EVALUATING PROGRESS IN THE 3Rs: THE NC3Rs FRAMEWORK

INPUTS

Activities and resources provided by the NC3Rs

1 Research funding
- Amount invested in awards
- Number of funding schemes and grants or contracts awarded

2 Training and development
- Number of studentships and fellowships awarded
- Number of lectures to BSc, MSc and PhD students

3 Forum for data sharing
- Number of data sharing projects, individuals and research organisations involved
- Number of drugs/chemicals/protocols per data sharing project

4 Symposia and other events
- Number of scientific symposia, workshops and other events organised

5 Collaboration with other organisations
- Number of collaborative projects and partners for research and in-house programmes
- Number of organisations co-funding research or events
- Number of individuals working with the NC3Rs on the in-house programmes

6 Information resources

7 Policy advice
- Number of guidelines developed
- Number of websites and guidelines
- Number of memberships on committees formulating policy
- Number of grant applications peer reviewed for the major funders

8 Income and in-kind contributions
- Amount of money invested in the NC3Rs
- Number and range of NC3Rs funders
- Range and value of in-kind contributions

OUTPUTS/OUTCOMES

Initial results (e.g. number of papers arising from funded research, event attendance rates)

- Number of applications to all funding schemes and other competitions (e.g. prizes)
- Number of grant holders, students, fellows, prize winners

1 Improved awareness and understanding of the 3Rs
- Percentage of grant applications in the fundable range
- Number of unique delegates at NC3Rs events
- Analysis of event feedback questionnaires
- Results of attitudinal surveys
- Number of enquiries from legislators, parliamentarians and media
- Number of media mentions and parliamentary questions
- Traffic to website by sector/discipline
- Number of newsletter subscribers by sector/discipline

2 Creation of new knowledge and 3Rs research materials
- Number of unique papers arising from research funding or in-house programmes
- Volume of intellectual property
- Number of research materials developed (e.g. new models, methods, databases, reagents, technologies, techniques, software)

3 Development of collaborative networks
- Number of collaborations as evidenced by tangible output such as exchange of staff/materials/expertise, access to facilities, co-funding of research, or co-authorship of papers

4 Dissemination activities
- Number of peer reviewed publications (including reviews, editorials) from grant holders and staff
- Citation rates for publications (benchmarked where appropriate)
- Number of other publications (e.g. guidelines, leaflets)
- Number of visits and unique visitors to the websites
- Number of newsletter subscribers
- Number of followers on Facebook and Twitter
- Number of press releases, briefings or responses to media enquiries
- Number of presentations by grant holders and staff, including type of event (e.g. international/national, size/attendance)
- Number of document downloads
- Entries in journal list of top cited papers/Faculty of 1000
- Number of delegates per event; total number of unique delegates for all events

INTERIM IMPACTS

Changes in perception, policy and practice as a result of the NC3Rs inputs and outputs

1 Increased range of scientific audiences for the 3Rs
- Number of research organisations funded or involved with the NC3Rs
- Number of disciplines and sectors represented in the NC3Rs research portfolio and in-house programmes
- Number of companies working with the NC3Rs
- Number of research funders, learned societies and other organisations involved with NC3Rs activities
- Number of countries represented in NC3Rs activities (e.g. international companies, delegates at events, website traffic)

2 Delivery of highly skilled scientists, knowledgeable about the 3Rs
- Number of research assistants trained on NC3Rs grants
- Next role/destination data - retention in academia
- Number of PhDs awarded
- Number of David Sainsbury Fellows

3 New uptake of 3Rs research materials (e.g. new models, methods, databases, reagents, technologies, techniques, software)
- Number of laboratories and companies adopting new research materials, developed with NC3Rs funding or from NC3Rs in-house programmes
- Number of publications reporting the use of new research materials developed with NC3Rs funding or from NC3Rs in-house programmes
- Citation rates and bibliometric analysis (including journal impact factors) of unique papers from NC3Rs research or in-house programmes

4 3Rs embedded in policy and regulations
- Number of NC3Rs researchers, Board members and staff involved in policy setting processes - including responding to national consultations, giving evidence to government reviews, participating in advisory committees and membership of guideline committees
- Number of funders or other organisations adopting NC3Rs guidelines and advice
- Policy maker testimonies
- Number of citations in policy documents (e.g. funders' guidelines, regulatory test guidelines)
- Regulatory change, with an evidence link to the NC3Rs
- Number of substantive influences on policy/landscape analysis

5 Trusted 3Rs information source
- Polls of scientific audiences
- Number and range of organisations consulting the NC3Rs for advice
- Number of downloads of NC3Rs briefing papers
- Website traffic, including number of unique and repeat visitors, number of document downloads, time per page
- Number and range of organisations expressing support for the NC3Rs
- Number and range of media outlets covering the NC3Rs
- Number of invited presentations from NC3Rs staff

6 Enterprise and economic benefit
- Number of people employed on NC3Rs grants, studentships and fellowships
- Number of SMEs receiving NC3Rs funding
- Staff employed per spin-out company
- Amount of further research funding (UK and non-UK, including private sector) secured on the back of NC3Rs grants (e.g. per pound invested by the NC3Rs); or number of follow-on grants
- Company testimonials
- Cost savings as a result of NC3Rs activities (e.g. due to fewer animals being used or shorter study duration)
- Number and quality of spin-out companies established (or grown) as a result of NC3Rs support

MATURE IMPACTS

Replacement to avoid the use of animals
Reduction in the number of animals used
Refinement to minimise suffering and improve animal welfare

1 Replacement: with an evidence link to the NC3Rs
- Number of animals no longer used

2 Reduction: with an evidence link to the NC3Rs
- Percentage reduction in animal use per procedure/test/drug or chemical/laboratory
- More data obtained per animal (without an increase in suffering for individual animals)

3 Refinement: with an evidence link to the NC3Rs
- Downgrading of severity limits for procedures/protocols
- Avoidance of specific procedures or adverse effects (e.g. surgery, restraint, paralysis, death, infection)
- Objective indicators of improved animal welfare (e.g. reduced mortality rates, faster recovery times, physiological measures)
- Improved housing, including environmental enrichment
- Substitution by a species of lower neurophysiological sensitivity

4 Better science: with an evidence link to the NC3Rs
- More predictive, reliable models
- New discoveries benefitting science, medicine and society

EVALUATING PROGRESS IN THE 3Rs: THE NC3Rs FRAMEWORK

OUTPUTS/OUTCOMES

Initial results (e.g. number of papers arising from funded research, event attendance rates)

Number of applications to all funding schemes and other competitions (e.g. prizes)

Number of grant holders, students, fellows, prize winners

1 Improved awareness and understanding of the 3Rs

Percentage of grant applications in the fundable range

Number of unique delegates at NC3Rs events

Analysis of event feedback questionnaires

Results of attitudinal surveys

Number of enquiries from legislators, parliamentarians and media

Number of media mentions and parliamentary questions

Traffic to website by sector/ discipline

Number of newsletter subscribers by sector/ discipline

2 Creation of new knowledge and 3Rs research materials

Number of unique papers arising from research funding or in-house programmes

Volume of intellectual property

Number of research materials developed (e.g. new models, methods, databases, reagents, technologies, techniques, software)

3 Development of collaborative networks

Number of collaborations as

4 Dissemination activities

INTERIM IMPACTS

Changes in perception, policy and practice as a result of the NC3Rs inputs and outputs

1 Increased range of scientific audiences for the 3Rs

Number of disciplines and sectors represented in the NC3Rs research portfolio and in-house programmes

Number of research funders, learned societies and other organisations involved with NC3Rs activities

Number of countries represented in NC3Rs activities (e.g. international companies, delegates at events, website traffic)

Number of research organisations funded or involved with the NC3Rs

Number of companies working with the NC3Rs

2 Delivery of highly skilled scientists, knowledgeable about the 3Rs

Number of research assistants trained on NC3Rs grants

Next role/destination data - retention in academia

Number of PhDs awarded

Number of David Sainsbury Fellows

3 New uptake of 3Rs research materials (e.g. new models, methods, databases, reagents, technologies, techniques, software)

Number of laboratories and companies adopting new research materials, developed with NC3Rs funding or from NC3Rs in-house programmes

Number of publications reporting the use of new research materials developed with NC3Rs funding or from NC3Rs in-house programmes

Citation rates and bibliometric analysis (including journal impact factors) of unique papers from NC3Rs research or in-house programmes

Number of NC3Rs researchers, Board members and staff involved in policy

provided by the NC3Rs

Amount invested in awards

2 Training and development

Number of lectures to BSc, MSc and PhD students

Number of data sharing projects, individuals and research organisations involved

4 Symposia and other events

5 Collaboration with other organisations

6 Information resources

Assessing our impact

We replace, reduce and refine the use of animals in research.

This is how we evaluate our progress.

There is wide scientific, political and societal support for efforts to replace, reduce and refine the use of animals in research and testing (the 3Rs).

Each year the Home Office publishes statistics on the number of scientific procedures conducted on living animals in Great Britain. These provide a broad-brush picture of national trends in animal use but overall they lack sufficient granularity to be useful in terms of measuring progress in the 3Rs.

As the organisation tasked by Government with delivering advances in the 3Rs it is important that the NC3Rs is able to measure and demonstrate its impact. To achieve this we have developed an improved evaluation framework. This is independent of the Home Office statistics, uses a range of quantitative and qualitative metrics and can be applied to the research funded by the NC3Rs and its in-house programmes.

To ensure that the evaluation framework is as effective as possible we will require greater participation from the scientific community in providing information on how our work impacts on 3Rs activities in their laboratory, institution or discipline. To facilitate this, we have launched an online 3Rs 'notice board' for information to be shared with us.

Catalysing activity in the 3Rs

The 3Rs have been used to guide the humane use of animals in scientific research in the UK and elsewhere for over 50 years.

There have, however, been few efforts to systematically benchmark progress in the 3Rs which is surprising given the interest that animal research attracts. In recent years the number of animals used in Great Britain has increased from 2.57 million in 2001 to 3.64 million in 2010. This has led to concerns about the commitment of the scientific community to the 3Rs and animal research continues to be one of the most contentious issues in science.

The NC3Rs was established in 2004 by the Government to accelerate the development and use of the 3Rs. Our strategy has been to modernise the 3Rs agenda to not only minimise animal use and improve animal welfare but to also help address some of the major challenges facing the life sciences sector – challenges such as the reliability of animal models, their relevance to man and costs. These challenges have significant implications for:

- Universities which are working to do better science at a time when there is increasing pressure to translate basic research for societal and economic benefits,
- Pharmaceutical and biotechnology companies which need to improve the ability of preclinical efficacy and safety studies to predict effects in the clinic and,
- Chemical and consumer product companies which operate in a complex regulatory environment with conflicting requirements for animal studies.

We have pioneered engagement of the mainstream scientific community in efforts to discover new ways of replacing, reducing and refining the use of animals. This has been achieved by funding research, training and career development, and through our in-house programmes which focus on working in partnership with universities, pharmaceutical, chemical and consumer product companies, research funders and regulatory bodies. Such partnerships are key to our success since we have no executive or regulatory powers to ensure that 3Rs methods are widely adopted.

Measuring and evaluating our impact is a critical, ongoing activity since it allows us to ensure that our strategy is effective, that our science programmes provide value for money and are on track, and that there is a benchmark for progress on the 3Rs. The latter is particularly relevant given our role in leading the Coalition Government's pledge to work to reduce animal use.

This year, guided by an expert working group, we have reviewed our approach to evaluating the impact of the NC3Rs. This report sets out a revised evaluation framework for our research funding and in-house programmes. It includes a summary of the challenges of measuring progress in the 3Rs plus illustrative case studies using the evaluation framework. The primary goal is to improve the assessment of *our* impact. Nevertheless, our partnerships with many of the UK's major scientific organisations provide a unique opportunity to use the framework to create a national 3Rs barometer which all those interested in this area can use to track progress or monitor their own performance.

Measuring progress in the 3Rs is challenging

Evaluating progress in the 3Rs can be difficult. Consequently, few organisations have attempted to determine mechanisms and metrics by which it can be done. As in other research fields, measuring 'inputs' such as funding and 'outputs' such as publications is generally easier than measuring actual 'impacts'.

There are also some specific challenges to determining progress in the 3Rs which have implications for assessing the impact of the NC3Rs. These include:

– The development of new 3Rs methods can in some cases be a long multi-staged process because of the scientific and technological innovation required.
– Even where 3Rs methods are available it can take many years before they become adopted as standard practice. Uptake can be particularly slow for methods for regulatory toxicology purposes, which require international validation, acceptance and harmonisation.
– There is limited information available in the public domain against which to measure progress. The Home Office statistics on scientific procedures on living animals cannot be used as a benchmark for progress in the 3Rs. This is discussed in more detail in Annex 1.

Our improved evaluation framework

We collate and publish a large amount of information on the impact of the research we fund and our in-house programmes. We are also subject to a five yearly review in which our impact and value for money is independently assessed. The last review was in 2009. This year we will join the online RCUK Research Outcomes System (ROS). Our grant holders will be able to use this to alert us to publications, collaborations and other research outputs and impacts as they arise, strengthening the monitoring and evaluation of the science we fund. Nevertheless, we recognise that as our budget and range of activities have grown we need a more effective mechanism for evaluating impact. As outlined there are a number of challenges to measuring 3Rs impacts and as a result any mechanism for evaluating the NC3Rs should encompass a wide range of inputs and outputs, allow for longitudinal monitoring, and not be reliant on information presented in the Home Office statistics.

With this in mind, we have developed an improved evaluation framework and associated metrics for assessing our performance and impact. The framework is shown in Figure 1 on pages 6-7 and metrics to support it in Table 1 on pages 8-11. The framework enables evaluation of all of our activities at one or more points along the trajectory from inputs, through output/outcomes, to interim and mature impacts. Metrics that are precise, quantifiable, independently verifiable and appropriate for an organisation the size of the NC3Rs have been selected.

– **Inputs**
  Activities and resources provided by the NC3Rs
– **Outputs/Outcomes**
  Initial results (e.g. number of papers arising from funded research, event attendance rates)
– **Interim Impacts**
  Changes in perception, policy and practice as a result of the NC3Rs inputs and outputs
– **Mature Impacts**
  Replacement to avoid the use of animals

  Reduction in the number of animals used

  Refinement to minimise suffering and improve animal welfare

FIGURE 1.

EVALUATION FRAMEWORK FOR THE NC3Rs

INPUTS

Activities and resources provided by the NC3Rs

1. Research funding
2. Training and development
3. Forum for data sharing
4. Symposia and other events
5. Collaboration with other organisations
6. Information resources
7. Policy advice
8. Income and in-kind contributions

OUTPUTS/OUTCOMES

Initial results (e.g. number of papers arising from funded research, event attendance rates)

1. Improved understanding and awareness of the 3Rs
2. Creation of new knowledge and 3Rs research materials
3. Development of collaborative networks
4. Dissemination activities

INTERIM IMPACTS

Changes in perception, policy and practice as a result of the NC3Rs inputs and outputs

1. Increased range of scientific audiences for the 3Rs
2. Delivery of highly skilled scientists, knowledgeable about the 3Rs
3. New uptake of 3Rs research materials
4. 3Rs embedded in policy and regulations
5. Trusted 3Rs information source
6. Enterprise and economic benefit

MATURE IMPACTS

Replacement to avoid the use of animals
Reduction in the number of animals used
Refinement to minimise suffering and improve animal welfare

1. Replacement
2. Reduction
3. Refinement
4. Better science

Table 1: Examples of metrics for the NC3Rs evaluation framework

INPUTS

1. Research funding

- Number of funding schemes and grants or contracts awarded
- Amount invested in awards

2. Training and development

- Number of studentships and fellowships awarded
- Amount invested in awards
- Number of lectures to BSc, MSc and PhD students

3. Forum for data sharing

- Number of data sharing projects, individuals and research organisations involved
- Number of drugs/chemicals/protocols per data sharing project

4. Symposia and other events

- Number of scientific symposia, workshops and other events organised

5. Collaboration with other organisations

- Number of collaborative projects and partners for research and in-house programmes
- Number of organisations co-funding research or events
- Number of individuals working with the NC3Rs on the in-house programmes

6. Information resources

- Number of websites and guidelines

7. Policy advice

- Number of grant applications peer reviewed for the major funders
- Number of guidelines developed
- Number of memberships on committees formulating policy

8. Income and in-kind contributions

- Amount of money invested in the NC3Rs
- Number and range of organisations funding the NC3Rs
- Range and value of in-kind contributions

OUTPUTS/OUTCOMES

1. Improved awareness and understanding of the 3Rs

- Number of applications to all funding schemes and other competitions (e.g. prizes)
- Percentage of grant applications in the fundable range
- Number of grant holders, students, fellows, prize winners
- Number of unique delegates at NC3Rs events
- Analysis of event feedback questionnaires
- Traffic to website by sector/discipline
- Number of newsletter subscribers by sector/discipline
- Results of attitudinal surveys
- Number of enquiries from legislators, parliamentarians and media
- Number of media mentions and parliamentary questions

2. Creation of new knowledge and 3Rs research materials

- Number of unique papers arising from research funding or in-house programmes
- Number of research materials developed (e.g. new models, methods, databases, reagents, technologies, techniques, software)
- Volume of intellectual property

3. Development of collaborative networks

- Number of collaborations as evidenced by tangible output such as exchange of staff/materials/expertise, access to facilities, co-funding of research, or co-authorship of papers

4. Dissemination activities

- Number of peer reviewed publications (including reviews, editorials) from grant holders and staff
- Number of other publications (e.g. guidelines, leaflets)
- Citation rates for publications (benchmarked where appropriate)
- Entries in journal list of top cited papers/Faculty of 1000
- Number of document downloads
- Number of presentations by grant holders and staff, including type of event (e.g. international/national, size/attendance)
- Number of delegates per event; total number of unique delegates for all events
- Number of visits and unique visitors to the websites
- Number of newsletter subscribers
- Number of followers on Facebook and Twitter
- Number of press releases, briefings or responses to media enquiries

INTERIM IMPACTS

1. Increased range of scientific audiences for the 3Rs

– Number of research organisations funded or involved with the NC3Rs

– Number of companies working with the NC3Rs

– Number of disciplines and sectors represented in the NC3Rs research portfolio and in-house programmes

– Number of research funders, learned societies and other organisations involved with NC3Rs activities

– Number of countries represented in NC3Rs activities (e.g. international companies, delegates at events, website traffic)

2. Delivery of highly skilled scientists, knowledgeable about the 3Rs

– Number of PhDs awarded

– Number of research assistants trained on NC3Rs grants

– Number of David Sainsbury Fellows

– Next role/destination data – retention in academia

3. New uptake of 3Rs research materials (e.g. new models, methods, databases, reagents, technologies, techniques, software)

– Number of laboratories and companies adopting new research materials, developed with NC3Rs funding or from NC3Rs in-house programmes

– Number of publications reporting the use of new research materials developed with NC3Rs funding or from NC3Rs in-house programmes

– Citation rates and bibliometric analysis (including journal impact factors) of unique papers from NC3Rs research or in-house programmes

4. 3Rs embedded in policy and regulations

– Number of funders or other organisations adopting NC3Rs guidelines and advice

– Number of NC3Rs researchers, Board members and staff involved in policy setting processes – including responding to national consultations, giving evidence to government reviews, participating in advisory committees and membership of guideline committees

– Number of citations on policy (e.g. funders' guidelines, regulatory test guidelines)

– Number of substantive influences on policy/landscape analysis

– Policy maker testimonies

– Regulatory change, with an evidence link to the NC3Rs

5. Trusted 3Rs information source

– Number and range of organisations consulting the NC3Rs for advice

– Number of downloads of NC3Rs briefing papers

– Number and range of organisations expressing support for the NC3Rs

– Number of invited presentations from NC3Rs staff

– Website traffic, including number of unique and repeat visitors, number of document downloads, time per page

– Polls of scientific audiences

– Number and range of media outlets covering the NC3Rs

6. Enterprise and economic benefit

– Number of people employed on NC3Rs grants, studentships and fellowships

– Amount of further research funding (UK and non-UK, including private sector) secured on the back of NC3Rs grants (e.g. per pound invested by the NC3Rs); or number of follow-on grants

– Number and quality of spin-out companies established (or grown) as a result of NC3Rs support

– Number of SMEs receiving NC3Rs funding

– Staff employed per spin-out company

– Cost savings as a result of NC3Rs activities (e.g. due to fewer animals being used or shorter study duration)

– Company testimonials

MATURE IMPACTS

1. Replacement: with an evidence link to the NC3Rs

– Number of animals no longer used

2. Reduction: with an evidence link to the NC3Rs

– Percentage reduction in animal use per procedure/test/drug or chemical/laboratory

– More data obtained per animal (without an increase in suffering for individual animals)

3. Refinement: with an evidence link to the NC3Rs

– Downgrading of severity limits for procedures/protocols

– Avoidance of specific procedures or adverse effects (e.g. surgery, restraint, paralysis, death, infection)

– Objective indicators of improved animal welfare (e.g. reduced mortality rates, faster recovery times, physiological measures)

– Improved housing, including environmental enrichment

– Substitution by a species of lower neurophysiological sensitivity

4. Better science: with an evidence link to the NC3Rs

– More predictive, reliable models

– New discoveries benefitting science, medicine and society

THE EVALUATION FRAMEWORK IN PRACTICE: CASE STUDIES

Case studies demonstrating how the framework and metrics can be used to evaluate the impact of four of the NC3Rs programmes are provided:

1. **Integrating the 3Rs into publicly funded animal research** to demonstrate how the framework can be used to measure changes in policy.
2. **Refining the use of non-human primates** to illustrate how the framework can be used to measure programmes which focus on raising awareness and how these translate to changes in practice.
3. **Challenging the requirement for acute toxicity studies in rodents** to highlight how the framework can be used to measure changes to regulatory requirements.
4. **Supporting 3Rs innovation in respiratory disease research** to show how the framework can be used to track long term programmes which require scientific and technological advances.

The evaluation framework provides a robust and transparent way of measuring and demonstrating impact. We will use it as a basis for our future annual reports, strategic reviews and funding bids. The framework will allow a more consistent approach to evaluation and the choice of metrics will make it easier to compare results across initiatives and over time. However, to ensure that the framework is as effective as possible we require everyone who engages with the NC3Rs, including those who use our website or attend our events, to take a more active role in providing feedback on how this impacts on the 3Rs within their own research projects, laboratory, institution or discipline. To facilitate this we have launched a new online 3Rs 'notice board' for sharing information (www.nc3rs.org.uk/noticeboard).

CASE STUDY

1

INTEGRATING THE 3Rs INTO PUBLICLY FUNDED ANIMAL RESEARCH

Reviewing research proposals

Around 20-30% of the research funded by the MRC, BBSRC and Wellcome Trust involves the use of animals.

We work with these organisations to embed the 3Rs in their policies and practice. This focuses on two main activities, reviewing grant applications and supporting contemporary good practice through the development of guidelines. Together these activities help to ensure that standards of animal welfare are genuinely high and exceed the legal minima, local issues relating to poor practice are addressed and overseas work is conducted to standards equivalent to those in the UK.

We are able to measure inputs and outputs as well as provide a qualitative assessment of interim and mature impacts. The evaluation framework is shown in Figure 4 on pages 24-25.

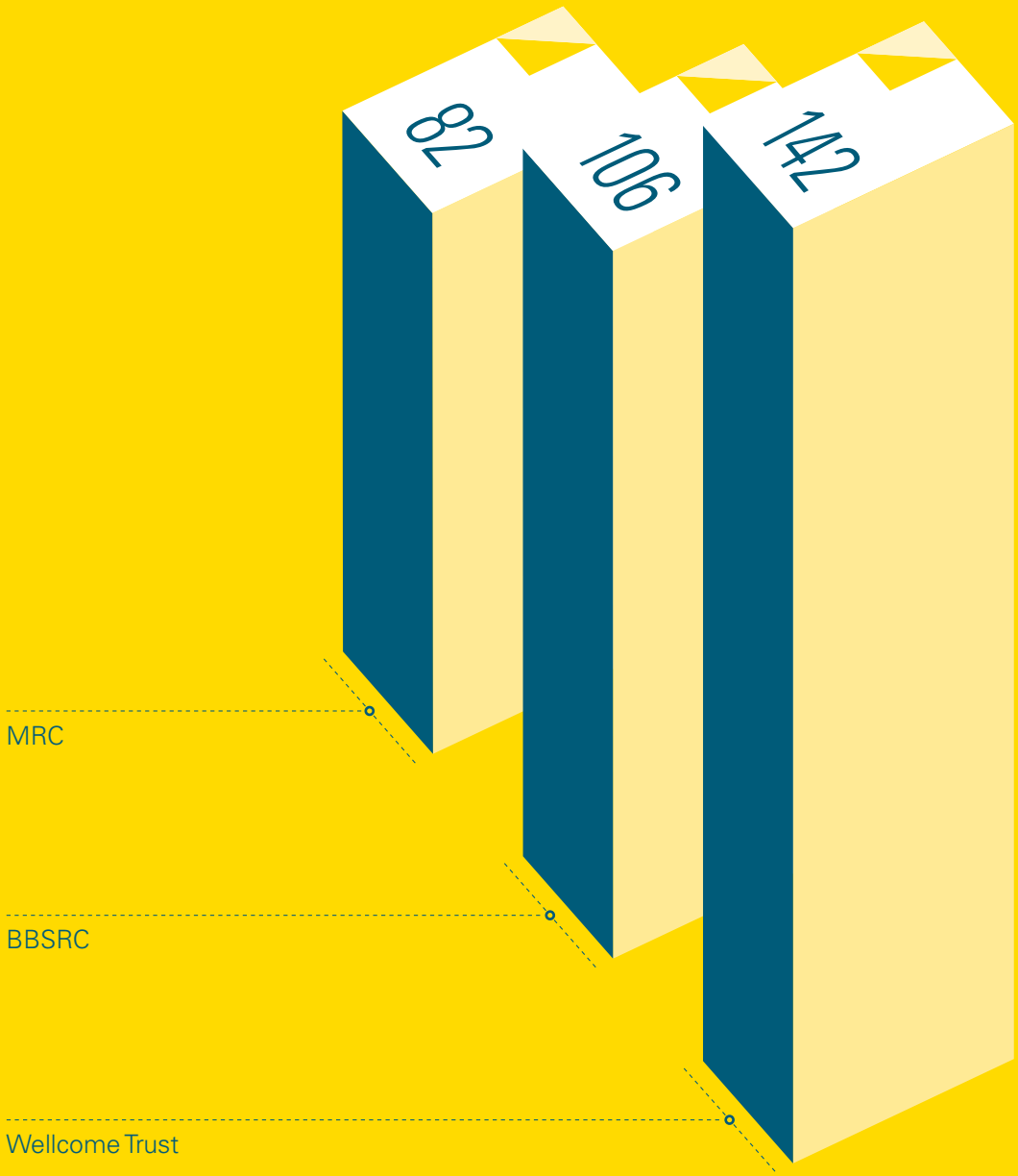
We review grant, studentship and fellowship applications to the MRC, BBSRC and Wellcome Trust, which propose to use non-human primates, dogs, cats and equines. Other research proposals that raise specific concerns may also be referred for review.

Our involvement in the peer review process means that we can advise on opportunities to implement the 3Rs, raise specific animal welfare concerns, highlight where good practice is not being adopted and monitor implementation of specific policies and guidance. Our advice is taken into account during decisions on funding and when drafting the terms and conditions of grant awards. We are therefore able to influence how the science that is supported is carried out.

We have reviewed 330 applications since 2004, involving 238 principal investigators from 81 research organisations – this is shown by funding body in Figure 2 on page 16. We have also advised on eight quinquennial reviews of MRC units and institutes. During this time the number of funding schemes included in our review has increased from six in 2004 to 37 in 2011. The number of applications we have reviewed has also increased annually as shown in Figure 3 pages 18-19.

FIGURE 2.

Number of research funding applications reviewed between September 2004 and May 2012, by funding body



Supporting good practice

We have published guidelines to support the funders' commitment to high standards in the design, conduct, analysis and reporting of animal research. This includes the guidelines *'Responsibility in the Use of Animals in Bioscience Research'* (www.nc3rs.org.uk/responsibility) which were published in 2008. All scientists funded by MRC, BBSRC, NERC, Defra and the Wellcome Trust, who use animals, are required to implement the guidance as a condition of grant funding. A key principle is the expectation that work conducted overseas should be carried out to standards consistent with those in the UK.

In 2010 the major funders also adopted the ARRIVE guidelines which we developed to improve the reporting of animal experiments (www.nc3rs.org.uk/ARRIVE). The guidelines are intended to maximise the information derived from *in vivo* research, avoiding subsequent unnecessary animal use. This year, the MRC, BBSRC and Wellcome Trust published an open letter urging universities and other research institutions to ensure that the ARRIVE guidelines are put into practice.

Examples of the 3Rs impacts on awarded grants that our review and guidelines have achieved are shown in Table 2 on pages 20-23. Many of these relate to neuroscience studies using macaques, which account for around half of the grant applications reviewed.

FIGURE 3.

Number of research proposals, and funding schemes included in the NC3Rs review, 2004 to 2011

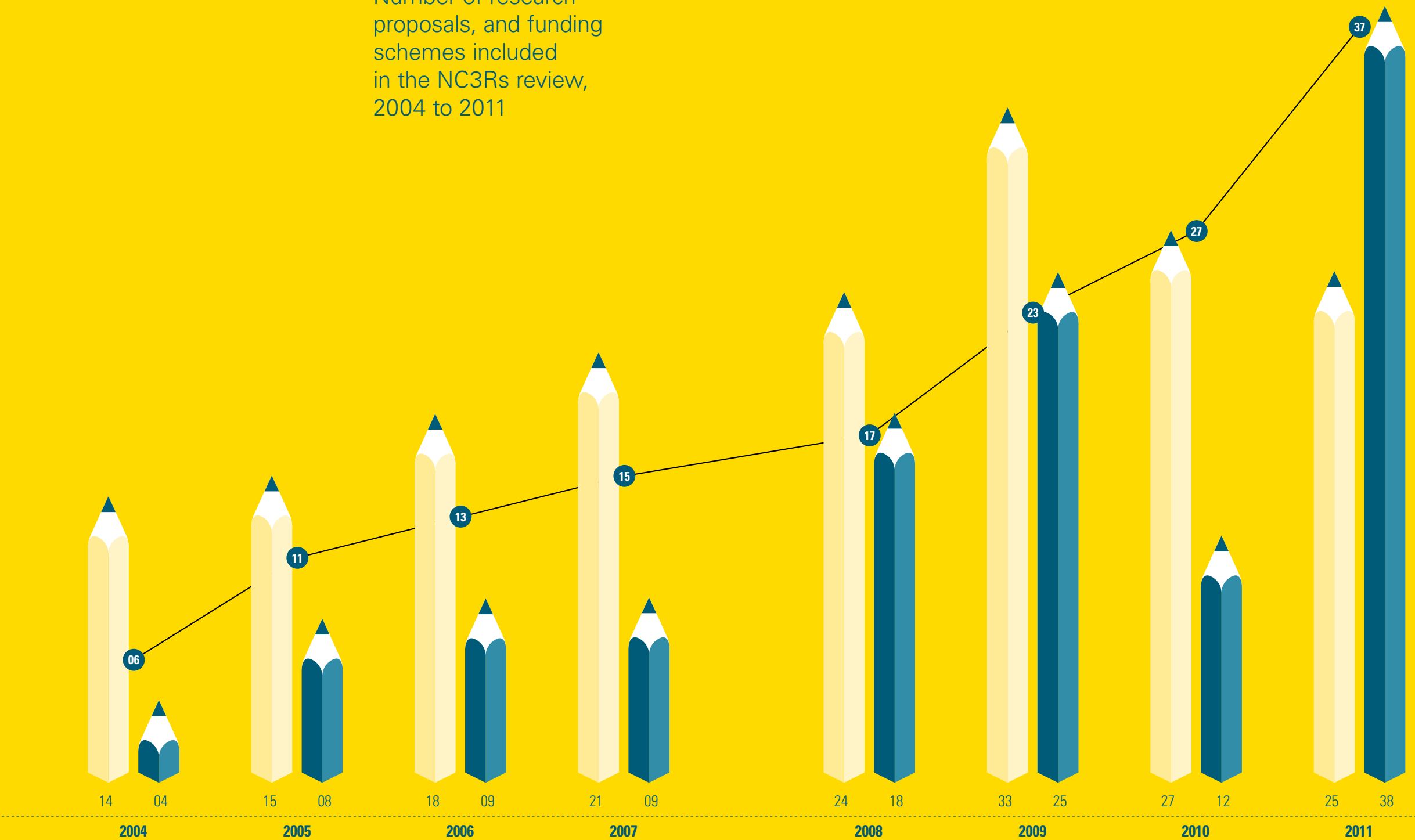
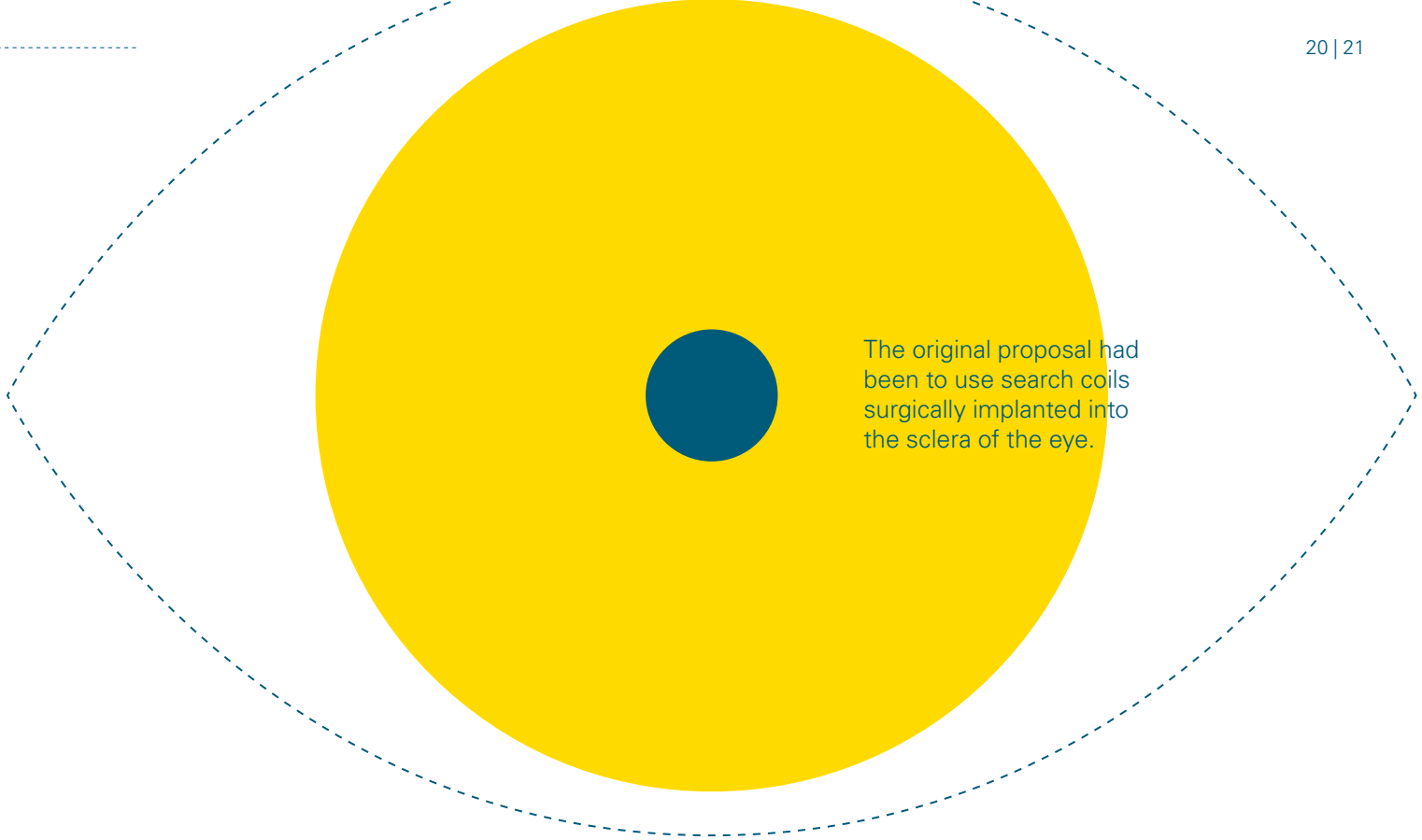


Table 2: Examples of 3Rs impacts arising from the NC3Rs review of research proposals



Use of non-invasive video recording methods for tracking eye movement in rhesus macaques in a UK study.

Non-human primates

Social rather than single housing of rhesus macaques used in Parkinson's disease research in a UK study.	Housing in compatible pairs or groups in cages that meet the minimum space allocations under Directive 2010/63/EU for 72 long-tailed macaques on an infectious disease study in the USA lasting up to 14 months.
Improved anaesthetic, with faster recovery, used for macaque neurosurgery.	Housing in pairs or trios in 2.2m³ of space with solid floors, perches and hammocks for 32 rhesus macaques in a study conducted in the USA. The monkeys were also provided with an additional play cage of 2m³ with wooden furniture and foraging opportunities. The original proposal had been to singly house the animals in grid floor cages, 0.5m³ in size. Staff members were also trained by an external primate behaviour consultant on training of the monkeys for handling and enrichment.
Introduction of new titanium head posts to restrain the head of rhesus macaques used in a UK study. The original proposal had been to use devices made from dental acrylic which cause tissue damage and are susceptible to infection.	Housing in pairs or groups in solid floor cages, with substrate and daily foraging for rhesus macaques in a study conducted in India. The new cages were compliant with the space allocations under Directive 2010/63/EU and, in addition, a play room (19.6m³) was provided so that the animals had regular opportunities for exercise. The original proposal had been to singly house animals in cages 0.5m³ in size. These improvements were paid for by the funding body. The monkeys were also trained using positive reinforcement to co-operate with handling and scientific procedures.
Halving of the number of macaques used in some studies after questioning the requirement for additional animals.	Introduction of pilot studies before the routine use of live long-tailed and pig-tailed macaques in a study of malaria vectors in South East Asia. The pilot studies were to establish if faecal samples alone could be used to assess monkey infection rates, rather than trapping wild macaques and anaesthetising for blood sampling; and if traps for insect sampling could be baited with macaque odour (e.g. from used bedding) rather than tethered pet or zoo monkeys.

Other species

Removal of the use of dogs for a UK repeat dose toxicity study prior to first in man studies.
Ensuring cats for a UK study were obtained locally and transported and housed in compatible pairs, rather than singly.
Requiring local anaesthetic to be used for muscle biopsy in wild cheetahs in Africa.

Housing in pairs in
full height cages of

3.6m³

for 40 owl monkeys
in a malaria study in
South America.

The original proposal had been to
singly house in double-tier cages
ten times smaller.

FIGURE 4: Working with the major funding bodies

EVALUATION FRAMEWORK FOR THE NC3Rs

INPUTS

- Collaboration with other organisations
- Policy advice

OUTPUTS/OUTCOMES

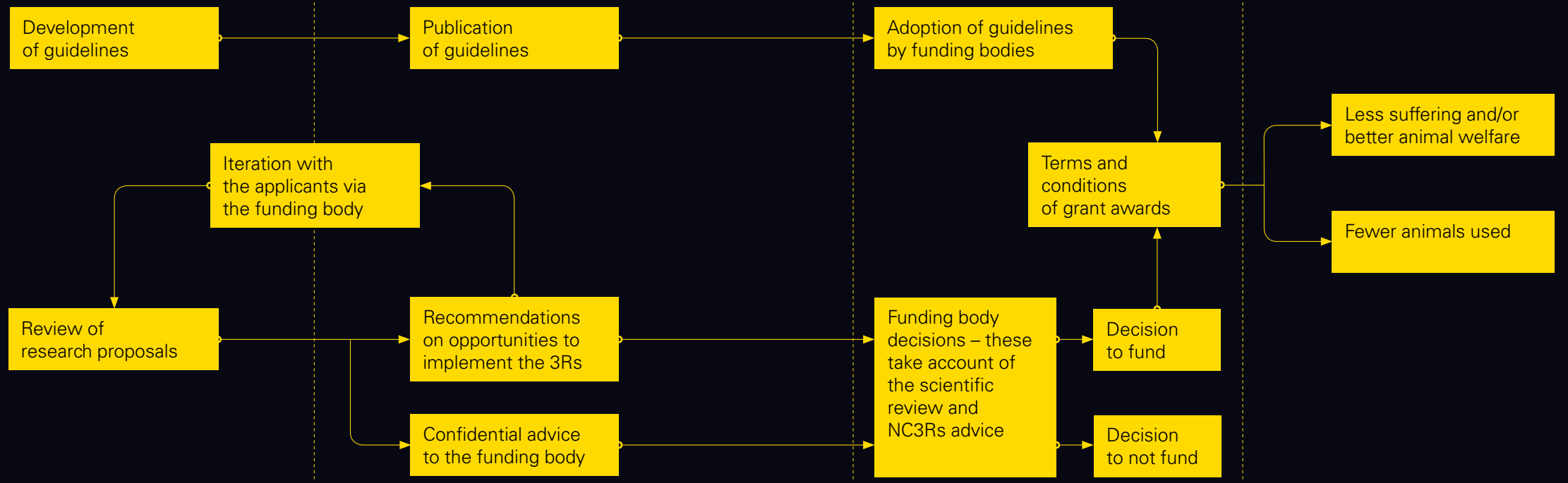
- Increased awareness and understanding of the 3Rs

INTERIM IMPACTS

- New uptake of 3Rs research materials
- 3Rs embedded in science and policy
- Trusted 3Rs information source

MATURE IMPACTS

- Refinement
- Reduction



NC3Rs TIMELINE

2004
Begin to peer review research proposals for the major funders

2006
Publish guideline: *Primate Accommodation, Care and Use*

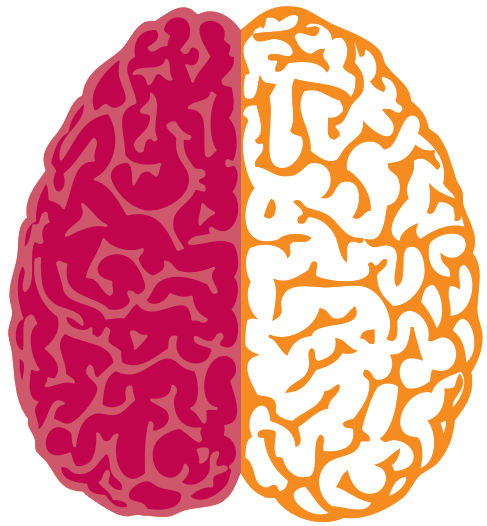
2007
Expand and harmonise questions on animal use in grant application forms

2008
Publish guideline: *Responsibility in the Use of Animals in Bioscience Research*

2010
Publish guideline: *ARRIVE*

2010
Visit UK laboratories to monitor compliance with 'primate guidelines'

Providing an animal welfare forum



Approximately 3,000 non-human primates are used in research in Great Britain each year.

We are delivering a comprehensive programme to improve the welfare of these animals. This primarily focuses on developing and sharing best practice through events, publications and other information resources. Together these have raised awareness, stimulated greater interest in welfare issues among users and resulted in new applications to the NC3Rs research funding schemes.

We estimate that over half of the UK's principal investigators working with non-human primates in neuroscience have applied for NC3Rs research funding, received an NC3Rs grant, or are actively involved with the NC3Rs refinement activities.

We are able to provide metrics on input and outputs as well as interim and mature impacts.

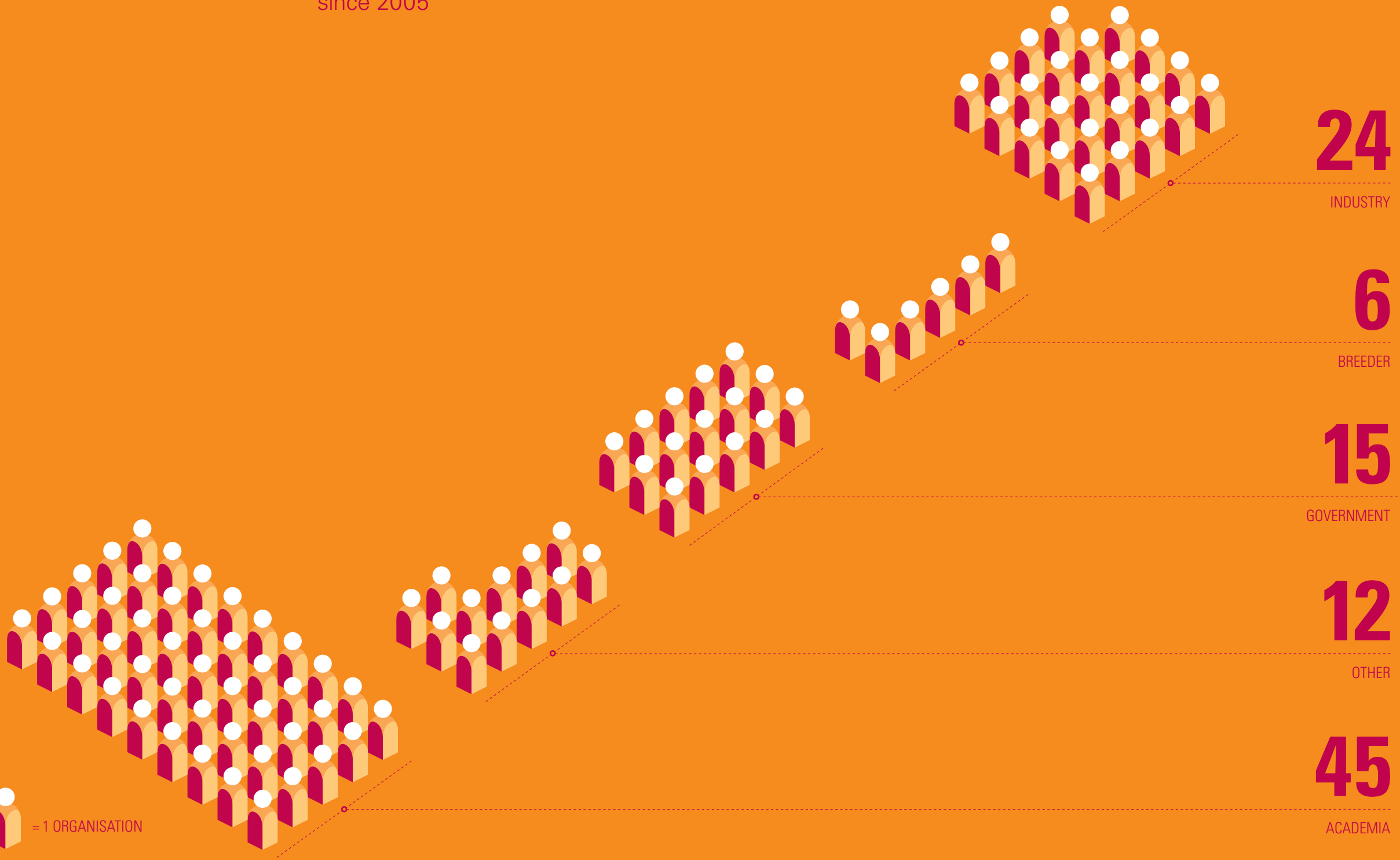
Our annual symposium focuses on promoting the welfare of non-human primates. It is a unique event which brings together scientists, veterinarians, animal care staff, policy makers and regulators.

Since the first event in 2005, attendance has grown from 50 to 150 delegates with around one fifth travelling from outside of the UK. Delegates have come from 102 organisations in 16 countries.

Representation by sector is shown in Figure 5 on pages 28-29.

FIGURE 5.

Number of organisations represented at the primate welfare meeting, by sector, since 2005



Publishing 3Rs information resources

This includes peer reviewed papers, guidelines and online resources.

Peer reviewed papers
We have worked with experts from 39 organisations including universities, contract research organisations, pharmaceutical companies and learned societies to produce 11 peer reviewed journal articles which describe contemporary best practice in many aspects of non-human primate care and use. This includes a seminal publication on refining the use of food and fluid control in macaques used in some types of neuroscience experiments.

Regulating food and/or fluid intake is used to motivate macaques to perform tasks for small food or fluid rewards during neuroscience and behavioural experiments which require the animals to perform reliably and for extended periods. This has been the subject of much debate as, depending on how food and/or fluid control are implemented, the monkeys may suffer adverse physiological and behavioural effects.

To identify opportunities for refinements we convened an expert working group which included many of the UK's leading neuroscientists. Based on an extensive review of the scientific literature, sharing and analysis of protocols and data, and the expertise of the members, a report recommending best practice was published in the *Journal of Neuroscience Methods* in 2010. The report also highlighted areas where further research is needed to provide an evidence base for refinements. As a result of this, in 2011 we awarded a PhD studentship to address whether fluid control can be avoided by using alternative rewards.

The evaluation framework for our work on refining the use of food and fluid control is shown in Figure 6 on pages 34-35.

Guidelines
In 2006, we published guidelines on the accommodation, care and use of non-human primates (www.nc3rs.org.uk/primatesguidelines). The standards set out in the guidelines exceed the minimum laid down in the Home Office Codes of Practice and have been instrumental in improving the accommodation and care of non-human primates at UK universities and other publicly funded laboratories through, for example, requiring increased space for the animals, social housing and foraging opportunities – all of which are critical for the expression of natural behaviours. Compliance with the guidelines is a condition of funding for all of the major bioscience funders in the UK.

Online resources
In 2011, we co-funded with the Primate Society of Great Britain an interactive website on common marmoset care produced by staff at the University of Stirling (www.marmosetcare.com). Six months since its launch, the site has had almost 7,000 unique visitors from 102 countries.

Funding refinement research

Our activities to raise awareness about the welfare of non-human primates have resulted in greater activity on refinement among users. This includes new research to provide an evidence base for best practice. We have awarded five project and pilot study grants and two studentships totalling £800k. A list of the awards is shown in Table 3 on pages 32-33.

One of the first awards made in 2005 demonstrates the welfare improvements that can be achieved with even modest amounts of funding. Professor Roger Lemon at University College London has developed a novel device for restraint of the monkey's head whilst recordings are made from the brain. The new, plastic device is tissue-friendly, lighter and easier to implant than the stainless steel devices typically used. It has the added advantage of being compatible with Magnetic Resonance Imaging which can be used to generate a three-dimensional model of the individual monkey's skull, enabling a custom-fitted implant. The new implants are more stable and secure, and remain free from infection for longer (up to three years in the longest case) than the traditional devices. This results in fewer welfare issues and also avoids animals having to undergo additional surgery to move or replace implants causing problems. The improved head restraint device has been adopted by at least three other research groups.

Table 3: NC3Rs awards for refining the use of non-human primates

Lead researcher

Professor Roger Lemon,
University College London

Project grant

£16,996 in 2005 over three years

Aims

To deliver a refined head implant that reduces tissue damage and infection helping to improve the welfare of monkeys used in studies where restraint of the head is necessary (e.g. to record from the brain).

Lead researcher

Professor Stuart Baker,
Newcastle University

Project grants

£149,176 in 2006 over two years

£71,994 in 2011 over 18 months

Aims

To design and test an electrical implant which can record and transmit data on muscle movement wirelessly through the skin. The current approach involves running wires under the skin to a connector on the back or head of the monkey. The connector prevents the skin from healing fully which means that the animals can be susceptible to infections that are difficult to treat. The new device should prevent this.

Lead researcher

Dr Matt Leach,
Newcastle University

Project grant

£247,800 in 2011 over three years

Aims

To investigate whether facial expressions can be used to assess pain and the effectiveness of analgesics in a range of animals including macaques. There is currently no objective measure for assessing pain in non-human primates and this work will help address this.

Lead researcher

Dr Andrew Jackson,
Newcastle University

Pilot study grant

£73,516 in 2011 over one year

Aims

To develop and test an automated system that allows monkeys to be trained while group housed and without the use food or fluid control, or restraint which may be required in behavioural neuroscience studies.

Lead researcher

Professor Hannah Buchanan-Smith,
University of Stirling

PhD Studentship

£120,000 in 2009 over four years

Aims

To compare the survival, development, behaviour and welfare of marmosets reared under different husbandry practices to identify the best breeding and rearing methods.

Lead researcher

Professor Alex Thiele,
Newcastle University

PhD Studentship

£120,000 in 2011 over four years

Aims

To measure how fluid control impacts on the physiology and behaviour of individual monkeys, and test whether more palatable fluids or other rewards might reduce or eliminate the need for fluid control.

FIGURE 6: Refining the use of food and fluid control

EVALUATION FRAMEWORK FOR THE NC3Rs

INPUTS

- Training and development
- Forum for data sharing
- Symposia and other events
- Collaboration with other organisations
- Policy advice

OUTPUTS/OUTCOMES

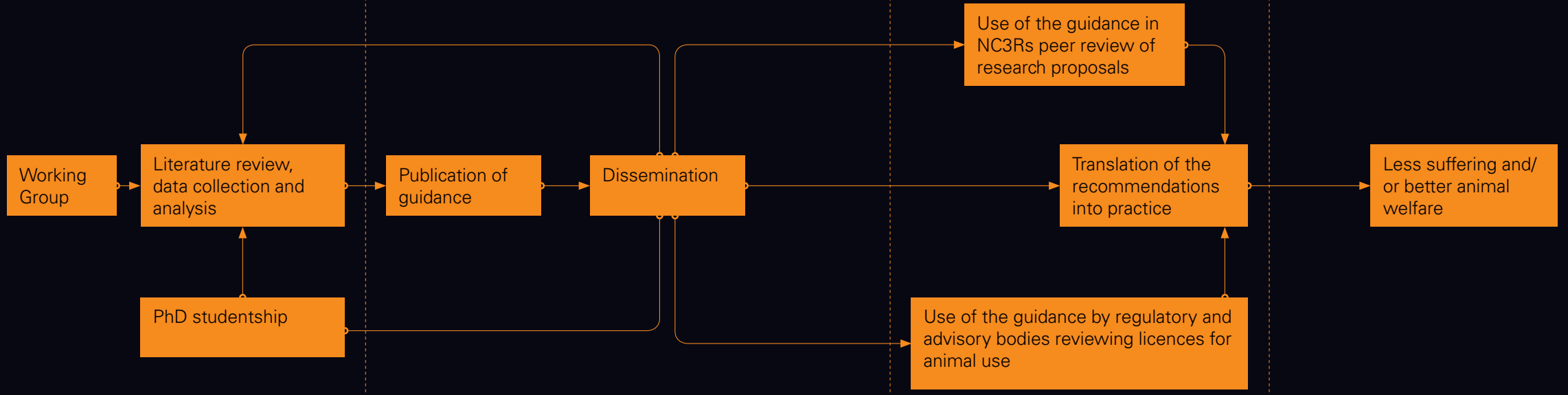
- Increased awareness and understanding of the 3Rs
- Creation of new knowledge and 3Rs research materials
- Development of collaborative networks
- Dissemination activities

INTERIM IMPACTS

- Increased range of audiences for the 3Rs
- Delivery of highly skilled scientists, knowledgeable about the 3Rs
- New uptake of 3Rs research materials
- 3Rs embedded in policy and regulations
- Trusted 3Rs information source

MATURE IMPACTS

- Refinement



NC3Rs TIMELINE

2004
Working Group established

2006
Presentation: NC3Rs Primate Welfare Meeting, London

2007
Presentation: World Congress on Alternatives, Tokyo

2008
Presentation: International Primatological Society Congress, Edinburgh

2010
Publication: *Journal of Neuroscience Methods*

Presentation: NC3Rs Primate Welfare Meeting, London

2011
Workshop: Weizmann Institute, Rehovot

Workshop: PRIM&R IACUC Conference, Chicago

2011
Presentation: CNRS, Marseille

Publication: *Journal of Neuroscience Methods*

2011
Presentation: INSERM, Lyon

2011
Studentship: Newcastle University

Using acute toxicity tests in pharmaceutical development

Animals are used for a variety of purposes in industry including for the safety assessment of drugs and chemicals. We collaborate with the pharmaceutical, chemicals and consumer products industries to accelerate uptake of 3Rs methods.

Activities primarily focus on data sharing and analysis, and supporting new research, including through the NC3Rs challenge-led competition CRACK IT. Together these activities have delivered 3Rs benefits, streamlined industry practices and stimulated regulatory change.

Here we give one example which describes our work on single dose acute toxicity studies and how this has facilitated changes to international guidelines. We are able to measure our input and outputs as well as provide a quantitative assessment of interim and mature impacts. The evaluation framework is shown in Figure 8 on pages 42-43.

Single dose acute toxicity studies in rats and mice have historically been required to support the registration of any pharmaceutical intended for human use and they are usually conducted prior to the first clinical trials. The main objective is to identify the dose of a candidate drug that causes major adverse effects in animals – providing a baseline for dose setting in other preclinical studies and the first clinical trials, as well as information to predict the effects of overdose in humans. It is the only test in pharmaceutical development where death of the animals is an endpoint.

Unlike other regulatory studies, single dose acute toxicity tests require the candidate drug to be administered to animals via the intended clinical route plus one other route. In practice this can mean a total of four studies are conducted per candidate drug – two species (rat and mouse) and two routes of administration.

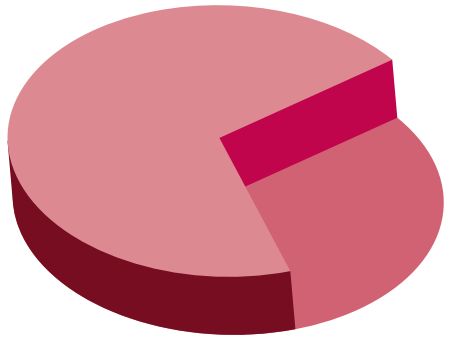
Reducing animal use through cross-company data sharing

Working with AstraZeneca and 17 other European pharmaceutical companies and contract research organisations, we have led a data sharing initiative to review the preclinical and clinical value of single dose acute toxicity studies in rodents. Data on over 70 candidate drugs were shared including information on the number of animals used, routes of administration and how the studies informed decision making within companies.

The initial data collection began in 2004 and continued until 2006 as more companies joined the initiative. The data sharing demonstrated that the majority of companies were conducting four acute toxicity studies per candidate drug – the rat with administration via the oral and intravenous routes and the mouse by the oral and intravenous routes.

There was, however, considerable variation in study design and practice, with around one fifth of companies conducting only one study per candidate drug. This variation also included the number of animals used, with some companies using over 100 animals per study and others using fewer than 20. One company was not conducting acute toxicity studies.

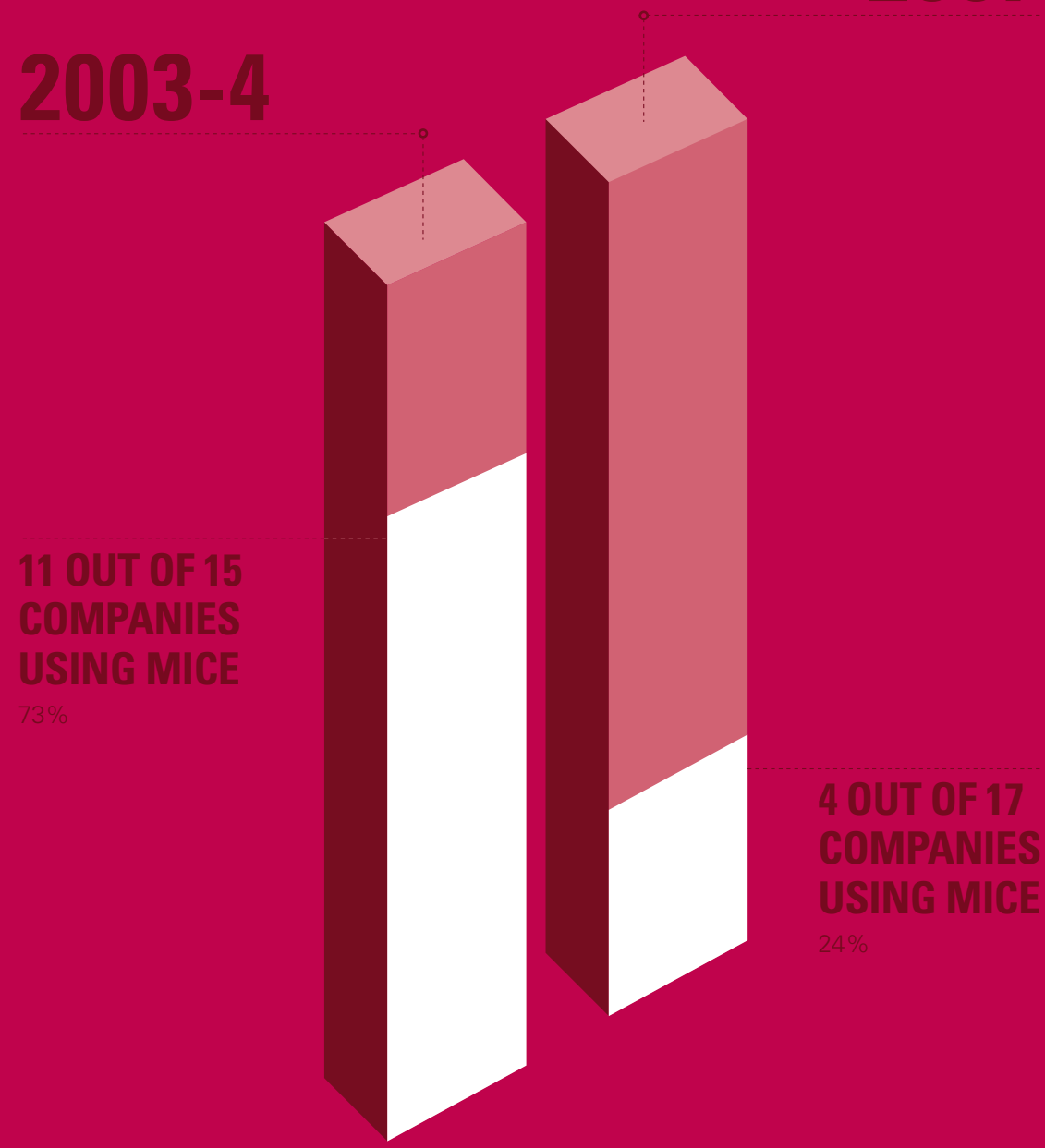
The data sharing and analysis provided a mechanism for reviewing and harmonising practice across the industry and by 2007 when we surveyed the companies again most had used this as an opportunity to reduce the number of studies carried out and animals used. This is shown in Figure 7 on page 39 for the number of mice used. A similar picture is observed for rats. This reduction in animal use for single dose acute toxicity studies across the participating companies equated to approximately 15,000 animals per year – a 70% reduction. The results of the data sharing were published in *Regulatory Toxicology and Pharmacology* in 2008.



70% reduction in animal use for single dose acute toxicity.

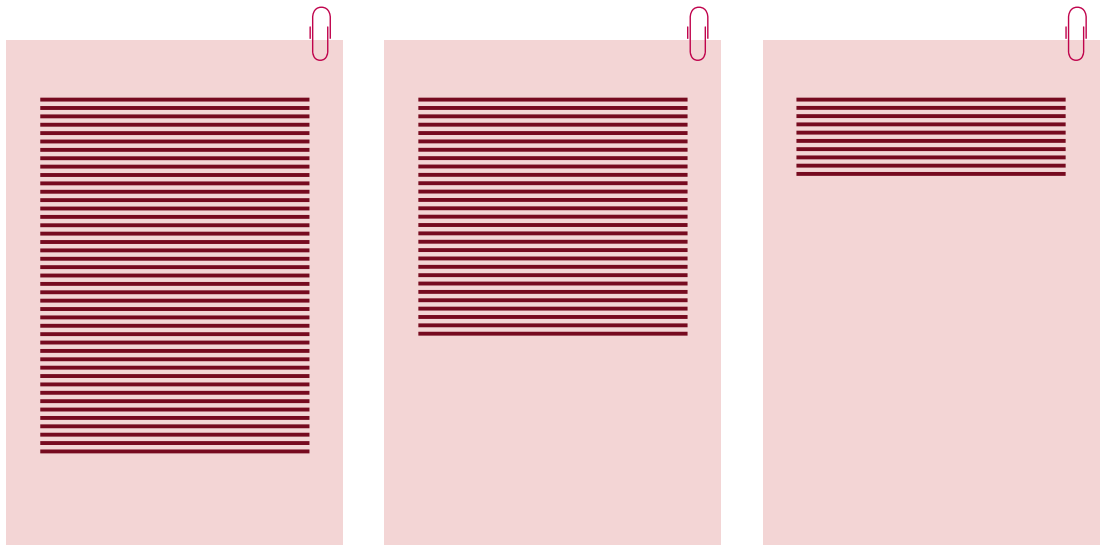
FIGURE 7.

Number of companies using mice in single dose acute toxicity testing



Changing regulatory requirements to avoid animal use

Proportion of clinical trial applications for drugs going into man for the first time in the UK which contain the results from single dose acute toxicity studies.



2007

86%

2011

58%

2012

19%

The next step was to analyse how data from single dose acute toxicity studies were used to support the drug development process. To facilitate this we organised a workshop in 2006 to bring together scientists from industry and representatives of regulatory agencies from the UK, Europe, USA and Japan. Discussion focused on how single dose acute toxicity data were used by companies and regulators. There was agreement that the tests had little value for dose setting for other preclinical studies or for first human clinical trials, and that information could be obtained from other studies already carried out during drug development which did not use death of the animals as an endpoint.

To address the remaining question on the issue of whether acute toxicity data informed the treatment of human overdose cases in 2009 we hosted a workshop with clinicians from companies and international Poison Centres. This again demonstrated that the data were of little value for pharmaceutical development. A report of the workshop was published in *Regulatory Toxicology and Pharmacology* in 2010.

Our work in this area resulted in 2009 in the removal of the requirement for single dose acute toxicity studies from the international guidelines, ICH M3. In 2010, the European guideline on single dose acute toxicity was withdrawn. The impact of this can be seen in figures from the Medicines and Healthcare products Regulatory Agency which show that in 2007, 67 out of 78 clinical trial applications for drugs going into man for the first time in the UK contained the results from single dose acute toxicity studies (86%). In 2011, this figure fell to 76 out of 132 applications (58%). In 2012 to date, the figure is seven out of 36 applications (19%).

Extending to other sectors

Working with industry scientists and regulators from the UK's Health and Safety Executive we have reviewed opportunities to apply the 3Rs to acute toxicity tests in the chemicals sector. This has focused on the testing requirements for six key acute toxicity endpoints commonly required by regulatory authorities: acute oral, dermal and inhalation toxicity, skin and eye irritation, and skin sensitisation. The review included an analysis of acute oral and acute dermal data for 438 chemicals and 240 pesticides. This demonstrated that the acute dermal study had little or no value in addition to the oral study – providing an evidence base for change.

This work was published in *Critical Reviews in Toxicology* and was in the top five most read articles in the journal in 2010.

Working with the European Partnership for Alternative Approaches to Animal Testing we have begun the process of engaging the wider regulatory community in order to remove routine requirements for acute dermal studies from regulatory guidelines in the EU and beyond. The new EU biocides regulation is expected to state that dermal testing is only necessary for substances which will come in contact with the skin during production and/or use and for which a significant rate of absorption through the skin is expected. Similar changes are currently included in new draft EU data requirements for plant protection products.

FIGURE 8: Challenging the requirement for single dose acute toxicity studies in rodents – pharmaceuticals

EVALUATION FRAMEWORK FOR THE NC3Rs

INPUTS

- Forum for data sharing
- Symposia and other events
- Collaboration with other organisations
- Information resources
- Policy advice

OUTPUTS/OUTCOMES

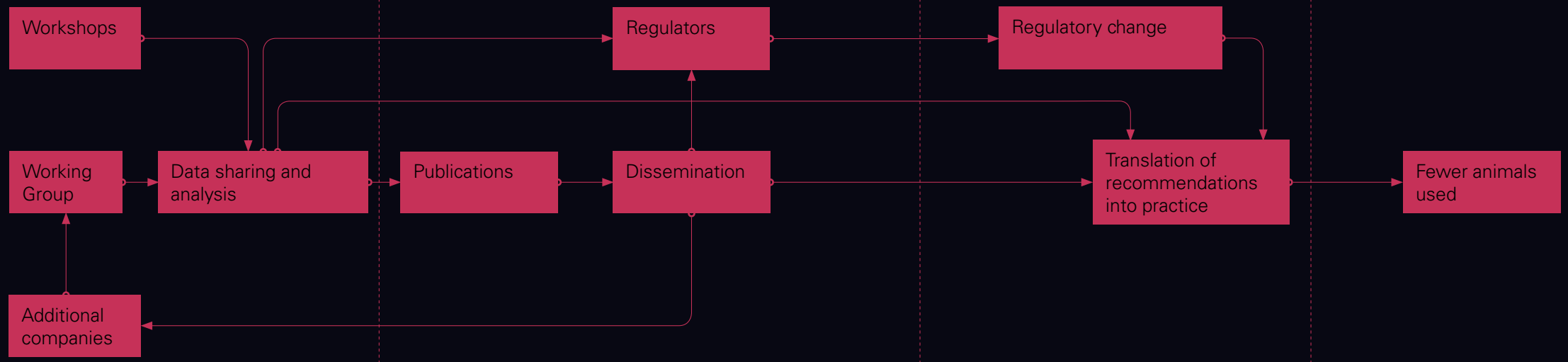
- Increased awareness and understanding of the 3Rs
- Creation of new knowledge and 3Rs research materials
- Development of collaborative networks
- Dissemination activities

INTERIM IMPACTS

- Increased range of audiences for the 3Rs
- 3Rs embedded in policy and regulations
- Trusted 3Rs information source
- Enterprise and economic benefit

MATURE IMPACTS

- Reduction



NC3Rs TIMELINE

2003
Working Group established

2004–7
>10 presentations at national and international level

2006
Publication: dissemination leaflet

Workshop, including regulators

2008
Publication: *Regulatory Toxicology & Pharmacology*

2009
Publication: *Regulatory Toxicology & Pharmacology*

Regulatory change: Removal from ICH M3

2010
Publication: *Regulatory Toxicology & Pharmacology*

Workshop, including poisons centres

2010
Regulatory change: Removal from EMA guideline

A range of animals from rodents to monkeys are used in asthma research. Mice are most commonly used with studies typically involving sensitisation with allergens such as ovalbumin to elicit an 'asthma-like' reaction.

Animal models have played an important role in understanding the disease and identifying potential drug targets but there are concerns about their translation and relevance to man.

Few new drug classes have made it to the clinic during the past 50 years, with many that perform well in preclinical studies subsequently failing due to a lack of safety or efficacy. This failure has led to demands for more predictive models and tools based on the latest technologies. To help address this, and concerns about the welfare of the animals used, we are working to discover new ways of applying the 3Rs to asthma research.

We are able to measure our inputs and outputs as shown in Figure 10 on pages 48-49. However, there are as yet no interim or mature impacts. This is a long term programme and our focus has been on establishing the foundations which will ultimately result in 3Rs innovations.

Applying the 3Rs to research in a complex disease

Asthma is a complex disease which involves the inflammation of the airways. It has a number of disease hallmarks such as airway hyperresponsiveness and mucus hypersecretion.

Animal models have differences in lung anatomy and immunological responses compared to man; nevertheless, they have been the mainstay of the asthma research community. Providing non-animal alternatives which are better able to mimic the disease will take time as there are considerable hurdles to overcome – scientific, technical and attitudinal.

Success requires ensuring firstly that the right expertise is brought together to deliver new research models that combine exposure to the environment, components of the immune system, the mechanical stimulation associated with breathing and microfluidics to mimic the circulatory system; and secondly that any reluctance in the asthma research community, to change from animal models because of concerns about comparisons with historic data, is addressed.

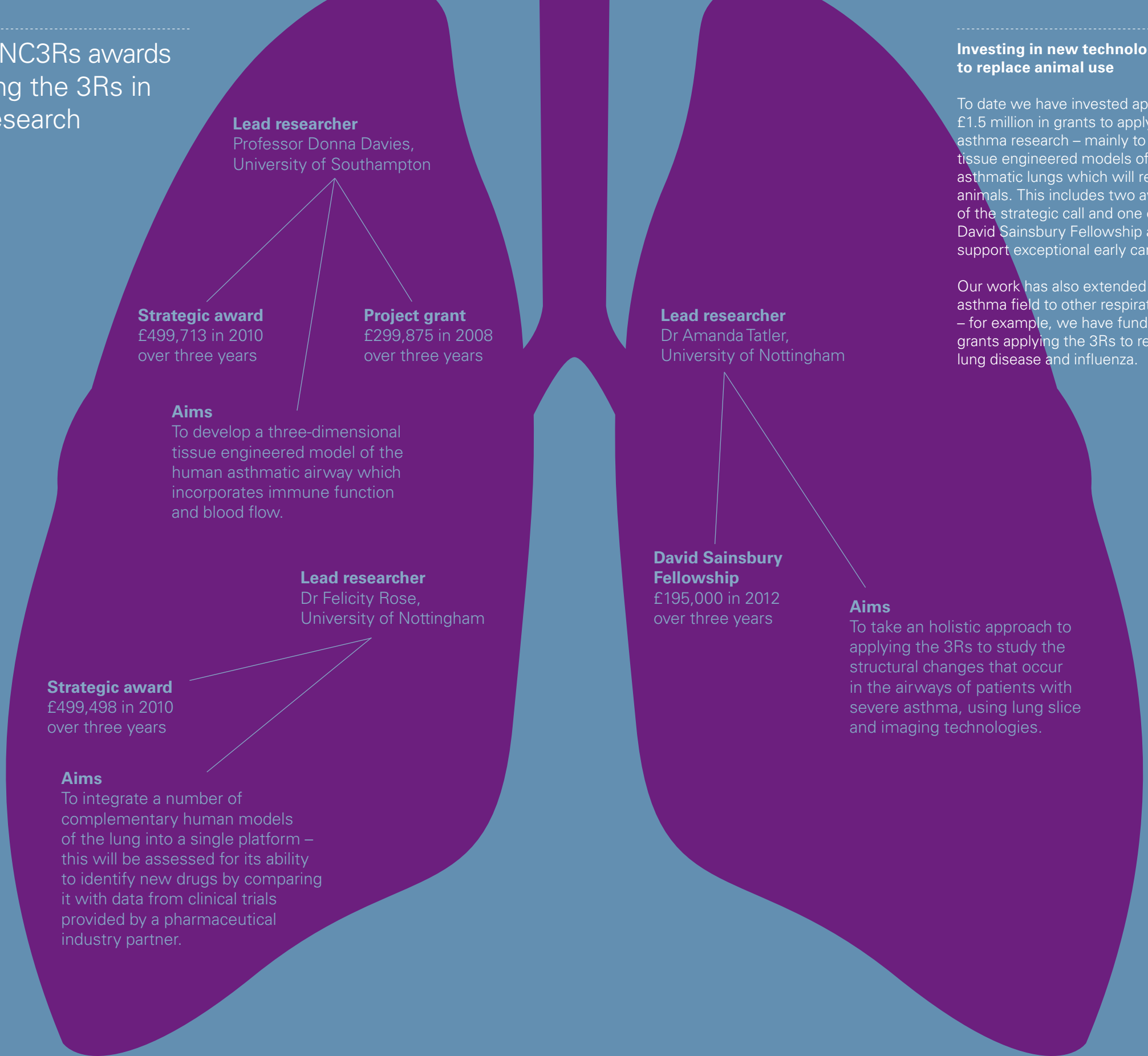
Building a 3Rs community

Our initial priority has been to engage the asthma research community to stimulate new collaborations between *in vivo* researchers, clinicians, mathematicians and tissue engineers. In 2009, we co-hosted a workshop with the MRC which was attended by representatives from all of the UK's leading asthma research teams. The aim was to review the current models used in asthma research and to highlight new opportunities for exploiting the latest technologies to minimise animal use. Based on this we launched a strategic call for research proposals in 2010, working with Asthma UK. The output of the workshop was published in *Drug Discovery Today*.

In 2011, working with the EPSRC-funded Maths in Medicine Study Group we co-sponsored, with scientists from the University of Nottingham, a challenge to explore the potential of mathematical modelling to replace and reduce animal use for studying airway smooth muscle turnover in asthma. The output of the workshop was published online in November 2011 (www.maths-in-medicine.org/uk/2011/asthma/report.pdf). This has led to a new collaboration, between asthma researchers from the University of Nottingham and mathematicians from four other UK universities, to exploit clinical information to address data gaps identified by the Study Group.

To ensure a coordinated approach to our activities, in 2012 we convened an expert group of asthma researchers from industry and academia. The group will help us to identify research priorities, stimulate greater cross-sector collaborations and raise the profile of 3Rs activities.

Figure 9: NC3Rs awards for applying the 3Rs in asthma research



Investing in new technologies to replace animal use

To date we have invested approximately £1.5 million in grants to apply the 3Rs to asthma research – mainly to develop human tissue engineered models of the normal and asthmatic lungs which will replace the use of animals. This includes two awards as a result of the strategic call and one of the inaugural David Sainsbury Fellowship awards, which support exceptional early career scientists.

Our work has also extended beyond the asthma field to other respiratory diseases – for example, we have funded two project grants applying the 3Rs to research in fibrotic lung disease and influenza.

FIGURE 10: Supporting 3Rs innovation in respiratory disease research

EVALUATION FRAMEWORK FOR THE NC3Rs

INPUTS

– Research funding
– Training and development
– Forum for data sharing
– Symposia and other events
– Collaboration with other organisations

OUTPUTS/OUTCOMES

- Increased awareness and understanding of the 3Rs
- Creation of new knowledge and 3Rs research materials
- Development of collaborative networks
- Dissemination activities

NC3Rs TIMELINE

2008 Project grant: University of Southampton

2009 Workshop co-hosted with MRC

2010 Strategic award: University of Nottingham

2010 Strategic award: University of Southampton

2011 Publication: *Drug Discovery Today*

2011 Publication: Maths in Medicine Study Group meeting report

2012 David Sainsbury Fellowship: University of Nottingham

2012 Asthma Advisory Group meeting

ANNEX 1: THE HOME OFFICE STATISTICS ARE NOT A GAUGE OF PROGRESS IN THE 3Rs

The annual statistics published by the Home Office on procedures performed under the Animals (Scientific Procedures) Act 1986 contain a large amount of information on animal use – numbers, species and purpose. At first sight it would be expected that they would be a good benchmark on 3Rs activities in the UK and indeed they are routinely used in this way by some campaign organisations. The statistics were, however, never intended to be a gauge of progress in the 3Rs, and in any case their utility for such a purpose is limited for a number of reasons.

Recent reviews of the Home Office statistics have not significantly changed either the format or the information provided although the requirement for harmonised statistical reporting under Directive 2010/63/EU on the protection of animals used for scientific purposes may lead to some changes. Even so, it is debatable whether collecting information on animal numbers through the annual statistical returns could be done in such a way as to provide better information on the 3Rs. More detail and clarity may be helpful but this has to be considered against the administrative burden and costs for those involved in providing, collecting and analysing the data.

Many factors influence animal use

The number of animals reported in the annual statistics is influenced by a range of scientific and strategic factors independent of the 3Rs. Such factors include:

- **Strategic investment in particular research areas or geographic locations:** Recent investment announcements by the major funding bodies (e.g. the Biomedical Catalyst Fund or UK Regenerative Medicine Platform) may increase animal use in specific fields of research. Strategic decisions by some companies to cut their research in the UK or to place animal studies overseas may on the other hand lead to a decrease in UK numbers.
- **Availability of new technologies:** The introduction of techniques to genetically modify animals has resulted in a 42% increase in animal procedures since 2001.
- **Regulatory requirements:** The EU's REACH (Registration, Evaluation, Authorisation and restriction of CHemical substances) regulation requires information on the potential hazards that chemicals pose to humans and the environment to be available by 2018 for over 30,000 chemicals already on the market in the EU. In many cases this will require new animal testing and estimates of the resulting increase range from 9 to 64 million animals. How much of the REACH testing will be conducted in the UK is not known but it is reasonable to predict that there will be a significant increase in numbers.

The statistics lack context

Information on species, numbers, genetic status and purpose of use are provided in the statistics. Some of this, such as the information on genetically altered animals, can potentially be helpful in terms of measuring our impact. For example, if the research we are funding to reduce the use of mice used in complex genetic experiments is successful, there should be a corresponding decrease in the figures in the statistics.

On the whole, however, the information presented lacks the necessary detail and context to allow it to be used for 3Rs purposes. In many instances the categories used are so broad and non-specific (e.g. nervous system) that it is impossible to know how many animals were used for a specific purpose and consequently they are of limited value for measuring 3Rs impacts. For example, it is impossible to determine from the 'nervous system' category whether the research we have funded in the areas of multiple sclerosis or epilepsy is reducing animal use. This information can only be obtained from the researchers we support and while this is helpful it is usually specific to their laboratories and therefore is difficult to extrapolate to other users.

The same is true for research to replace the use of animals. For example, we have funded the development of *in vitro* assays which directly replace the use of mice in tests to quantify some types of clostridial toxins and toxoids during vaccine manufacture. This has replaced the use of hundreds of mice at the vaccine manufacturer MSD Animal Health but this success is not readily identifiable in the statistics because information on veterinary vaccines is included in the broad category 'applied studies – veterinary medicine'.

3Rs advances may be masked

The statistics can hide important information on the 3Rs. Reductions in animal use for some studies have been achieved but this may not be apparent if there is an overall increase in the number of such studies performed. For example, most monoclonal antibody drugs are tested in non-human primates because of their target and species specificity. Working with the pharmaceutical and biotechnology industries we have identified opportunities to reduce the number of non-human primates used in the development of monoclonal antibody therapies by 64%.

Implementation of this reduced animal use strategy by the companies and contract research organisations, however, may not be reflected in a decrease in the number of non-human primates recorded in the statistics for pharmaceutical testing. This is because the number of monoclonal antibodies in the drugs pipeline is increasing and therefore the overall number of studies using non-human primates may rise, even though fewer are used per antibody.

Developments which avoid animal use are not easily counted

There are many examples, including in the research we fund on cancer drug screening, where new methods allow animal studies to be avoided. These are not one to one replacements for the animal studies. Instead new *in vitro* tools are used to screen drugs so that only those that are likely to be suitable for further development are taken into animal studies. This avoids wasting animals on drugs destined to fail in preclinical development – animals which would, if used, have been recorded in the statistics. It is difficult to envisage how collecting information centrally on efforts to avoid unnecessary animal use could be done in practice (without an unnecessary burden on scientists and institutions) but it does illustrate the complexity of measuring the 3Rs.

Not all animals are included

The statistics only include information on those animals used in scientific procedures likely to cause pain, suffering, distress or lasting harm. Not all animals used for a scientific purpose are counted such as those killed for tissues or organs. Consequently, the impact of some 3Rs efforts will not be manifest in the statistics. For example, research we have funded to develop pseudoislets to study pancreatic beta cell function in diabetes has resulted in a reduction in animal use by 1000 mice per year in one UK laboratory alone – this would not be reflected in the statistics.

There is little information on animal welfare

Little information is presented in the statistics that could be used to examine progress on refinement, either at a generic or specific level. The emphasis on numbers means that our work to refine animal models associated with significant suffering or mortality, such as models of pulmonary embolism and fish acute toxicity studies, would never be captured in the statistics.

Acknowledgements

We are grateful to members of the NC3Rs metrics working group for their expert advice and guidance in developing the evaluation framework:

Professor Jamie Davies (Chair)	Professor of Experimental Anatomy, University of Edinburgh NC3Rs Board member
Mr Kevin Dolby	Evaluation Adviser, Wellcome Trust
Dr Maggy Jennings OBE	Head of Research Animals Department, RSPCA
Dr Maggie Leggett	Head of the Centre for Public Engagement, University of Bristol
Professor Paul Matthews OBE	Chair in Clinical Neuroscience, Imperial College London Vice President for Imaging, GlaxoSmithKline
Dr Mark Prescott	Head of Research Management and Communications, NC3Rs
Mr David Smith CBE	Independent Previously Director, Special Projects, Department for Business, Innovation and Skills

Acronyms

ARRIVE	Animal Research: Reporting *In Vivo* Experiments
BBSRC	Biotechnology and Biological Sciences Research Council
CNRS	Centre National de la Recherche Scientifique
Defra	Department for the Environment, Food and Rural Affairs
EMA	European Medicines Agency
EPSRC	Engineering and Physical Sciences Research Council
IACUC	Institutional Animal Care and Use Committee
ICH M3	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
INSERM	Institut National de la Santé et de la Recherche Médicale
MRC	Medical Research Council
NERC	Natural Environment Research Council
PRIM&R	Public Responsibility in Medicine and Research
RCUK	Research Councils UK
SME	Small and medium enterprises

National Centre for the Replacement, Refinement and Reduction of Animals in Research

provided by the NC3Rs

Amount invested in awards

2 Training and development

Number of lectures to BSc, MSc and PhD students

Number of data sharing projects, individuals and research organisations involved

4 Symposia and other events

5 Collaboration with other organisations

6 Information resources

OUTPUTS/OUTCOMES

Initial results (e.g. number of papers arising from funded research, event attendance rates)

Number of applications to all funding schemes and other competitions (e.g. prizes)

Number of grant holders, students, fellows, prize winners

1 Improved awareness and understanding of the 3Rs

Percentage of grant applications in the fundable range

Number of unique delegates at NC3Rs events

Analysis of event feedback questionnaires

Results of attitudinal surveys

Number of enquiries from legislators, parliamentarians and media

Number of media mentions and parliamentary questions

Traffic to website by sector/ discipline

Number of newsletter subscribers by sector/ discipline

2 Creation of new knowledge and 3Rs research materials

Number of unique papers arising from research funding or in-house programmes

Volume of intellectual property

Number of research materials developed (e.g. new models, methods, databases, reagents, technologies, techniques, software)

3 Development of collaborative networks

Number of collaborations as

4 Dissemination activities

INTERIM IMPACTS

Changes in perception, policy and practice as a result of the NC3Rs inputs and outputs

1 Increased range of scientific audiences for the 3Rs

Number of disciplines and sectors represented in the NC3Rs research portfolio and in-house programmes

Number of research funders, learned societies and other organisations involved with NC3Rs activities

Number of countries represented in NC3Rs activities (e.g. international companies, delegates at events, website traffic)

Number of research organisations funded or involved with the NC3Rs

Number of companies working with the NC3Rs

2 Delivery of highly skilled scientists, knowledgeable about the 3Rs

Number of research assistants trained on NC3Rs grants

Next role/destination data - retention in academia

Number of PhDs awarded

Number of David Sainsbury Fellows

3 New uptake of 3Rs research materials (e.g. new models, methods, databases, reagents, technologies, techniques, software)

Number of laboratories and companies adopting new research materials, developed with NC3Rs funding or from NC3Rs in-house programmes

Number of publications reporting the use of new research materials developed with NC3Rs funding or from NC3Rs in-house programmes

Citation rates and bibliometric analysis (including journal impact factors) of unique papers from NC3Rs research or in-house programmes

Number of NC3Rs researchers, Board members and staff involved in policy