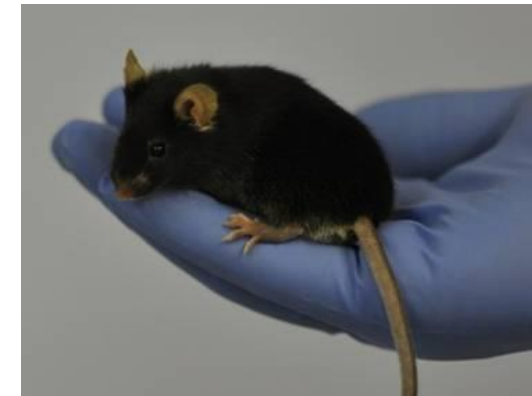
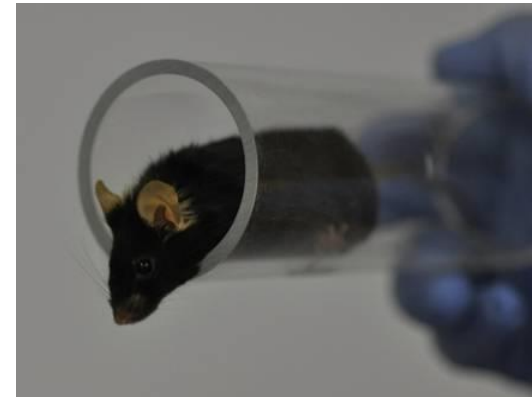
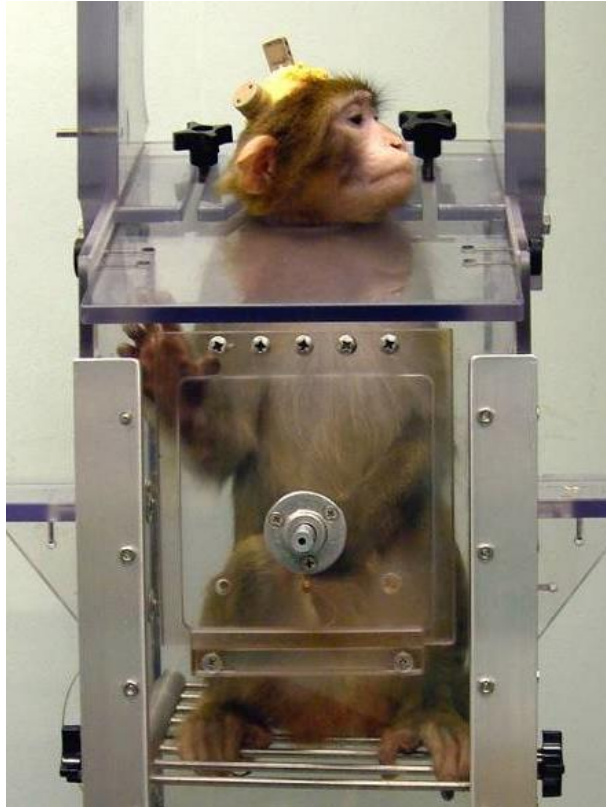


"We have combined three cutting edge technologies to use tissue from patients as an alternative to animals for studying asthma."

DAVID COOPER
Professor in Respiratory Cell and Molecular Biology
University of Southampton

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and Reduction of Animals in Research

Funding for evidence base to support animal welfare and link with science



Support with online resources and e-learning

Menu

- 1. Introduction
 - 1.1. Title
 - 1.2. Welcome
 - 1.3. Section 1 Aims
 - 1.4. Intro to Module
 - 1.5. Intro to Anaesthesia
 - 1.6. Q. 1 & 2**
 - 1.7. Q. 3 & 4
- 2. Planning
- 3. Injectables
- 4. Inhalational
- 5. Post-Op

EU20_Web_v.0.1

Glossary Resources

LABORATORY ANIMAL ANAESTHESIA

Introduction

The lab manager takes you to meet the students.



Hi, I'm Matt. Can you answer a few questions for me?

- 1. Anaesthesia is defined as?**
 - ☐ A loss of pain perception
 - ☐ A loss of sensation
 - ☐ A loss of consciousness
- 2. During general anaesthesia, blood pressure is often:**
 - ☐ Increased, because of the stress caused by anaesthesia.
 - ☐ Unchanged from the level before anaesthesia
 - ☐ Depressed, because of the effects of anaesthetic agents

Submit



Data sharing for 3Rs benefits

- Role as an honest broker for data sharing between companies, regulators and academic groups
- Areas include toxicology studies, safety pharmacology, disease models – expert working groups
- Data shared include confidential and non-confidential information, study designs e.g. animal numbers, endpoints
- Delivered changes in practice and regulations
- More than 100 organisations, national and international, involved in data sharing activities
- Example of impact – single dose acute toxicity

Are conventional single dose acute toxicity studies needed?

- Used in pharmaceutical and chemical development
- Pharmaceuticals - used to determine target organ toxicity, set doses for further animal studies, set starting dose in man, help treat overdose
- Shared data from 18 companies, 70 compounds
- Most companies used two species, two routes

Regulatory framework

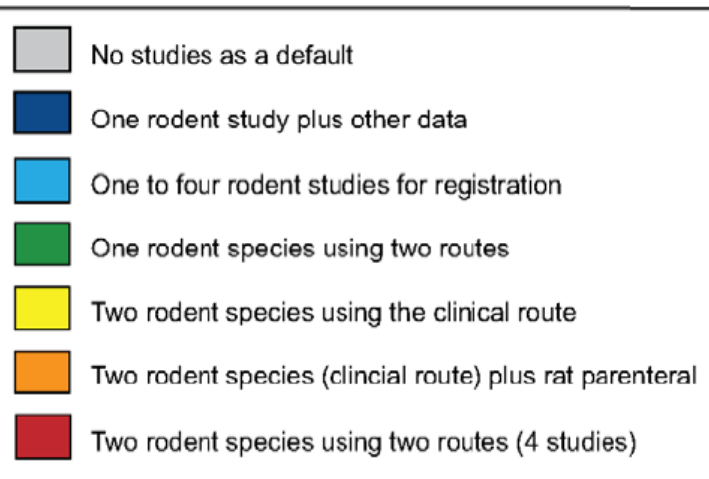
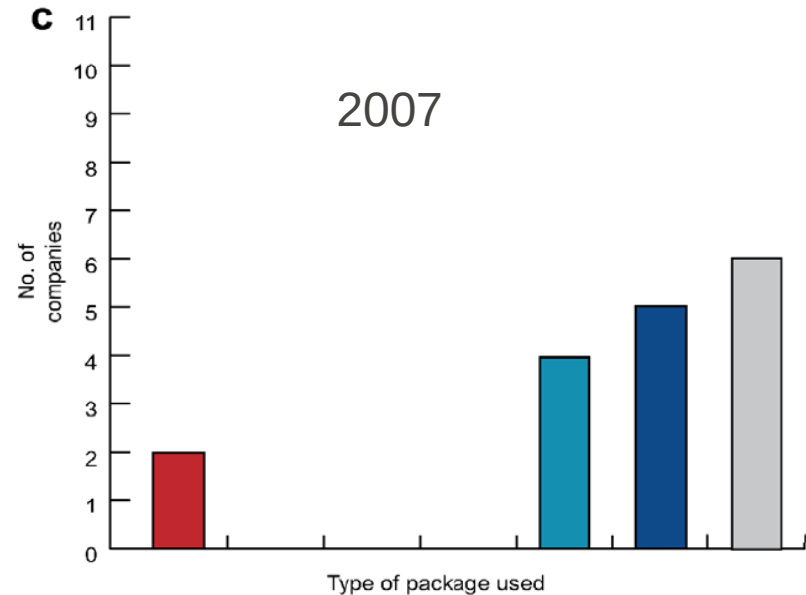
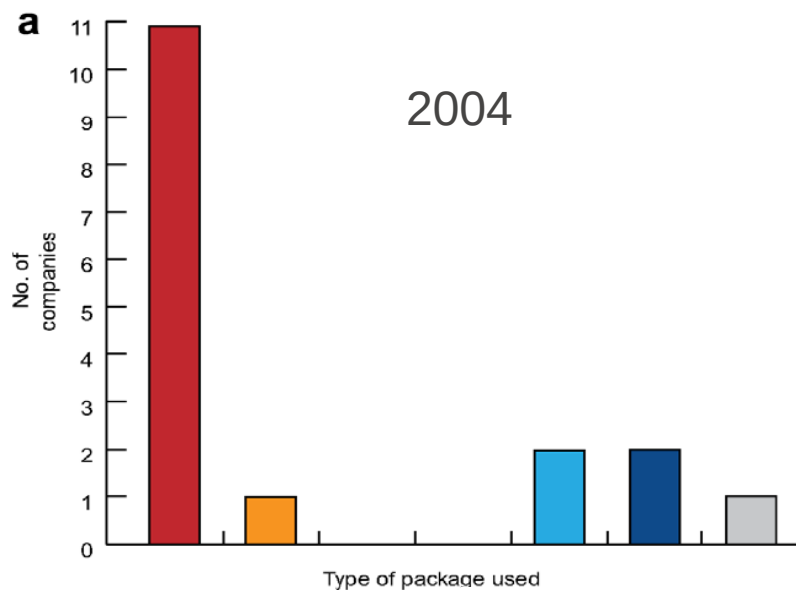
EEC	US	Japan
2 Species ^a	2 Species ^b	2 Species ^b
2 Routes, clinical route plus a route ensuring exposure ^c	2 Routes (as EEC)	Clinical
7–14-Day observation	14-Day observation	14-Day observation

Findings from data sharing

- Extremely limited with regard to the parameters examined
- No used in practice to set doses for other animal studies
- Do not provide information on the nature of toxic effects
- Not used in practice to set doses in the first human clinical trial
- Other studies routinely carried out in drug development are more informative



Shift in industry practice – prior to regulatory change



Regulatory change to ICH M3 in 2009

The proportion of clinical trial applications for drugs going into humans for the first time in the UK which contain the results from conventional single dose acute toxicity tests.

2007	2011	2012	2013
86%	58%	20%	16%
(67/78)	(76/132)	(27/134)	(15/93)

CRACK IT

CRACK IT

- Collaborative funding scheme from the NC3Rs connecting the industrial, academic and SME sectors
- Aims to improve business processes and develop marketable products
- **CRACK IT Challenges** solve scientific and business problems identified by the biosciences sector
- **CRACK IT Solutions** is a technology partnering hub designed to accelerate the translation of technologies with potential 3Rs impacts

CRACK IT Challenges: the process

3Rs problem - the Challenge - with business benefit proposed by Sponsors

Sponsors are typically from industry and will be the immediate end-user



Challenge-led competition for academics and SMEs with deliverables defined by sponsors

Consortia with access to science base plus route to market



Up to four Phase 1 winners receive £100k for six months

NC3Rs funding plus in-kind contributions from sponsors



One winner for Phase 2 selected by Dragons' Den Panel – up to £1 million over three years

NC3Rs funding plus in-kind contributions from sponsors – milestone-driven



Marketable product or service with 3Rs benefits

CRACK IT Challenges to date

- Launched in 2011
- 21 Challenges
- High levels of SME involvement (60 to 90% in 2012)
- ~£15 million invested
- 18 large industry Sponsors, 1 academic Sponsor, 1 research charity
- Some organisations have provided additional funding for Challenges



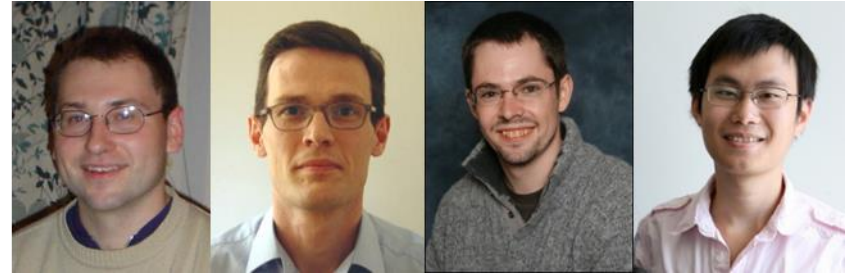
CRACK IT Sponsors



CRACK IT Challenge: Cognition

A miniature wireless EEG system for continuous monitoring of mice brainwave activity

Imperial College
London



"This is an incredibly exciting and challenging project pushing the boundaries of microelectronics design. CRACK IT is a great opportunity to make people think out of the box in order to find solutions to research problems which will have a massive impact."

Esther Rodriguez Villages, Imperial College London

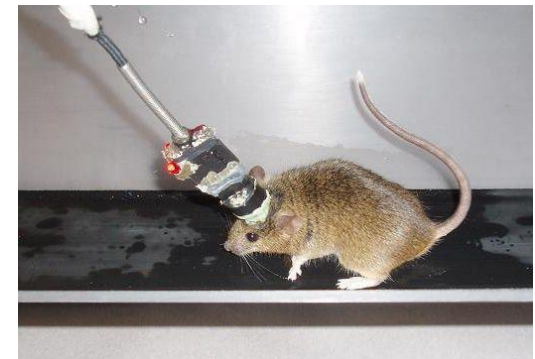


"CRACK IT has been one of the most rewarding projects I've ever participated in, and it is genuinely exciting from a scientific perspective. The NC3Rs and Lilly have found an excellent team in Esther and her colleagues, and this ability to quickly match the best scientific minds to pressing industry needs is what makes CRACK IT exceptional."

John Huxter, Lilly scientist

NC
3R^s

Lilly



Experimental design and reporting

Background – NC3Rs study

Quality of published animal research

Experimental design

Only 12% of publications report randomisation and 14% report blinding

Sample size justification – missing in 100%



Statistical analysis

Only 70% of publications fully described the statistical methods and presented the results with a measure of variability



Reporting of studies

Animal characteristics – missing in 25%

Only 59% stated the study hypothesis, number and characteristics of animals used



Survey reviewed 271 publications and identified key areas for improvement

Kilkenny C, Parsons N, Kadyszewski E, Festing MF, Cuthill IC, Fry D, *et al.* (2009). Survey of the quality of experimental design, statistical analysis and reporting of research using animals. *PLoS One* 4(11): e7824.

The ARRIVE guidelines and the Experimental Design Assistant (EDA)

ARRIVE

EDA

Experimental
Design
Assistant

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of Animals in Research

The ARRIVE Guidelines

Animal Research: Reporting of In Vivo Experiments

The ARRIVE (Animal Research: Reporting of In Vivo Experiments) guidelines were developed as part of an NCRR initiative to improve the design, analysis and reporting of research using animals - maximising information published and minimising unnecessary studies. The guidelines were published in the online journal *PLoS Biology* in June 2010 and are currently endorsed by scientific journals, major funding bodies and learned societies.

The guidelines are intended to	The guidelines are NOT intended to	What kind of research uses the guidelines apply to?	How might these guidelines be used?	Acknowledgements
- Improve reporting of research using animals - Guide authors as to the essential	Provide uniformity, either creating or discouraging authors to follow specific standards in the checklist. Some of the text	The guidelines will be most appropriate for comparative studies, where most or many groups of experimental animals are	The guidelines provide a checklist for those preparing to submit a manuscript for publication	The NCRR gratefully acknowledge the expertise and advice that all the authors have been given in developing the guidelines. We would particularly like

ITEM	RECOMMENDATION	Comments and Guidance
1. Title	Provide an accurate and concise title that describes the content of the article.	
2. Abstract	Provide an accurate summary of the background, research objectives, including details of the methods used, results and conclusions of the study.	
3. Introduction	- Introduce authors to the research background including relevant references to previous work and the current study. - Introduce the aims and objectives of the study and the experimental approach. - Introduce the methods used and the experimental approach.	
4. Objectives	Clearly describe the primary and any secondary objectives of the study or the experimental approach.	
5. Methods	Introduce the nature of the experimental procedures, relevant literature (e.g. Animal Research: Reporting of In Vivo Experiments) and the experimental approach.	
6. Study design	- The experimental design and details of the study design including: a. The number of experimental and control groups. b. The randomisation method used to allocate animals to the different groups. c. The experimental units (e.g. single animal, group or cage of animals). d. The experimental units (e.g. single animal, group or cage of animals).	
7. Experimental procedures	- Describe the experimental procedures used in the study, including details of the experimental procedures used in the study. - Describe the experimental procedures used in the study, including details of the experimental procedures used in the study.	
8. Experimental results	- Provide the experimental results for each experimental group, including details of the experimental results for each experimental group, including details of the experimental results for each experimental group. - Provide the experimental results for each experimental group, including details of the experimental results for each experimental group, including details of the experimental results for each experimental group.	
9. Discussion	- Summarise the results of the study, including details of the experimental results for each experimental group, including details of the experimental results for each experimental group. - Provide the experimental results for each experimental group, including details of the experimental results for each experimental group, including details of the experimental results for each experimental group.	

NC
3R^s

ARRIVE

Animal Research: Reporting of In Vivo Experiments. Originally published in *PLoS Biology*, June 2010.

EDA

Experimental
Design
Assistant

NC
3R^s

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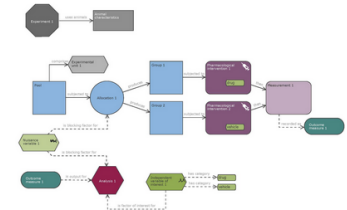
HOME ABOUT EDA USER GUIDE EXPERIMENTAL DESIGN FEEDBACK EDA APP

SEARCH

The Experimental Design Assistant is a web application to support the efficient design of animal experiments, providing dedicated support for sample size calculations, randomisation and blinding.

The EDA allows you to build a stepwise visual representation of your experiment. This, combined with specific feedback and advice on the experimental design, allows you to analyse, review and change your plans - ensuring robust study design and reliable and reproducible findings.

Check the [video tutorial](#) and the [user guide](#) for general information on the EDA process.



Step 1

Login or Register

Start using the EDA application

Step 2

Plan your experiment as a diagram

Check the [examples](#) and the [user guide](#) for more information

Step 3

Critique your design

The critique function enables you to get feedback and advice on your diagram, find more information [here](#)

Step 4

Improve your design

Modify your experimental plan based on feedback from the system

Accessibility

Contact

Terms and Conditions

Data Protection and Privacy

The ARRIVE guidelines

Animal Research: Reporting of *In Vivo* Experiments

The ARRIVE guidelines were developed to improve the reporting of biomedical research using animals.

- Checklist of 20 items, containing key information necessary to describe a study comprehensively and transparently.
- Consensus between:
 - Scientists
 - Statisticians
 - Journal editors
 - Research funders
- Used to ensure reproducibility of animal research and avoid unnecessary animal use.



Our ARRIVE resources



The ARRIVE Guidelines Checklist

Animal Research: Reproductive Physiology, Development, Behaviour and Production of Animals in Research, London, UK; ⁶ School of Veterinary Medicine, University of Bristol, Bristol, UK; ⁷ Department of Veterinary Clinical Science, University of Bristol, Bristol, UK; ⁸ National Institute for Research in Dairying, Shimla, India; ⁹ Department of Veterinary Preclinical Sciences, University of Oxford, Oxford, UK.

GENERAL RESEARCH OBJECTIVES	
Title	1. Provide a concise and brief overview and description of the content of the article
Abstract	2. Provide an overview of the article's content, including research objectives, methodology, results, and conclusions
Introduction	3. Provide an overview of the topic or area of interest, including background information, the purpose or scope of the study, and the research objectives
Methodology	4. Provide a detailed description of the research methodology, including the research design, data collection methods, and data analysis techniques
Results	5. Provide a detailed description of the research results, including the data collected, the statistical analysis performed, and the findings of the study
Discussion	6. Provide a detailed description of the research discussion, including the interpretation of the results, the implications of the findings, and the limitations of the study
Conclusion	7. Provide a detailed description of the research conclusion, including the summary of the findings, the overall conclusions, and the recommendations for future research
References	8. Provide a list of the references cited in the article, including the author, year, and title of the work
Appendix	9. Provide a detailed description of the research appendix, including the data collected, the statistical analysis performed, and the findings of the study
Study design	10. Provide a detailed description of the research study design, including the research objectives, the research questions, the research hypotheses, and the research methods
Empirical	11. Provide a detailed description of the research empirical data, including the data collection methods, the data analysis techniques, and the findings of the study
Empirical	12. Provide a detailed description of the research empirical results, including the data collected, the statistical analysis performed, and the findings of the study
Empirical	13. Provide a detailed description of the research empirical discussion, including the interpretation of the results, the implications of the findings, and the limitations of the study
Empirical	14. Provide a detailed description of the research empirical conclusion, including the summary of the findings, the overall conclusions, and the recommendations for future research
Empirical	15. Provide a detailed description of the research empirical references, including the author, year, and title of the work
Empirical	16. Provide a detailed description of the research empirical appendix, including the data collected, the statistical analysis performed, and the findings of the study

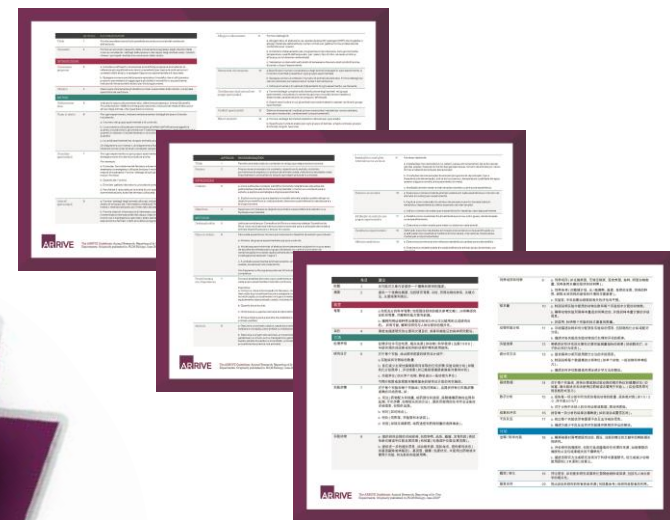
The ADOPT guidelines. Originally published in 1997.



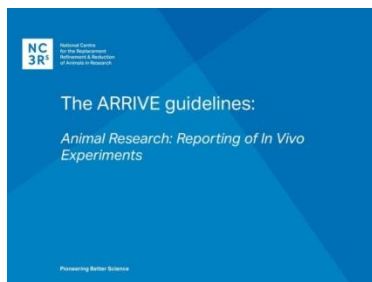
Checklist



Z cards



Translations



Presentation and speaker notes



The ARRIVE guidelines - Examples
Animal Research: Reporting *In Vivo* Experiments

Carol Kilkenny¹, William J Browne², Innes C Cuthill³, Michael Emerson⁴ and Douglas G Altman¹

¹Cardi Research, vietnam 23rd line, street 10, Hanoi, Vietnam; ²Department of Veterinary Medicine, University of Bristol, Bristol, UK; ³The National Centre for the Replacement, Refinement and Reduction of Animals in Research, London, UK; ⁴School of Veterinary Science, University of Bristol, Bristol, UK; ⁵School of Biological Sciences, University of Bristol, Bristol, UK; ⁶National Heart and Lung Institute, Imperial College London, UK; ⁷Centre for Statistics in Medicine, University of Oxford, Oxford, UK.

The ARRIVE guidelines are designed to improve the reporting of animal research. This document demonstrates how the ARRIVE guidelines can be used in practice to report animal research, by providing specific examples for each point of the guidelines. The examples given are from a wide range of research using a range of animal species. Each example has been chosen for meeting the criteria of the checkpoint mentioned and does not imply the entire manuscript complies with the ARRIVE guidelines.

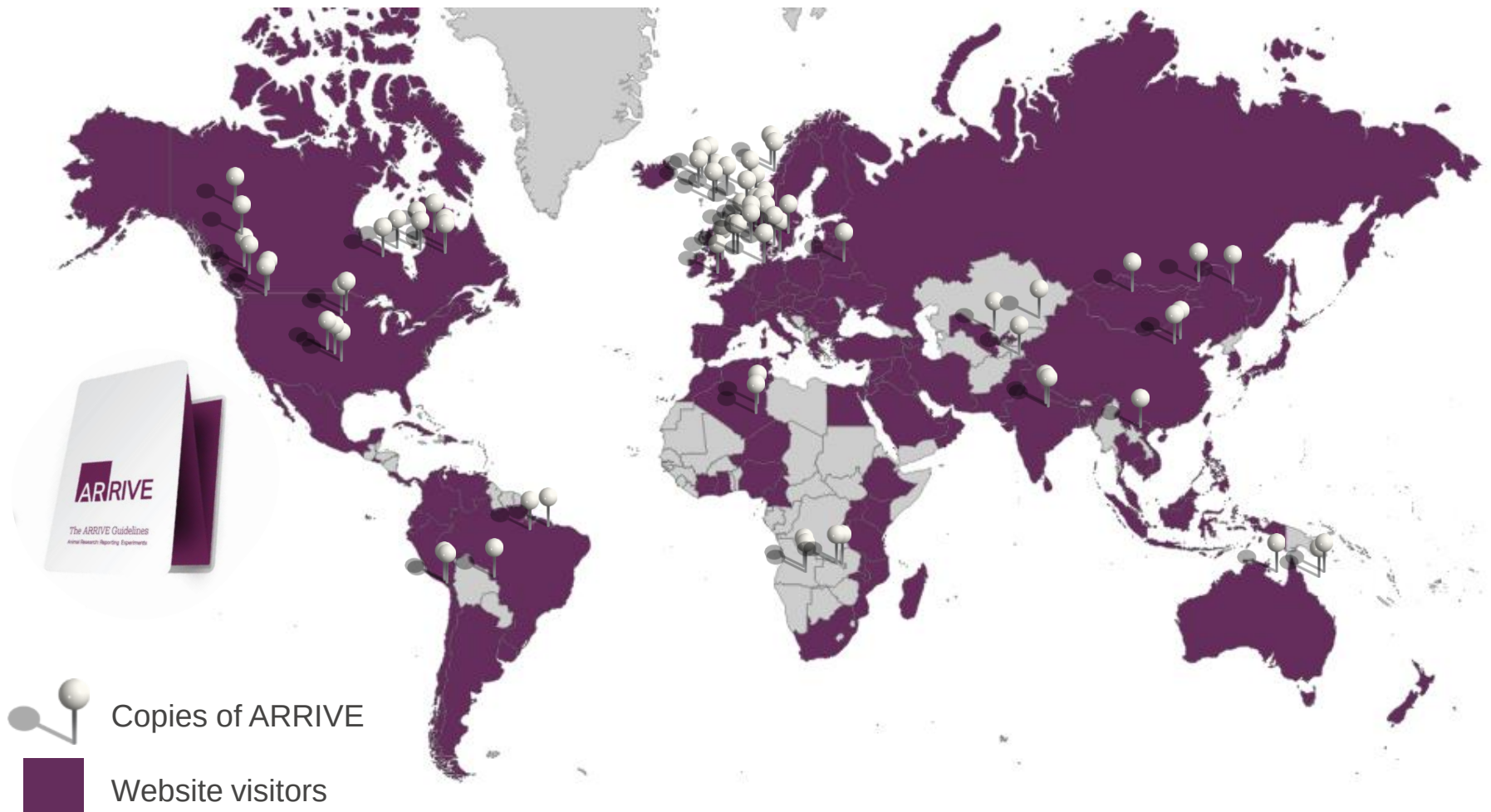
	ITEM	RECOMMENDATION	EXAMPLE
TITLE	1	Provide an accurate and concise a description of the content of the article as possible	<i>Therapeutic gas plentistry in prepubertal New Zealand white rabbits subjected to T1-T12 dorsal arthrodesis: controlled biologically evaluation, electrographic-electrocardiographic and cardio-pulmonary measurements.</i> Chenais et al., 2009
ABSTRACT	2	Provide an accurate summary of the background, research objectives, including details of the species or strain of animal used, key methods, principal findings and conclusions of the study.	BACKGROUND AND PURPOSE: Asthma is an inflammatory disease that involves airway hyperresponsiveness and hyperinflation. Paracetamol have been associated as anti-inflammatory and antitussive activities and may represent a potential therapeutic treatment of asthma. Our aim was to evaluate the effects of the sacralpneumotaxic treatment in several models of experimental asthma model in mice. EXPERIMENTAL APPROACH: Male BALB/c mice were sensitized to ovalbumin (OVA) on days 0 and 14, and were challenged with aerosolized ovalbumin 18, on days 24, 28 and 32. Ovalbumin sensitized animals received saline (saline and ovalbumin 18), dexamethasone (dexamethasone 100 mg/kg) or dexamethasone 10 mg/kg + 100 mg/kg saline (dexamethasone 100 mg/kg + saline 100 mg/kg) on day 28. On day 28, we performed the airway hyperresponsiveness, inflammation and remodeling and airway hyperinflation (AHR) RANTES, IL-6, IL-4, IL-13, IL-5, TNF- α and IFN- γ levels in bronchoalveolar lavage (BAL) and homogenized were determined by ELISpot assay, and IL-6 and IL-13 and IFN- γ activation were visualized in inflammatory cells by immunohistochemistry.

Examples

ARRIVE guidelines – dissemination

Over **8,000** copies of the ARRIVE guidelines have been sent to **30** different countries.

Website visitors from **110** countries (www.nc3rs.org.uk/ARRIVE)



Endorsement

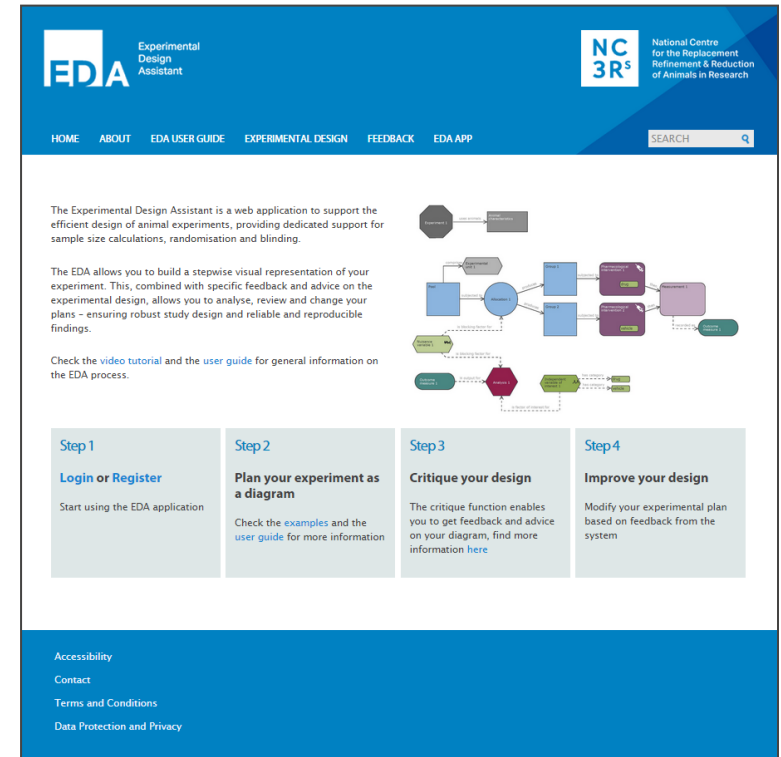
- The ARRIVE guidelines are endorsed by
 - over 580 journals
 - major funders and universities in the UK and abroad



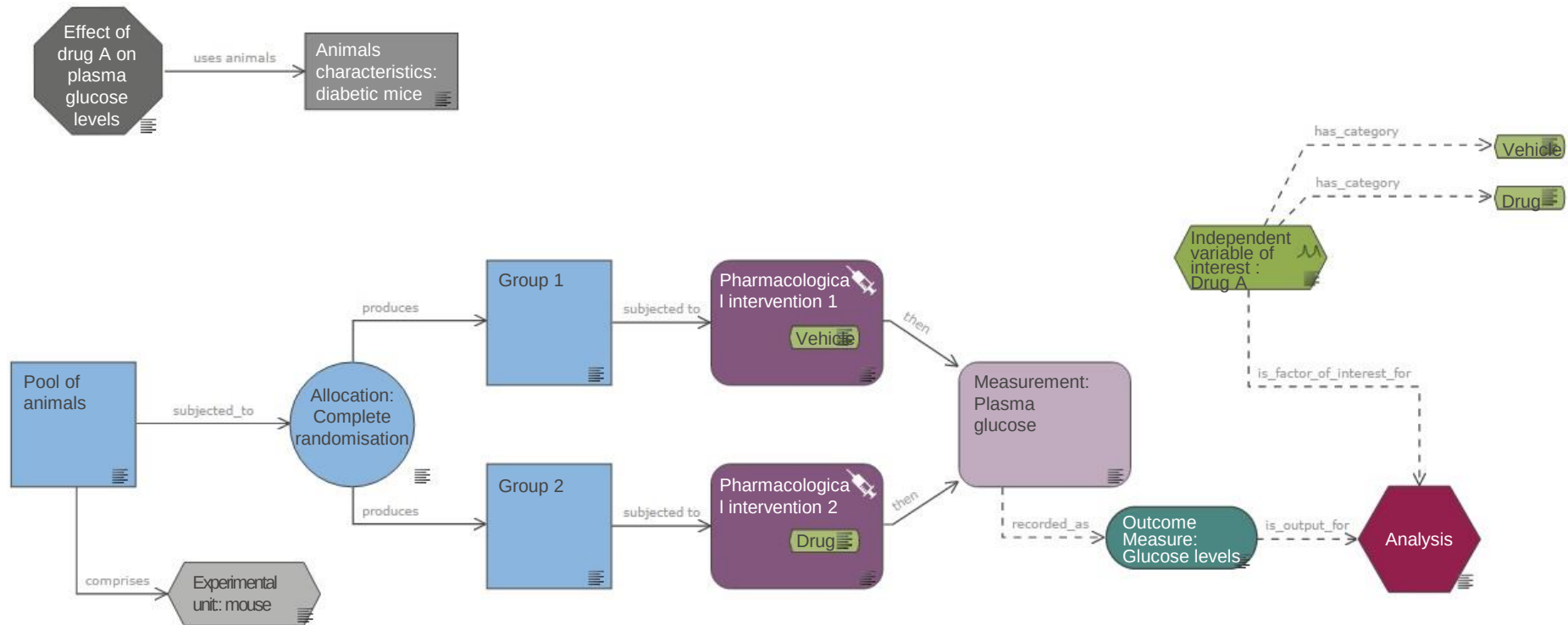
The EDA

Developed to improve the design of animal experiments

- Web-based tool
- Developed as a collaboration between:
 - *In vivo* researchers
 - Statisticians
 - Academia and industry
 - Software designers specialised in artificial intelligence
- Road tested by researchers and statisticians
- Launched in October



The EDA diagram



Benefits of the EDA

- Build of the diagram enables users to get a greater understanding of experimental design
- Feedback from the system improves experimental design
- Dedicated support for randomisation, blinding and sample size calculation
- Improves transparency of the experimental plan and helps communication
- Website contains a wealth of practical information on experimental design

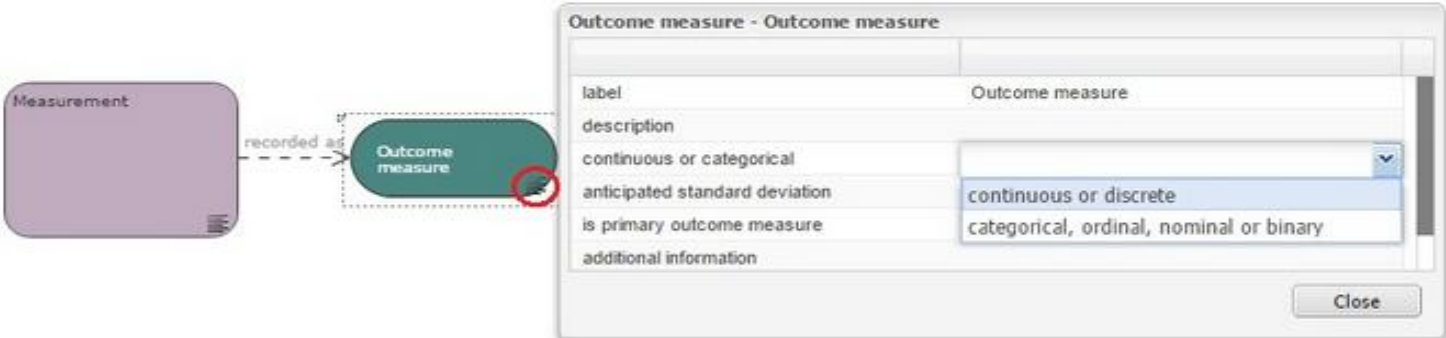
Feedback and advice from the EDA

Specify whether the outcome measure is continuous or categorical | NC3Rs EDA - Google Chrome

<https://eda.nc3rs.org.uk/RT0016>

Specify whether the outcome measure is continuous or categorical

Please indicate within the properties of this outcome measure node whether it is continuous or categorical; this information is used to generate a recommendation regarding appropriate methods of analysis. The properties can be accessed by clicking on the node's properties icon, highlighted in yellow in the image below.



The diagram shows a purple box labeled 'Measurement' with a dashed arrow labeled 'recorded as' pointing to a green oval labeled 'Outcome measure'. A red circle highlights a small icon on the 'Outcome measure' node. The properties dialog box, titled 'Outcome measure - Outcome measure', is open, showing a table with the following fields:

	Outcome measure
label	
description	
continuous or categorical	continuous or discrete
anticipated standard deviation	
is primary outcome measure	
additional information	

Close

Continuous data are sometimes referred to as quantitative data and are measured on a numerical scale. Continuous measures include truly continuous data but also discrete data. Examples of true continuous data include bodyweight, body temperature, blood/CSF concentration or time to event, while examples of discrete data include litter size, number of correct response or clinical score.

Categorical measures are measured on a non-numerical scale, they can be ordinal (e.g. severity scores)

Institutional activities

An institutional framework for the 3Rs

1	Improve access to information and resources – e.g. intranet links to Procedures With Care; NC3Rs newsletter (events, funding...)	✓
2	Champion the 3Rs – e.g. individual champions (scientists); regular seminars or journal clubs; lab meeting agendas	✓
3	Involve the wider institutional community – e.g. themed scientific workshops; opportunities for new collaborations and publishing	✓
4	Reward 3Rs developments – e.g. annual 3Rs prize	✓
5	Support 3Rs training – e.g. NC3Rs events; research and licensee training courses	✓
6	Disseminate 3Rs advances – e.g. staff papers, posters and presentations; ARRIVE guidelines	✓
7	Take a strategic approach – e.g. Ethics committees or Department sets priorities (animal numbers, severity, model utility); pilot study funding	✓

Embedding regional NC3Rs staff

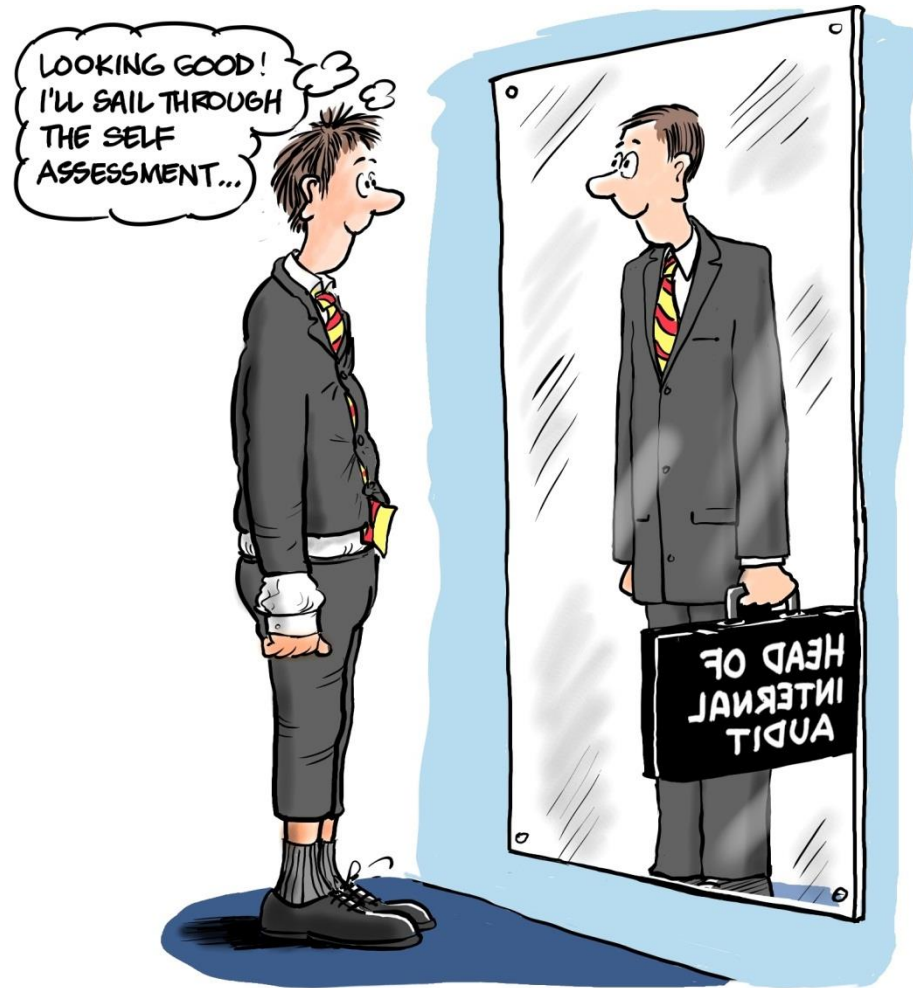
The role

- Provide expert advice and disseminate the work of the NC3Rs
- Support university staff involved in *in vivo* research with the latest information on the 3Rs
- Horizon scan for the research and technologies with 3Rs potential and connect them with potential end-users
- Facilitate improved knowledge exchange across institutions

The model

- Co-funded (50:50) by NC3Rs and a consortium of universities; aggregate cost between universities
- Trial with 1-2 staff – build trust; learn from successes; generate case studies

An institutional 3Rs self-assessment tool: benchmarking and tracking of 3Rs activities





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Thank you

Further information

- Email: enquiries@nc3rs.org.uk
- Website: www.nc3rs.org.uk
- E-newsletter: www.nc3rs.org.uk/subscribe/newsletters
- Twitter: [@NC3Rs](https://twitter.com/NC3Rs)