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

Experiences from the UK 3Rs Centre – the NC3Rs

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NC3Rs Board member

Pioneering Better Science

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.

NC 3Rs

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

NC 3Rs

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

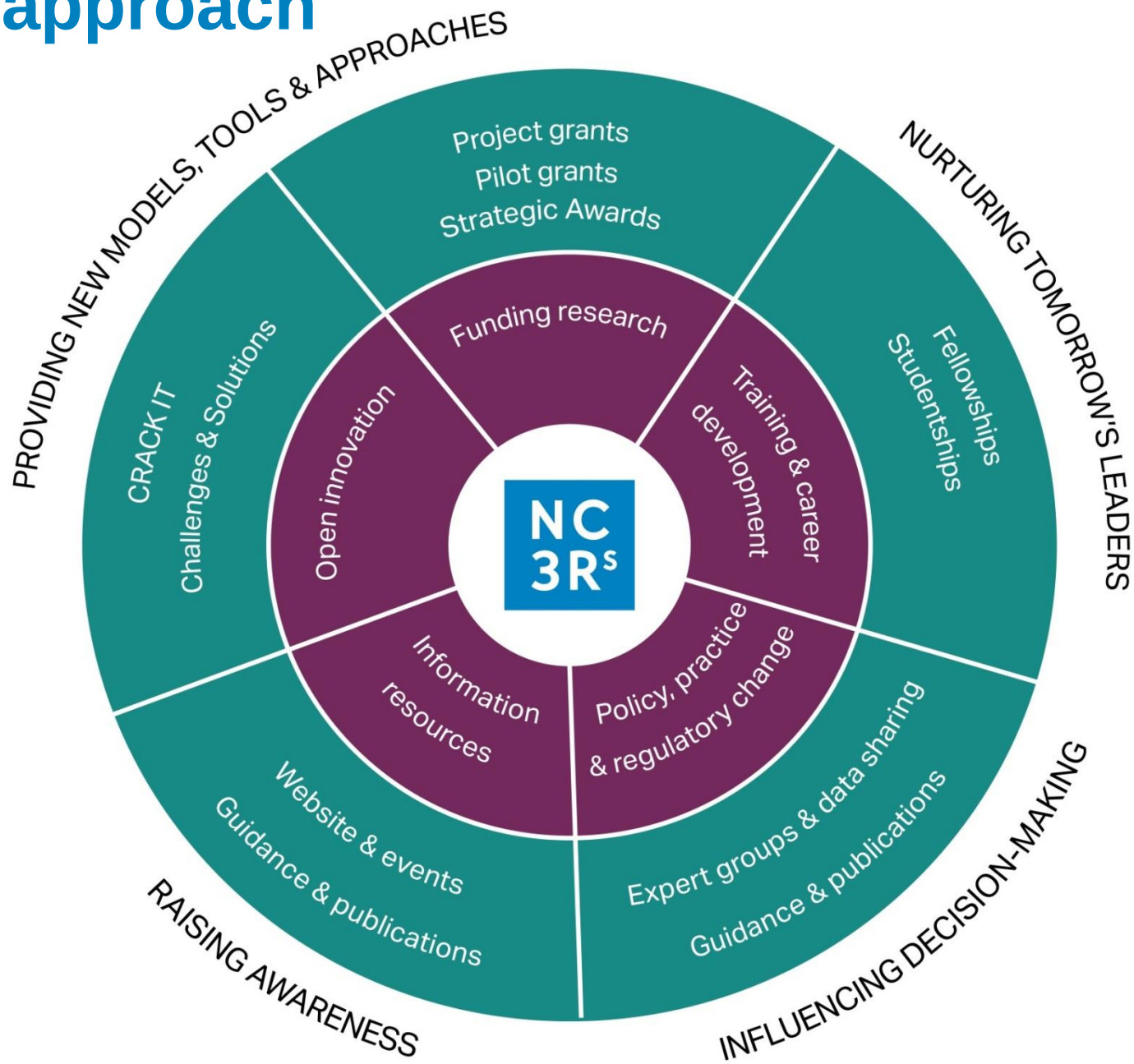
- Opportunities to address concerns & gain support

NC 3Rs

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

NC 3Rs

www.nc3rs.org.uk/funding

The scientists we fund

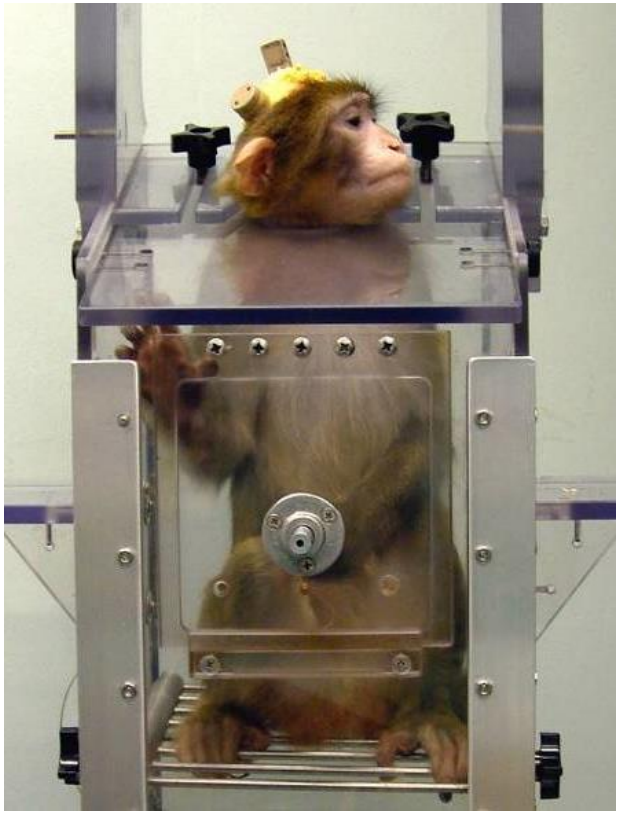
"We now have a model that avoids paralysis in our mice and has also led to the development of a new clinical trial design."

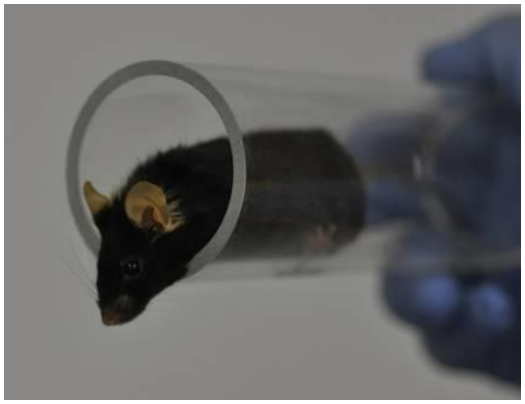
"Our *in vitro* model challenges the traditional dogma that animal studies of spinal cord injury can never be replaced."

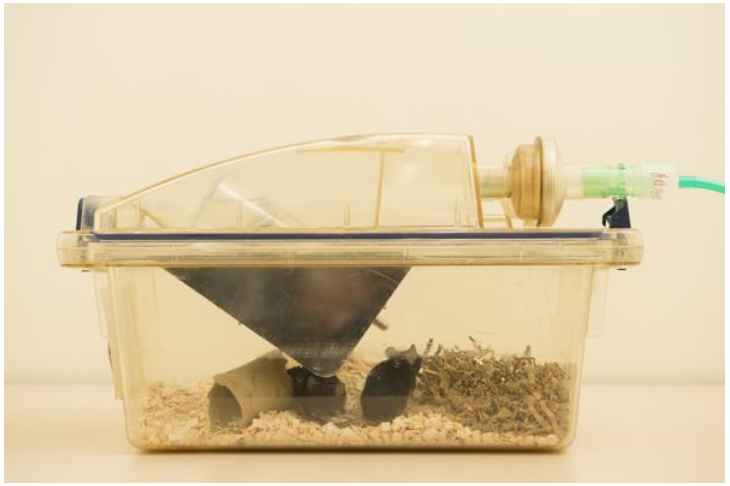
"We have combined three cutting edge technologies to use tissue from patients as an alternative to animals for studying asthma."

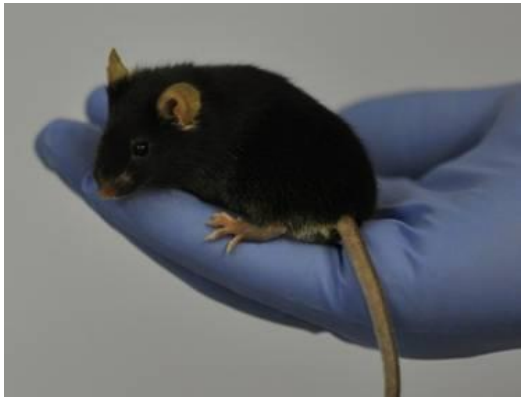
NC3Rs

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

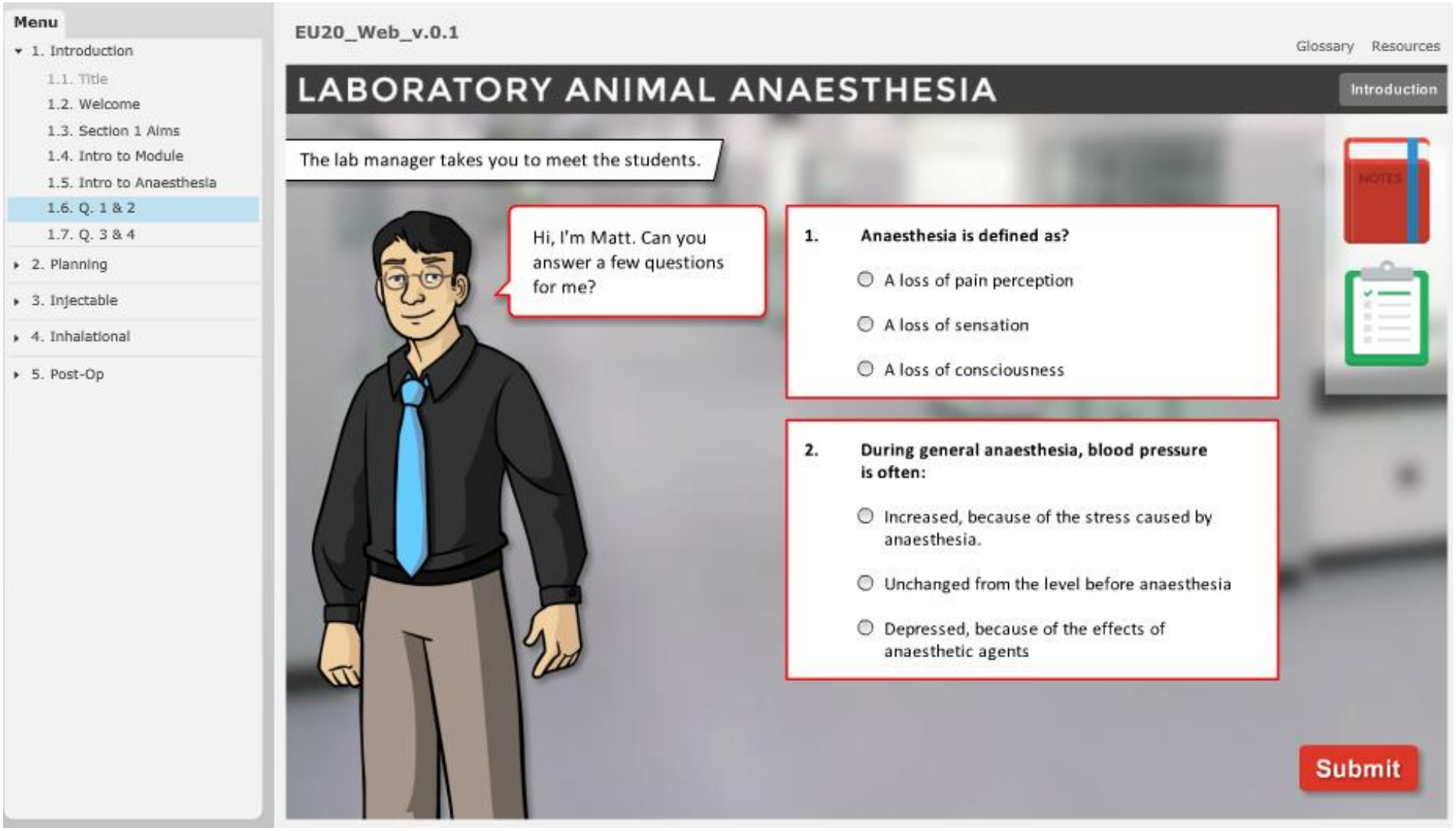








Support with online resources and e-learning



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

NC 3Rs

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

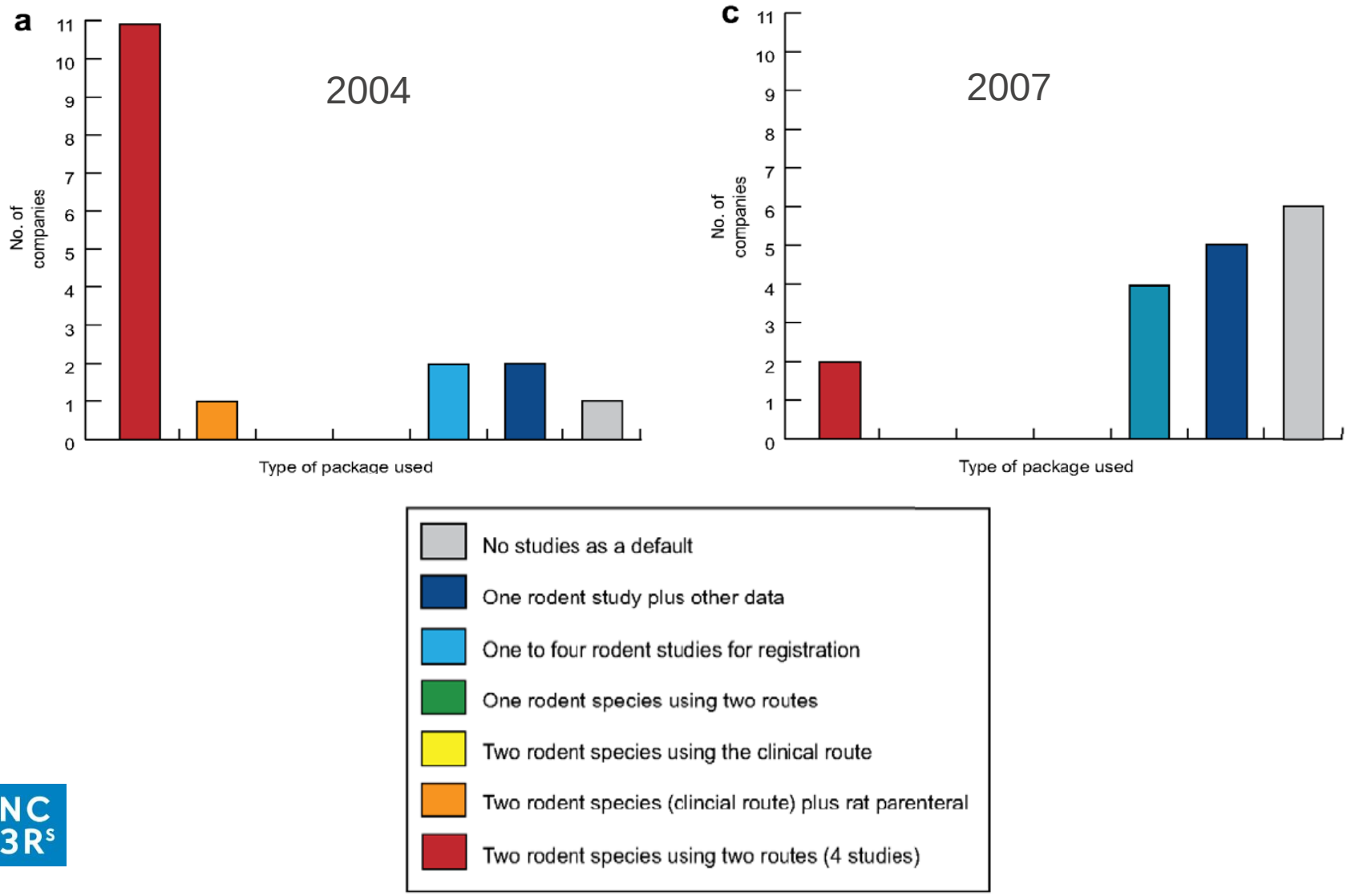
Regulatory framework

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.

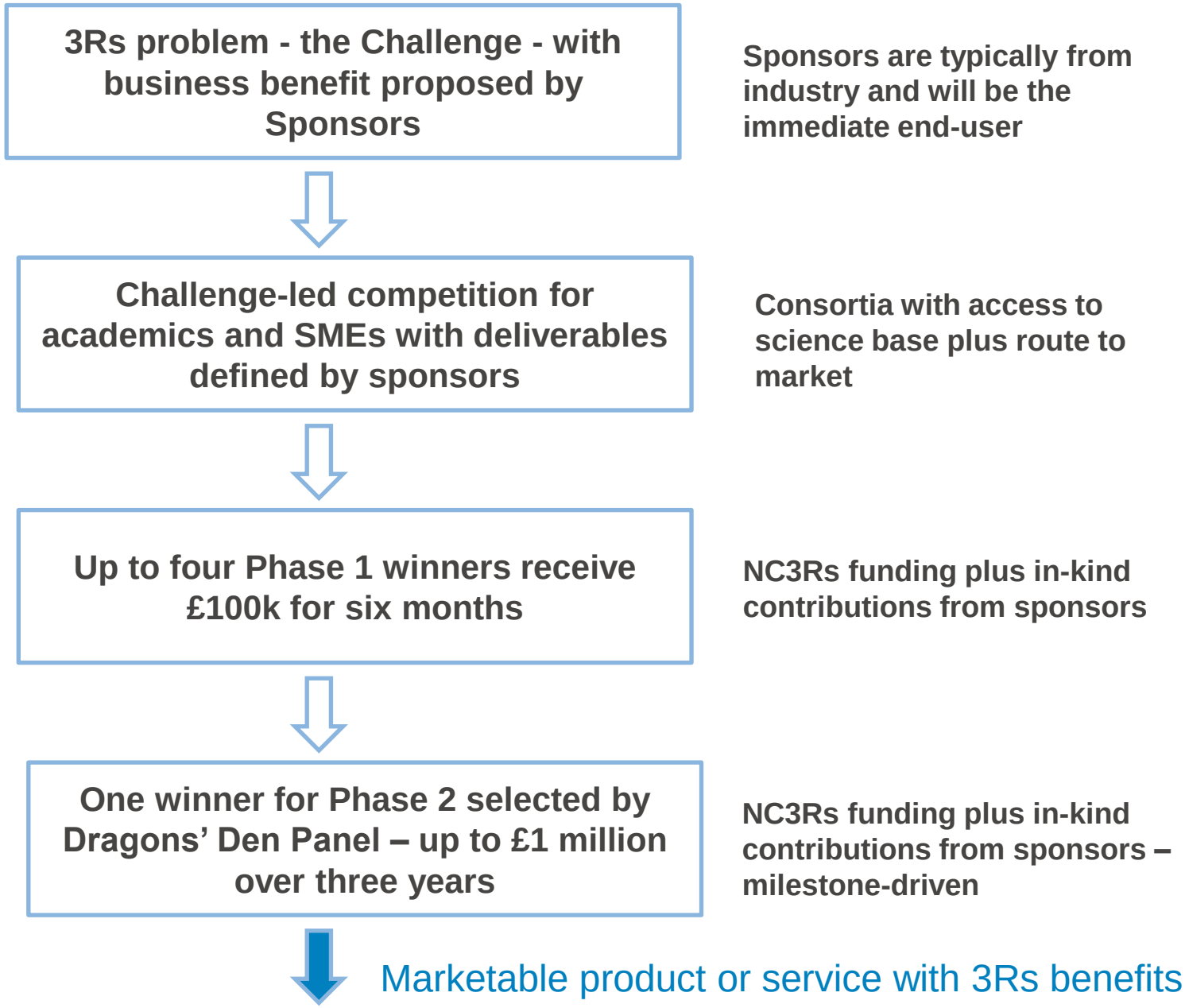
2007	2011	2012	2013
86% (67/78)	58% (76/132)	20% (27/134)	16% (15/93)

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



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

Alzheimer's Research UK
Defeating Dementia

SBRI Government challenges. Ideas from business. Innovative solutions.

MRC Medical Research Council

defra
Department for Environment Food and Rural Affairs

Technology Strategy Board
Driving Innovation

[dstl]

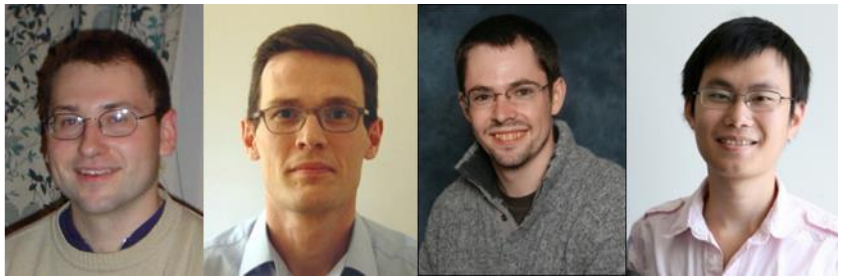
NC 3Rs

CRACK IT Sponsors

CRACK IT Challenge: Cognition

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

Imperial College London

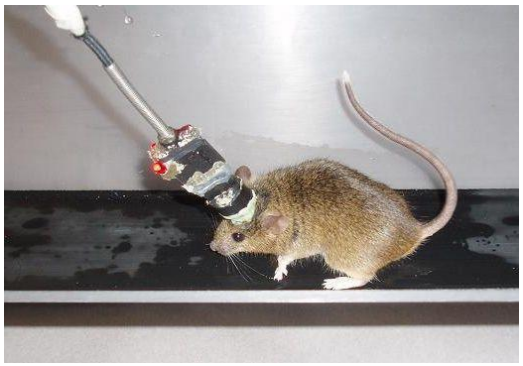


“This is an incredibly exciting and challenging project pushing the boundaries of microelectronics design. CRACK IT is a great opportunity to make people think out of the box in order to find solutions to research problems which will have a massive impact.”
Esther Rodriguez Villages, Imperial College 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 3Rs

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

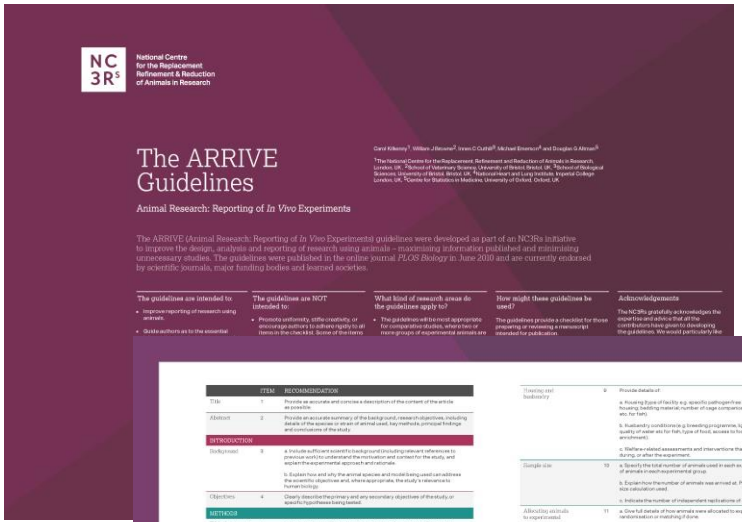
Survey reviewed 271 publications and identified key areas for improvement

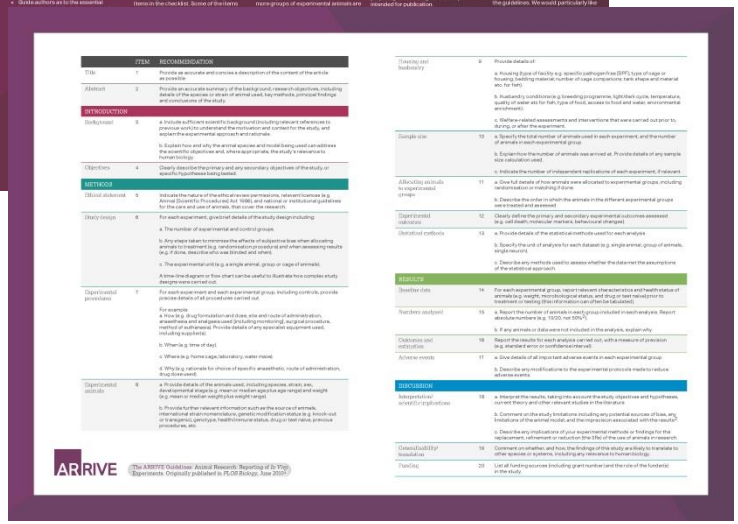
Kilkenny C, Parsons N, Kadyszewski E, Festing MF, Cuthill IC, Fry D*, et al.* (2009). Survey of the quality of experimental design, statistical analysis and reporting of research using animals. *PLoS One* **4**(11)**:** e7824.

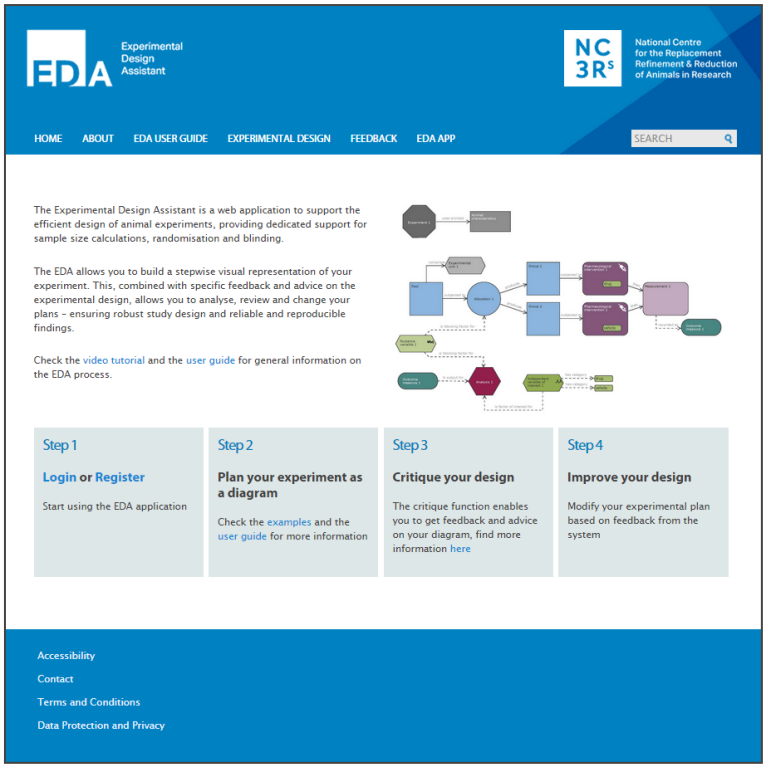
The ARRIVE guidelines and the Experimental Design Assistant (EDA)

ARRIVE

EDA Experimental Design Assistant







NC 3Rs

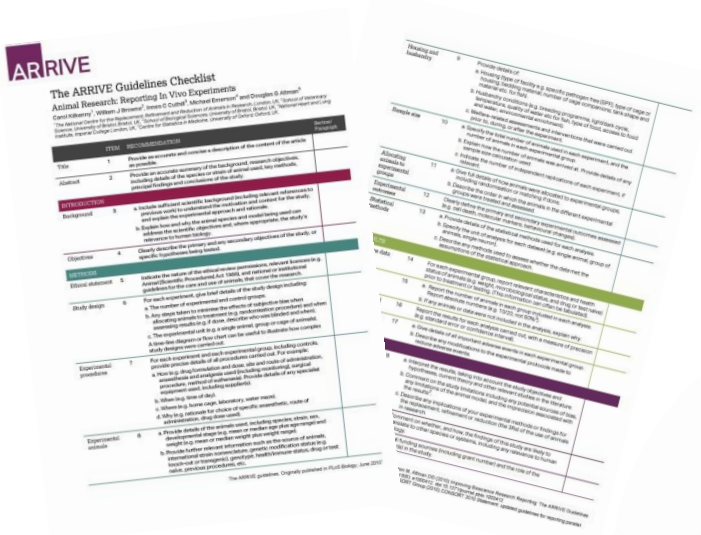
The ARRIVE guidelines

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.

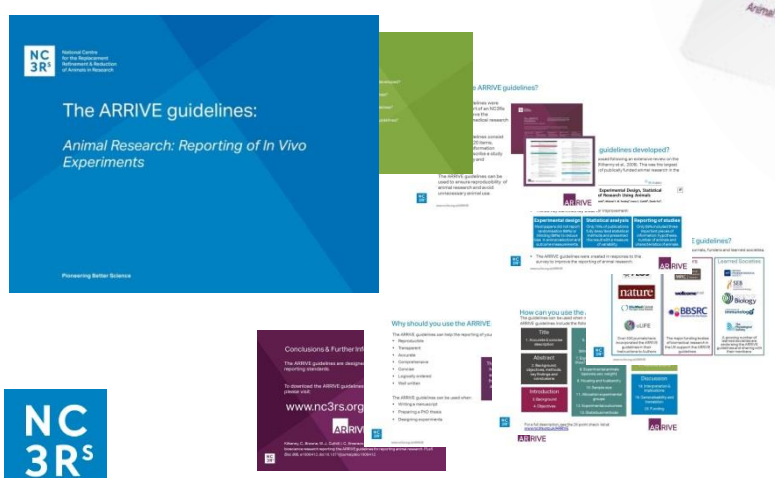
Our ARRIVE resources



Checklist

Translations

Z cards



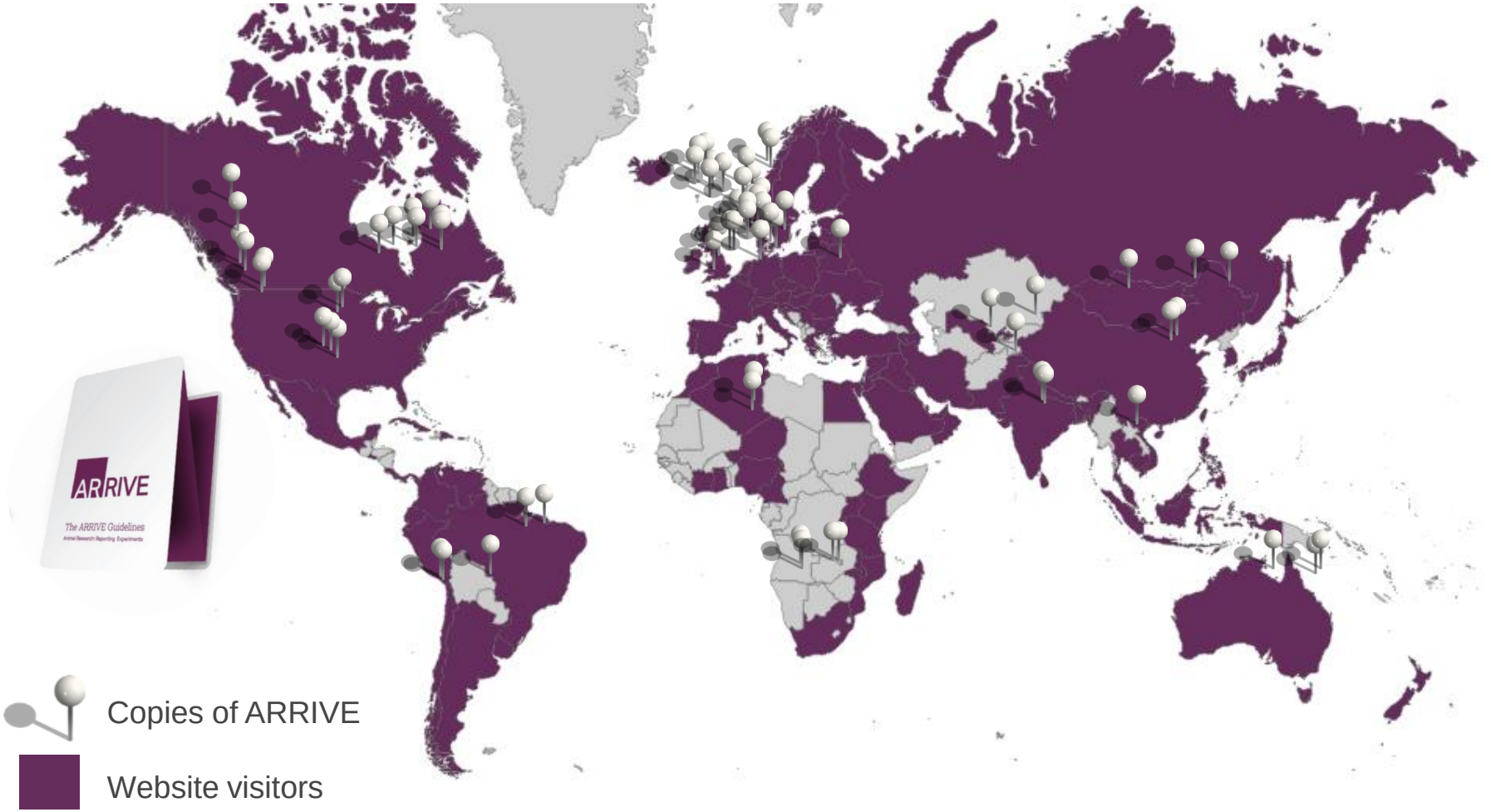
Presentation and speaker notes

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

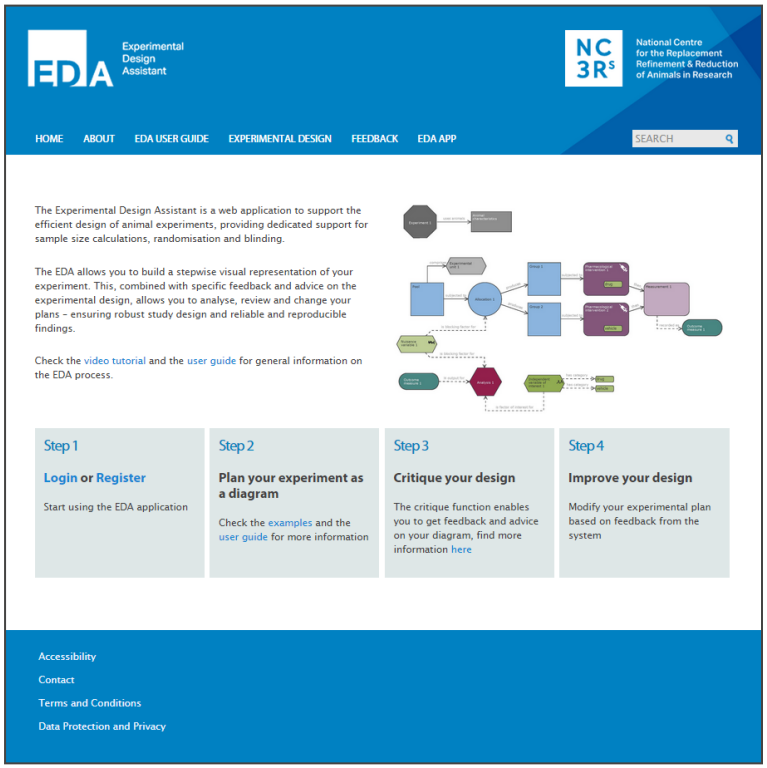
- The ARRIVE guidelines are endorsed by
  - over 580 journals
  - major funders and universities in the UK and abroad

The full list of journals can be found here:
ww.nc3rs.org.uk/ARRIVEjournals

The EDA

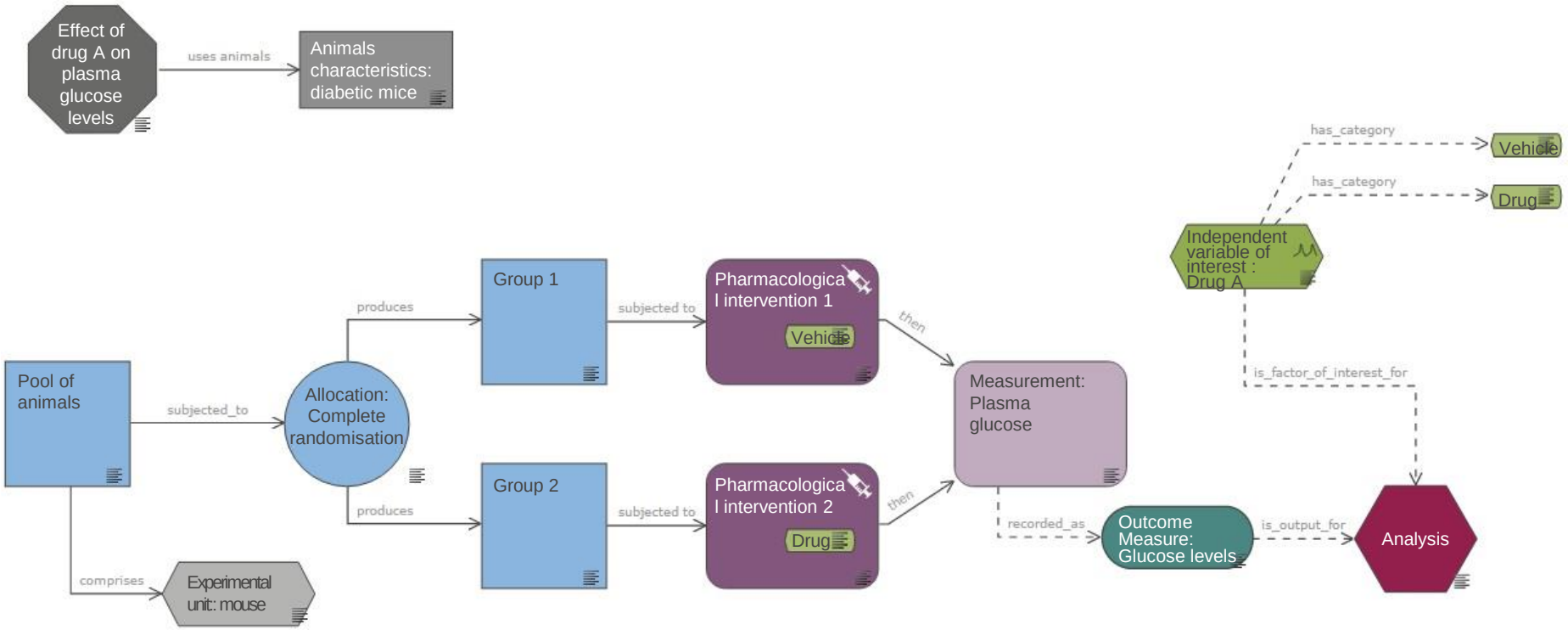
Developed to improve the design of animal experiments

- 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



https://eda.nc3rs.org.uk/

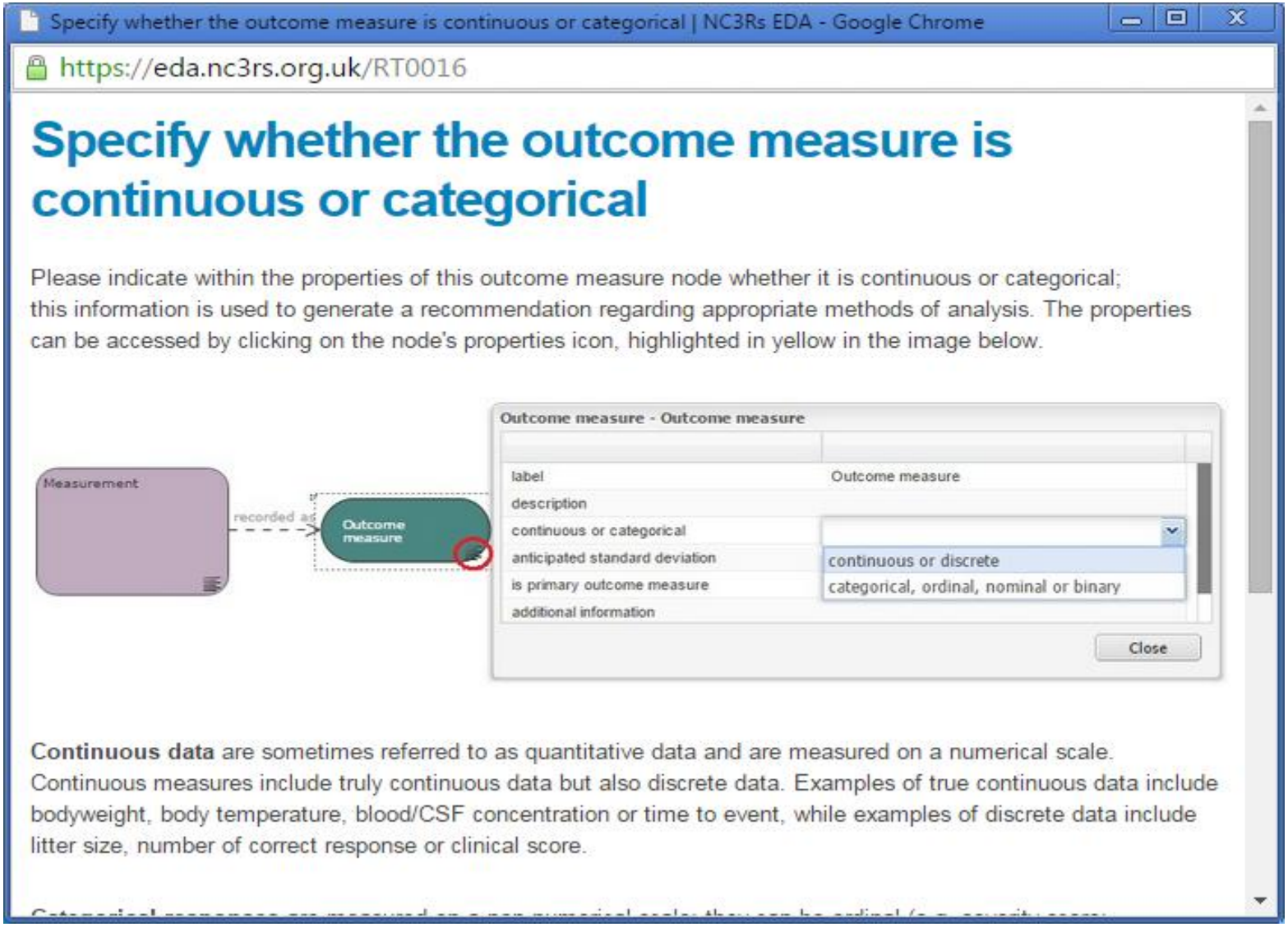
The EDA diagram



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



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	✓

NC 3Rs

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/subscribenewsletters
- Twitter: @NC3Rs