Review of Research Using Non-Human Primates

Report of a panel chaired by Professor Sir Patrick Bateson FRS

Section 1
Executive summary

1.1 In 2006 a Working Group chaired by Sir David Weatherall recommended (Recommendation 4) that the major funding organisations should undertake a systematic review of the outcome of all their research using non-human primates (NHPs) supported over the last decade.

1.2 The Biotechnology and Biological Sciences Research Council (BBSRC), Medical Research Council (MRC) and Wellcome Trust jointly commissioned and funded this review in order to:
- assess the quality, outputs and impacts of research in this area on advancing knowledge in human and animal health;
- identify the strengths and weaknesses of the funded science in this field;
- inform their future science and funding strategies; and
- feed the outcomes of the review into any Government strategy on NHP use.

1.3 The review encompassed all NHP research funded by the BBSRC, MRC, Wellcome Trust and NC3Rs and begun within the period from January 1997 to December 2006. Every effort was made to ensure that the review process was as systematic as possible and met the following criteria:
- an explicit, reproducible methodology;
- a systematic search that attempts to identify all studies that would meet the eligibility criteria;
- an assessment of the quality and value of the research to the advancement of scientific understanding;
- an assessment of the benefits, actual and potential, arising from the research to science, human and veterinary medicine, animal welfare and any other identifiable public good; and
- an assessment of the health and welfare costs imposed on the non-human primates involved in the research.

1.4 In addition to the progress reports and published papers relating to the research, each grant-holder was requested to complete a questionnaire (Appendix 1) detailing the nature of the work, the methods employed, NHPs utilised and the outcomes of the research. A bibliometric analysis of the published papers resulting from the research was also commissioned.

1.5 All the available data were scrutinised by a Review Panel made up of internationally eminent scientists in the fields of neurobiology, neurology, psychology, zoology, reproductive biology and translational research, chaired by Professor Sir Patrick Bateson FRS. All Panel members were appointed as individuals and not as representatives of their affiliated organisations.

1.6 In order to judge each piece of research, three separate dimensions were assessed independently: the scientific quality and importance of the research, the probability of medical and public benefit, and the likelihood of animal suffering. These were then brought together to make an overall judgement about whether or not the research project was acceptable and justifiable in all the circumstances. The availability of alternatives was also taken into account.

1.7 The Panel noted that the bibliometric analysis supported the conclusion that the NHP research under review was generally of good quality and was highly cited. Some work was of outstanding quality and highly cited. However, some work raised specific concerns. The Panel also noted that the identification and tracing of medical benefit derived from specific research projects was difficult in most cases, although this was in part because of the short time which had elapsed between the commissioning of the research and the review.

1.8 Overall, the Panel agreed that in many cases the use of NHPs was justifiable even in the context of current understanding of animal welfare and advances in knowledge that might now render some work on living animals unnecessary. However, the Panel was concerned about the small proportion (approximately 9%) of research programmes from which no clear scientific, medical or social benefit had emerged.

1.9 Effective knowledge transfer from the research laboratory to areas of wider application is a key issue in many areas of science, but is arguably even more pressing when the welfare of sentient creatures has been compromised during the search for improvements in understanding. A key concern in some instances, therefore, related to failures to publish results, whether positive or negative, and the effectiveness of mechanisms employed for knowledge and technology transfer.

1.10 Other areas for attention noted by the Panel included the skills base and training of research teams, and the barriers to the pursuit of research on NHPs in the UK imposed by relative costs, harassment of workers and administrative burdens.

1.11 The recommendations of the review are justified in the main body of the report. They were as follows:

Recommendation 1
The Panel noted that the processes needed to maximise scientific quality and impact are already in place as part of mechanisms for the funding of NHP research, and concluded that each application for funds to support research using NHPs should be subject to rigorous review of the scientific value of the research, the probability of medical or other benefit, the availability of alternative approaches, and the likelihood and extent of animal suffering. In particular, care should be taken to ensure that the review is a dynamic process that keeps pace with and employs best current knowledge concerning animal welfare, scientific advances and changes in public perceptions.

Recommendation 2
In considering research proposals, peer reviewers and panel members should critically examine the justification for the choice of species and whether human subjects could be used as alternatives. Consideration of the potential for alternatives should extend beyond rodent models; the potential of *in vitro* and *in silico* approaches should be considered, and the potential of other species as models should be fully explored before a decision is made to employ NHPs. Care should be taken to ensure that peer reviewers and panel members collectively possess the full breadth of knowledge and experience to assess all the relevant options.

Recommendation 3
It is an ethical imperative that maximum benefit be derived from studies employing NHPs. When considering research proposals, funders should take into account the nature of the organisation to which the researcher is affiliated, with regard to the extent of integration of teams working in different fields and at different points along the spectrum of science from fundamental to applied. They should consider whether any structures or processes are in place to facilitate knowledge transfer or to ensure the exploitation of outcomes of the proposed work. They should also take into account the researcher's plans for knowledge transfer or other exploitation. Funders should encourage data-sharing and should consider creating or supporting online repositories for digitised data which may be made freely available to other researchers.

Recommendation 4
Science policy-makers together with the public sector, private sector and charitable funders of research should commission a working group to develop proposals for a mechanism (output-scanning) to identify research results with potential to deliver improvements to healthcare or other significant benefits to society, and to assess the extent to which the potential benefits are achieved. The stakeholder bodies should develop mechanisms to facilitate exploitation of new knowledge derived from NHP studies for clinical or other benefits to society.

Recommendation 5
The Review Panel applauded the efforts by some of the grant-holders to deliver 3Rs improvements as part of or alongside their major research outcomes, and particularly their willingness to publish the results of such work. The Panel also noted that funders require implementation of the principles embodied in *Responsibility in the use of animals in bioscience research: Expectations of the major research council and charitable funding bodies* as a precondition for receiving funds. In defining research grant terms and conditions, funders should take particular care to encourage, and where appropriate require, the active dissemination of 3Rs improvements through the international research community and should ensure that appropriate monitoring and enforcement procedures are in

place to encourage full compliance with all aspects of the *Responsibility* guidance.

Recommendation 6
Researchers using NHPs have a moral obligation to publish results – even if negative – in order to prevent work being repeated unnecessarily. In considering grant applications, funding bodies should take into account the previous publication performance of applicants and their research groups. Where there has been a history of limited dissemination or exploitation, the funders should consider with particular care the likely balance of the animal welfare cost against the potential benefits arising from funding that application.

Recommendation 7
Conducting the highest quality NHP research demands a range of skills and resources. Funders should take care to ensure that the teams and infrastructure involved in a funding bid are fully appropriate to the requirements of the intended research.

Recommendation 8
Highly invasive and long-term NHP research often carries a high welfare cost. In such cases, funders should take particular care only to fund projects with a very high likelihood of producing scientific, medical or social benefit. Wherever possible, funders should take steps towards encouraging a preferential or complementary use of less invasive techniques such as neuroimaging and transcranial magnetic stimulation.

Recommendation 9
The Panel noted that all funded NHP research, regardless of where it is conducted, should comply with the *Responsibility* guidance and NC3Rs guidelines *Primate accommodation, care and use*, and that the NC3Rs had visited laboratories in the UK and overseas to give advice and to monitor compliance. The Panel's view was that funding bodies should take all necessary steps to satisfy themselves that work on NHPs funded by them outside the UK meets the standards acceptable in the UK.

Recommendation 10
The Home Office should review its performance with the regard to the operation of the Animals (Scientific Procedures) Act to ensure that inefficiencies of processes or inconsistent advice to researchers do not create unreasonable delays or obstacles to appropriate NHP research. Accreditation of the enforcement processes to the appropriate ISO standard should be considered.

Recommendation 11
The recommendations of the Weatherall Report (Recommendations 13–15) concerned with addressing the impact of both the costs of work in the UK and harassment by activists should be followed up as a matter of urgency. Researchers in the UK using NHPs still experience an unacceptable level of personal risk. The risks and the high costs of NHP research are increasingly perceived as barriers to continued work in the UK.

Recommendation 12
In their public engagement, the funders and researchers should avoid overstating and generalising the medical benefit of NHP research, since this cannot be substantiated in many cases. Instead, the statements should reflect the actual basis for funding decisions, recognising that these are often based on scientific value.

Recommendation 13
The Panel noted that since the period under review, the funders had made progress in improving the collection of research outputs through standard end of grant templates and, in some cases, through annual data collection. The Panel recommended that a culture of routine output reporting should be embedded in all funded researchers and that provision of such data should be a condition of the grant. In particular, where grants were awarded on the promise of human health benefits, the grant-holders should provide evidence of interest in and use by the medical and biopharmaceutical sectors. Failure to update funders regularly with relevant data should disqualify grant-holders from further funding.

Recommendation 14
The Home Office should reconsider its advice to research workers to destroy records after five years.

Recommendation 15
Further reviews of the outcomes, benefits and impact of NHP research should be carried out periodically.

Section 2
Background to the review

2.1 The Weatherall Report and its recommendations

2.1.1 In 2006 a working group chaired by Sir David Weatherall FRS FMedSci examined the scientific and ethical case for the use of NHPs for research into the prevention or treatment of disease. It also considered fundamental research with the long-term potential to achieve the same end. The members of the working group accepted a moral case for careful, well monitored and meticulously regulated NHP research, provided it was of high quality and had the potential to benefit mankind, and if it was the only way of solving important scientific or medical questions. After an assessment of submitted written and oral evidence, together with the relevant scientific literature, the group concluded that the scientific case was strong for maintaining work on NHPs for carefully selected research problems. The group emphasised the continued need for each case to be judged individually, according to a rigorous assessment of the welfare costs to animals involved, the potential scientific or medical benefit of the work and the availability of other approaches. It also argued that a continuum existed between fundamental and applied research.

2.1.2 The working group noted the body of work directed at developing alternatives to NHPs in research, including advances in molecular and cell biology, non-invasive imaging, computer modelling and systems biology approaches. While some of this work had already borne fruit, it was not possible to predict how much time needed to elapse before many of these projects attained their objective. The view was expressed that all those involved in NHP research must ensure that their decisions were supported by an ongoing assessment of the biological and medical importance of the work, including approaches that did not require the use of NHPs, together with consideration of every aspect of the welfare of the animals involved; and that such ongoing assessments should be based on and supported by a breadth of knowledge of the most current developments in the relevant fields. The working group therefore recommended, *inter alia*, that "*as part of their ongoing programmes to assess the outcomes of their research, the major funding organisations should undertake a systematic review of the outcome of all their research using NHPs supported over the last decade*". The current review was conducted as a response to that recommendation.

2.1.3 Since 1997 there have been a number of developments in the supply of NHPs in the UK and in the approach to the welfare of animals used in research which have impinged on the conduct of the projects considered in this review. A timeline of these relevant events is set out in Appendix 2.

2.2 The funding of NHP research

2.2.1 Funding of academic research involving NHPs in the UK is mainly undertaken by the Biotechnology and Biological Sciences Research Council (BBSRC), the Medical Research Council (MRC), the Wellcome Trust and the National Centre for the Replacement, Refinement and Reduction of Animals in Research (NC3Rs) (the funders).

2.2.2 Although the funding of research using animals is an important part of the funders' research portfolios individually and collectively, NHP research constitutes a very small proportion of the total. In the case of the MRC this amounted to an average of 0.43% of total annual expenditure on research per year over the 10 years 1997–2007. The Wellcome Trust's average spend on research using NHPs was 0.16% per year of their total spend on research over 1999–2009, while the BBSRC spent an average 0.12% per year of their total spend on research per year over the same 10 year period. Whenever possible, bioscience research avoids the use of animals altogether. Where the use of animals is required, a number of considerations must be adhered to, including that the research:

- is fully compliant with current Home Office legislation;
- has been approved by a local ethics committee;
- has been successfully independently peer reviewed; and

- due consideration has been given to the replacement, reduction and refinement (the 3Rs) of animal use and no viable non-animal alternatives exist.

In addition to scientific peer review organised by the funders, since 2004 all grant, fellowship and studentship applications to the MRC, BBSRC and Wellcome Trust involving the use of NHPs, cats, dogs and equines are reviewed by the NC3Rs. Other research proposals that raise ethical issues or animal welfare concerns may be referred to the NC3Rs as appropriate. The Centre's role is to help identify and address any animal welfare issues, to help ensure that any 3Rs opportunities are exploited, and to monitor the implementation of guidelines, such as *Responsibility in the use of animals in bioscience research: Expectations of the major research council and charitable funding bodies* and *Primate accommodation, care and use,* produced with the funders to support best practice.

2.2.3 NHP research is funded across a wide range of awards:

- BBSRC – response mode and research initiative grants;
- MRC – research grants, programme grants, centre grants, fellowships and unit programmes;
- Wellcome Trust – all research grants and fellowships ranging from PhD studentships up to Principal Research Fellowships;
- NC3Rs – research grants, PhD studentships and small awards.

2.3 Objectives of the review

2.3.1 In accordance with Recommendation 4 of the Weatherall Report, the BBSRC, MRC and Wellcome Trust jointly commissioned and funded this review in order to:

- assess the quality, outputs and impacts of research in this area on advancing knowledge in human and animal health;
- identify the strengths and weaknesses of the funded science in this field;
- inform their future science and funding strategies; and
- feed the outcomes of the review into any Government strategy on primate use.

2.3.2. The funding bodies noted that the review could not be a "*systematic*" review in the formal sense normally used in medical research, as the research in question does not lend itself to that approach. This was partly because of the different methodologies used and partly because in the case of studies involving NHPs both the number of comparable studies and the study sample sizes are small. In addition the quality of the reporting on some animal studies varies. Notwithstanding these constraints, the aim was to undertake as thorough and as comprehensive a review as the data would allow, encompassing all NHP research funded by the BBSRC, MRC, Wellcome Trust and NC3Rs initiated in the period from January 1997 to December 2006.

Section 3
Methodology

3.1 The review process

3.1.1 As has been acknowledged above, given the variety of research approaches, reporting and outputs within the remit of this review, it was not possible to follow the classical approach to a systematic Cochrane Review[1]. For example, meta-analysis of such a varied collection of studies would not have been meaningful. Moreover, the only pre-defined eligibility criteria for inclusion within this review's remit were that the research:

- was funded by one of the parties to the review;
- was initiated between January 1997 and December 2006; and
- involved the use of NHPs.

3.1.2 Nonetheless, every effort was made to ensure that the review process was as thorough as possible and met the following criteria:

- an explicit, reproducible methodology;
- a systematic search that attempted to identify all studies that would meet the eligibility criteria;
- an assessment of the quality and value of the research to the advancement of scientific understanding;
- an assessment of the benefits, actual and potential, arising from the research to science, human and veterinary medicine, animal welfare and any other identifiable public good; and
- an assessment of the health and welfare costs imposed on the NHPs involved in the research.

3.1.3 The methodology adopted therefore consisted of the following key steps:

- the identification of the studies meeting the criteria;
- data collection; and
- peer assessment by a Review Panel.

3.2 Identification of studies meeting the criteria

3.2.1 Each of the funders trawled their grants management databases for research where the use of NHPs was identified either through the request of funding for purchase of these animals, or NHPs being in the title of the grant or abstract. The detailed process undertaken by each funder was as follows:

- BBSRC funded grants involving the use of NHPs were identified from the BBSRC's Oasis database, which holds data on all grants and projects funded since 1997. A free-text search of relevant data fields (title, abstract, classifications applied) was undertaken and checked by the animal sciences programme manager. All relevant awards starting between 1.01.1997 and 31.12.06 were included in the review.
- MRC funded programmes involving the use of NHPs were identified from the MRC's Information Systems based on the classifications applied to the scientific abstracts of project and programme grants, programmes in MRC Units and Institutes, and fellowship awards. Additionally, grants which included a request for funding for the purchase or maintenance of NHPs were identified. All relevant awards starting or renewed between 1.01.1997 and 31.12.06 were included in the review. Abstracts of individual MRC funded PhD studentships based in HEIs during this period were not available for searching, but it was considered likely that any such awards involving NHPs would have been associated with other grant funding.
- Wellcome Trust funded grants were identified through the AS400 system, identifying where animals had been requested or where the grant noted that NHPs were used. All relevant awards starting or renewed between the period of 1.01.1997 and 31.12.06 were included in the review, including PhD studentships and travel awards.
- NC3Rs funded grants were identified using its searchable research portfolio. One research grant involving NHPs was activated during the period 1.01.97 to 31.12.06.

3.3 Data collection

3.3.1 In order to supplement, but not replace, the data already available to the funders in grant applications and end-of-grant reports, all those grant-holders identified by the processes described above were requested to complete a questionnaire.

Table 1: Participation rates in the survey by number of questionnaires

NO. OF QUESTIONNAIRES							
Funder	**Potential questionnaires**	**Participation declined/did not respond**	**Could not be contacted**	**Questionnaires completed by grant-holder**	**% completed by grant-holder**	**Total no. considered by Panel***	**% considered by Panel**
Wellcome Trust	33	2	3	28	85%	28	85%
MRC	27	1	1	25	93%	27	100%
BBSRC	11	0	1	10	91%	11	100%
NC3Rs	1	0	0	1	100%	1	100%
Total	**72**	**3**	**5**	**64**	**89%**	**67**	**93%**

* Includes three populated by funders with information held on file.

The questionnaire was designed to gather information about the nature of each research project and its outcomes and impacts. A copy of the questionnaire is at Appendix 1.

3.3.2 The funders first approached those researchers who had held qualifying grants seeking their agreement to participate. Those who agreed to participate were contacted by Brian Jamieson & Associates, who had been engaged by the funders to facilitate the survey and, in particular, to ensure completeness within each individual questionnaire and consistency across the questionnaires.

3.3.3 Over the period early November 2010 to early February 2011 Brian Jamieson & Associates liaised with several dozen researchers, encouraging them to complete questionnaires, advising on the scope and the level of detail of information required. In general his approach was to provide in an accessible and consistent format the information that the Review Panel would need for its assessment. Much of the dialogue with researchers was conducted by telephone and email. A few researchers chose face-to-face interviews. The subsequent report was used extensively when drafting the present report.

3.3.4 The outputs from the survey were:

- 67 completed questionnaires, most including a completed questionnaire form and a publication list;
- a spreadsheet listing the grants included within the survey, noting which were the subject of a completed questionnaire and capturing details of responses; and
- a summary report.

3.3.5 Table 1 shows the overall participation rate after progress chasing by the funders. Only two researchers responded to say they were unwilling to participate; one of these has retired from research and the other has left the UK. Several could not be contacted for a variety of reasons; some had moved out of research, retired, moved overseas or died. No recognisable common characteristics could be discerned across those who, for whatever reason, did not return their questionnaires.

Further detail on how the issue of non-responders was addressed is given in paragraphs 5.9.2–5.9.5.

3.4 Bibliometric analysis

3.4.1 Since science that is not communicated delivers no benefit, it was decided early in the review process that it would be helpful to have data on bibliometric indicators to assist in the assessment of the outputs and impact of the research under review. The funders commissioned Thomson Reuters' Evidence to provide bibliometric data and analyses of research published between 1997 and 2009 by 37 named individuals supported by the BBSCR, MRC, Wellcome Trust and NC3Rs. The aim was to provide a quantitative assessment of the quality and impact of the research by reference to volume output and citation impact.

3.4.2 Publication lists, collated by individual grant-holders (37 grant-holders, 480 publications) were supplied to Evidence together with supplementary researcher and grant information (researcher name, affiliation, research grant title and funding body). Collated publications were matched to records in Thomson Reuters Web of Knowledge using standard bibliographic information and linked to records in the citation databases to enable bibliometric analyses. It should be noted that these grant-holders were those who responded to the initial request for information. Later responders are not therefore represented in the Thomson Reuters review.

3.5 Applying the cost-benefit approach

3.5.1 The UK Act of Parliament specifically concerned with the protection of animals used for experimental or other scientific purposes states: "*In determining whether and on what terms to grant a project licence the Secretary of State shall weigh the likely adverse effects on the animals concerned against the benefit likely to accrue as a result of the programme to be specified in the licence*"[2]. In practice the Animals (Scientific Procedures) Inspectorate performs this cost-benefit assessment on behalf of the Home Secretary. The Animal Procedures Committee (APC) provides independent advice to the Home Secretary on matters related to the operation of the Animals (Scientific Procedures) Act. Members of the APC must have regard to both the legitimate requirements of science and industry, and the protection of animals against avoidable suffering and unnecessary use in scientific procedures. Certain types of licence application are referred to the APC for an independent view, including those involving NHPs in procedures of high severity, and the use of wild-caught NHPs. The 'weighing' required by law is not an exact process since the assessment of scientific and medical or other significant public benefits and that of animal suffering, in as much as either can be quantified, are not expressed in the same terms. The assessments are incommensurate and, therefore, referring to the judgement as cost-benefit assessment is strictly speaking misleading. For the purposes of judging the overall acceptability of a piece of research, three separate dimensions need to be assessed independently: the scientific importance of the research, the likelihood of medical or other significant benefit, and the degree of animal suffering. The availability of alternatives should also be taken into account. These may be brought together to make an overall judgement about whether or not the research project was acceptable (see Appendix 3).

3.5.2 The scientific approach to the problems of assessing suffering in animals has to be evidence-based and collecting evidence requires orderly methods. Many debates about what should and should not be measured in welfare studies suggest that a variety of approaches are more likely to benefit understanding than a single approach[3]. All of the following approaches contribute to an assessment of adverse welfare: (a) measurements of physical damage to the animal, (b) measurements of the extent to which it has been required chronically to operate homeostatic mechanisms that would normally operate acutely, (c) measurements of physiological states that would be found in suffering humans, (d) measurement of the animal's preferences, and (e) considerations of the ecological conditions to which the animal is adapted, its normal social structure and the ways in which it maximises its reproductive success.

3.5.3 UK law on the use of animals in scientific procedures protects all living vertebrates except humans, including some immature forms, and one invertebrate (*Octopus vulgaris*). Under the Animals (Scientific Procedures) Act, NHPs can only be used where animals of no other species are suitable for achieving the scientific objective. Since 1995, an administrative ban has been placed on the use of Great Apes in scientific procedures, a ban on the use of wild-caught NHPs except where exceptionally and specifically justified, and further controls on the acquisition and use of NHPs. Where no replacement alternative is available, then experimental protocols must be refined in such a way as to reduce any pain, suffering, distress or lasting harm to a minimum using, for example, analgesics and humane end-points. Finally, the number of animals used must be reduced to the minimum consistent with achieving the scientific objectives of the study. These general points are derived from Russell and Burch[4], who developed the principle of the 3Rs (Replacement, Refinement, Reduction).

3.6 Scrutiny by the Review Panel

3.6.1 All the available data were scrutinised by a Review Panel made up of internationally eminent scientists in the fields of neurobiology, neurology, psychology, zoology, reproductive biology and translational research, chaired by Professor Sir Patrick Bateson FRS. Members of the Panel were identified on the basis that they were experts in areas of science that used NHPs, but did not use NHPs themselves. Experts in animal welfare and the industry-academia interface were also chosen for the Panel. They were appointed as individuals and not as representatives of their affiliated organisations (see Appendix 4). On three occasions during discussion of specific grant-holders, one of the Panel withdrew from discussion on grounds of potential conflict of interest.

3.6.2 While the review was initiated and funded by the BBSRC, MRC and Wellcome Trust, members of the Review Panel were autonomous in their work and in reaching their conclusions.

3.6.3 The role of the Panel was to carry out a scientific review on behalf of the funders of the outputs and outcomes of the NHP grants funded by them over the last decade (January 1997 to December 2006). The Panel was asked specifically to consider the following in its review:

- using the information gathered from desk research and the survey of grant-holders, to carry out an independent assessment of the quality, outputs and impact of the research outcomes against the proposed objectives of the research;
- to identify highlights, weaknesses and outcomes of NHP research;
- to assess the extent to which this type of research is contributing to both human and animal health; and
- to make recommendations to the funders regarding ways to develop and progress successful research in this area, and how to address identified gaps and weaknesses.

3.6.4 Two lead discussants were assigned to each grant, asked to complete an assessment template with brief bullet points for each of those grants and to introduce the discussion by the Panel. A copy of the assessment template is at Appendix 5.

3.6.5 The Panel was asked to provide separate assessments of the scientific quality of the grant-holders' research, the medical or other benefit, and the welfare costs to the individual animals used (low/medium/high in each case). Note that high scientific quality and medical benefit are good and high welfare costs are bad. An assessment of the scientific quality was retrospective and that of medical or other benefit was usually prospective, given the time that generally elapses between publication of an original piece of research and its translation into medical application. Assessments of welfare costs in terms of animal suffering were retrospective but based on current standards of assessing animal welfare which did not necessarily apply at the time the research was conducted. The Panel was asked to consider whether a research programme might have been conducted on subjects or material other than NHPs. They were also asked to consider whether the statistical design of the research had successfully reduced the number of subjects to the minimum necessary for meaningful statistical analysis.

3.6.6 The review report was considered by the Review Panel in draft, discussed at a further meeting and amended by the Chairman in the light of comments received.

Section 4
Discussion of the research grants reviewed

4.1 Overview

4.1.1 Some of the main features of the 67 questionnaires can be summarised as follows:

Species

4.1.2 Common marmosets (*Callithrix jacchus*) and macaques (both *Macaca mulatta* and *M. fascicularis*), in almost equal numbers, were the predominant species used in the research. However, due to the specific research questions being addressed, while marmosets were often used in relatively large numbers in a small number of projects, macaques were typically used in much smaller numbers (less than 10) in the majority of projects. One project used baboons (*Papio sp.*) and one vervet monkeys (*Chlorocebus pygerythrus*). Another used tissue from dead NHPs in a museum and two studies used populations in zoos. Numbers used in research programmes ranged from just two to 240 over seventeen years.

Source

4.1.3 Almost all the NHPs used in the UK were bred in the UK.

Location of the research

4.1.4 Almost all UK-based researchers carried out the animal work in the UK. However, the Wellcome Trust funds internationally and several Wellcome awards were to overseas scientists who undertook the animal experimentation overseas. The USA, Germany, the Netherlands, India and China were cited as overseas locations for the work.

Home Office licence

4.1.5 With the exception of a few behavioural and other studies, all the UK-based research required a Home Office licence. The project severity bands reported by the grant-holders in the questionnaires were unclassified, mild, moderate and substantial. These bands were not exactly the same as those used by the Panel, namely low, medium and high.

Re-use/euthanasia

4.1.6 Most animals were euthanised, though some respondents reported re-use for further experimentation before final euthanasia. Tissue from euthanised NHPs was a source for further research in a few cases.

Other models

4.1.7 Several respondents used rats in related studies. Human subjects and computer models were also used in some of the research projects.

Communications

4.1.8 The most common method of communicating results was by peer-reviewed publication, preceded or followed by academic workshops and conferences. With a few notable exceptions, little evidence of a structured approach to knowledge or technology transfer was provided. A small minority of respondents embraced public engagement with enthusiasm and commitment, while others reported that their institutions had a policy of not engaging with the media or the lay public on research using NHPs.

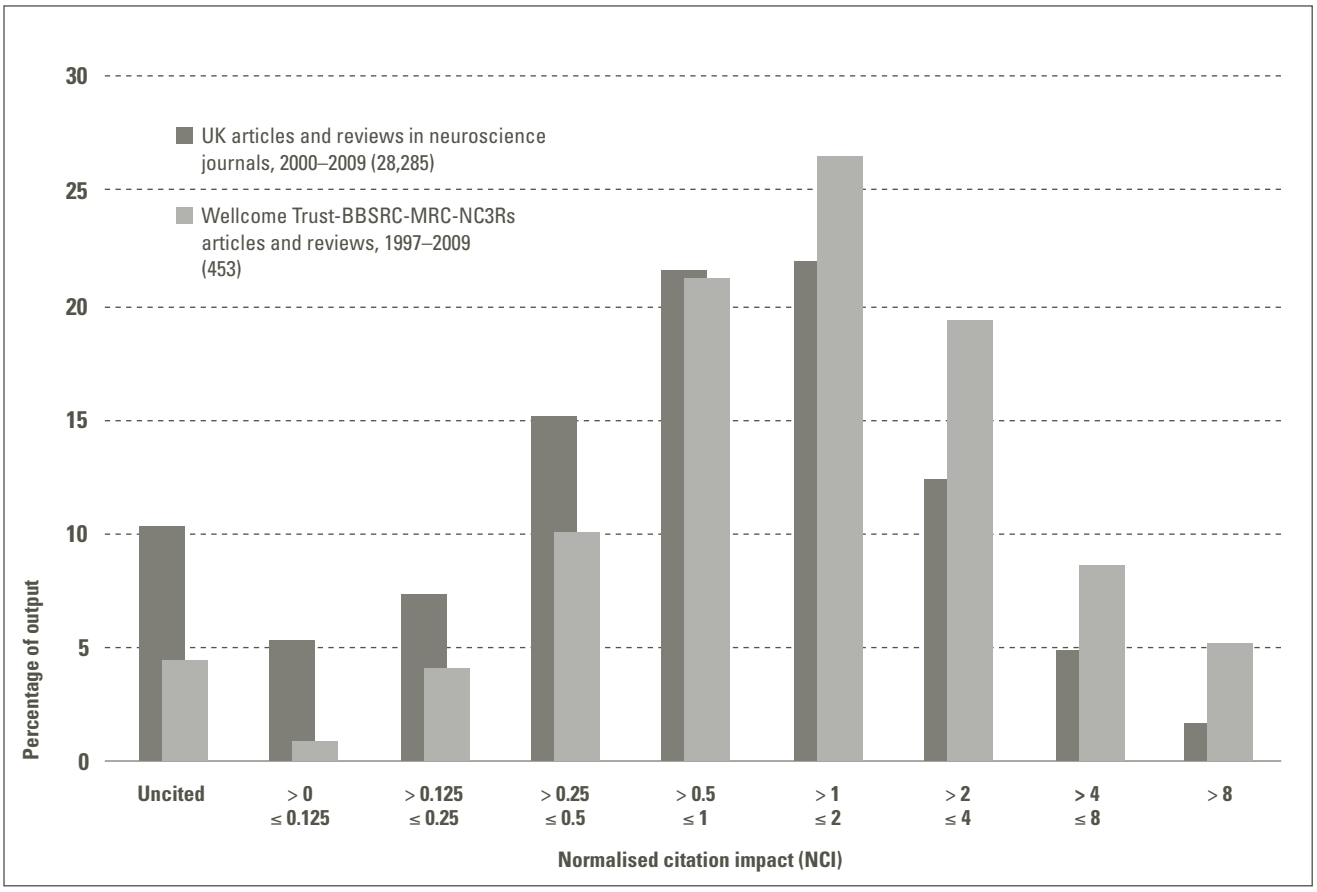
Intellectual property

4.1.9 Few respondents report any intellectual property outcomes, probably reflecting the basic or strategic nature of much of the research. One or two mention databases that are shared internationally with fellow researchers. In one case, the need to protect commercial intellectual property was postulated as a possible explanation for the lack of published papers.

Results of the bibliometric analysis

4.1.10 Supported grant-holders were most frequently published in journal titles associated with neurosciences, including high impact titles such as *Nature Neuroscience* and *Neuron*. Elite multidisciplinary journals such as *Nature, Science* and *Proceedings of the National Academy of Sciences USA* were also used quite frequently, with the latter among the top twenty most frequently used journals. The majority of the portfolio under review related to grants for neuroscience research

Figure 1. Impact profile for research published by the supported grant-holders (1997–2009) benchmarked against UK neurosciences. The data are from Thompson Reuters and the analysis is by Evidence Ltd.



and just under a third of all papers were published in journals associated with neuroscience.

4.1.11 Research published by the supported grant-holders was found to be well cited in general. The average citation impact was more than double the world average and markedly above the average citation impact of the benchmark in UK neurosciences. The impact profile for work published by the grant-holders, benchmarked against UK neurosciences, is illustrated in Figure 1.

It should be noted, however, that in a few cases it was difficult to exclude work derived from the grants under review but not directly involving work on NHPs. Research published in journals associated with experimental psychology had an average citation impact at least double the world average, while that published in journals associated with research and experimental medicine (relating to SIV/HIV) had an average citation impact approaching four times the world average.

Assessment of research outputs

4.1.12 As explained above, the approach underpinning all assessments was based on the following premise (Weatherall Recommendation 1):

> *"There is a strong scientific case for the carefully regulated use of NHPs where there are no other means to address clearly defined questions of particular biological or medical importance."*

In relation to each study reported, the Review Panel therefore sought to determine, with the benefit of hindsight and more data than was available at the time the grant was awarded:

- Was the question of biological or medical importance?
- Was there any other means to address the question, e.g. by methods that did not involve animals, or utilised animals of other species, or lessened the welfare impact?

- Was the science carried out of high quality? What was the extent of the increase in understanding that it provided, the stimulation of future science or other impact?
- What was the impact on improvements in medical science and particularly in addressing medical problems that damage the health and welfare of large numbers of people in the developed or less developed parts of the world?
- Had the research delivered or contributed to any other public benefits such as the public understanding of science, the training of researchers, development of public policies, conservation and biodiversity and the 3Rs (including improvements in NHP procedures and husbandry)?
- What was the impact of the methodology adopted in the study on the welfare of the animals involved, assessed with reference to the Five Freedoms (Freedom from hunger and thirst, Freedom from discomfort, Freedom from pain, injury or disease, Freedom to express normal behaviour, Freedom from fear and distress)? Welfare impact was assessed from the perspective of the individual animal on the basis of the procedures to which it had been subject, independently of the number of animals involved, which was recorded separately.

4.1.13 Special attention was therefore paid to research which imposed a high welfare impact on the animals. Concern was aroused in the minority of cases where it appeared that alternatives to the use of NHPs had been insufficiently explored, or where the benefits delivered did not appear to be commensurate with the welfare costs. Further details are given below.

4.1.14 One of the assessments that the Review Panel found most difficult to establish with confidence was the impact of a specific piece of research on developments in medicine. While it was relatively straightforward to suggest that improved knowledge of a particular biological process was relevant to questions of medical science, researchers typically did not provide information allowing evaluation of the specific consequences of their research such as measures of the extent to which the advances in knowledge provided by their work had been picked up and utilised by medical researchers and taken forward into medical applications. In order to explore the potential for improved evidence of knowledge and technology transfer the Review Panel requested that, in specific named examples, the medical literature be analysed to assess whether the work in question had subsequently been cited in relation to published papers of applied medical research. This further analysis was carried out in relation to three specific papers. In these cases the initial number of citations was 53, 58 and 93. Those primary citations were in turn cited 833, 1076 and 1574 times in scientific, medical and clinical journals. The Panel concluded that explicit guidance should be given to researchers in the future to assist funders and other reviewers in making this assessment. In particular, where grants were awarded on the expectation of human health benefits, on review the grant-holders should be asked to provide evidence of interest in and use by the medical and biopharmaceutical sectors. (See also para 5.9.9 and Recommendation 15.)

4.2 Neuroscience

4.2.1 Of the 67 questionnaires considered, 31 (46.2%) related to grants in the area of neurobiology. Most studies utilised macaques as experimental animals, most frequently in low numbers (13 studies used fewer than 10 animals).

4.2.2 These studies reviewed a wide range of questions in neuroscience including improving the understanding of the functional interactions between neurons and neural circuits, exploring the potential for therapeutic use of a range of interventions including gene therapy, and improving understanding of how neural structures worked. Asked about the potential health benefits of the work, the justification given was commonly that an understanding of development and normal functioning are a prerequisite to devising medical solutions to

developmental or traumatic abnormalities which express themselves as psychiatric or other clinical conditions. In most cases reference was made in the questionnaire returns to the potential significant impact on human health and welfare of specific health problems such as Parkinson's disease, Alzheimer's disease and other dementias, schizophrenia, bipolar disorder, and obsessive compulsive disorders as well as disturbances of motor control caused by stroke or trauma. Clearly these are major health issues, but the size of the problem to which the science relates should not be accepted as sole justification for individual items of research. It is important that the justifications offered for research projects are soundly based and demonstrable. Health benefits should only be claimed when their potential is real. If the primary justification for the work is its scientific (or other) value alone, this should also be made clear.

4.2.3 Good evidence was provided of researchers' efforts both to reduce the numbers of animals used to the absolute minimum, to obtain as much data as possible from each animal, and, on occasion, to share data and tissues with other researchers. This should be commended.

4.2.4 The research tools commonly employed included both direct and indirect measures of brain activity. Electrophysiology studies in the awake, behaving state were generally assessed as imposing a high welfare impact due to the numerous procedures involved, their likely effects on the monkeys, and the lengthy duration of the experiments. The creation of experimental lesions, surgically or pharmacologically, resulted in a medium welfare impact assessment, unless the studies had been conducted under terminal anaesthesia (in which case the welfare impact was low), or resulted in significant and lasting impairments to the monkeys' welfare (in which case the impact was rated as high).

4.2.5 Of these 31 neuroscience studies, half were assessed as having imposed a high welfare impact on the animals as judged by current standards. Most of these studies were also assessed as being of high scientific value, as evidenced by the quality and number of published reports and the citation record. A few were also assessed as delivering, or having the potential to deliver, significant medical benefit. One had resulted in patents being filed, in new surgical treatments being established and development of new medical treatments. In most cases, however, little direct evidence was available of actual medical benefit in the form of changes in clinical practice or new treatments. This dearth might have been because no link with medicine existed. However, the time that elapsed between the research and the review may have been too short for a move to practical applications to be seen. More difficult to assess and also potentially important was that the trail linking discovery by researchers to developments benefiting medicine was difficult to establish. This is something that the investigators – as experts in their fields – need to help make visible for funders and future reviewers.

4.2.6 Two of the studies were of concern in that they imposed a high welfare impact, but were assessed as only medium against the 'quality of science' criterion, and low against the 'medical benefit' criterion. In both cases relatively large numbers of marmosets had been used in research on aspects of brain function. On the principle that work that imposes a high welfare burden should only be undertaken if it has the capacity to deliver a high quality of science and ideally significant benefit to human health, this funding decision might have been different if hindsight had been available to assessors at the time funding decisions were taken. The questions that need to be addressed are therefore: given the state of knowledge at the time the research proposal was considered, could the study have reasonably been expected to deliver high quality science and/or significant medical benefit? And in considering that issue, were all relevant alternative routes explored? The second question was probably key in these two instances.

Selection of research species

4.2.7 A strong case was made for using NHPs to answer specific and important questions in these areas of work on the grounds of their unique similarity of brain structure to the human brain, and their capacity for exhibiting, and being trained to exhibit complex behaviour patterns. In the case of some of the work carried out on marmosets, particular reference was made to their small brains and cortical anatomy facilitating observation of effects at the neuron level. In most of the studies reviewed the Review Panel agreed that these justifications were reasonable. However, it was noted that in a few instances it was not clear that the precise research aims could not have been addressed using other species. Some researchers tended to compare and contrast the benefits of using NHPs versus those of using rodents, while overlooking the potential use of other species such as cats or ferrets. In other cases the Panel were of the view that it would have been possible to carry out the work on humans. For example, fMRI offers opportunities to replace some NHP work with human studies in such areas as spinal cord injury.

4.2.8 Similarly, another study had used both rodents and macaques. Of five papers resulting from the work, only one was on the NHP work and this was the least cited of the five. The Panel expressed concern about the justification for the NHP component, given that the work in rats had provided the proof of concept and evidence supporting translation was already available or could be made available from functional imaging studies in humans.

Knowledge transfer

4.2.9 A key issue for the Review Panel was the extent to which advances in fundamental science were effectively translated into more applied research and ultimately into practical application. As an example, a study into two specific neurotransmitter systems had delivered a promising progress report. However, the resulting publications were not in the top rated journals and although some useful steps had been achieved towards target validation through receptor mapping, it had not led to sustained drug development in the two years since the work had been completed.

4.2.10 Similarly, a study which the panel characterised as "*one of the best grants reviewed*" had focused on mapping the spatial dissociation of different cognitive processes in the frontal lobe in order to lead to the possibility of more targeted treatments for cognitive symptoms. This was therefore addressing an important biological question with a clear potential translation into a medical field. However, notwithstanding the publication of twelve papers in good quality journals, the overall citation rate was relatively disappointing. As a general issue with regard to bibliometric data, the Panel noted that citation rates can be affected by matters other than the quality and relevance of the work. For example, it was possible that part of the reason for work with rats being more highly cited than the NHP work was because of the relatively large field of people working in rats rather than NHPs. Concepts generated by investigators from their own work with NHPs may be presented by them in more highly cited reviews or work based on studies of humans or other species, reducing the perceived impact of the reports on the NHP research. However, a practical concern also was that even publication of a good paper in a high impact journal does not alone constitute an adequately reliable means of ensuring knowledge transfer impact. This was recognised as a general concern not limited to NHP research, but given the ethical imperative to ensure that research involving NHPs delivered the maximum benefit possible, it was a particular concern in this context. The Panel was aware that assessing knowledge transfer simply through bibliometric analysis is limited. In the future, researchers should be encouraged to provide other relevant data to ensure that reviewers can appreciate the value of the research to other scientists and to society more broadly.

4.2.11 Conversely, some studies had been carried out in institutes that were designed to

facilitate the development of work along the trajectory from basic science into clinical applications. Two studies involving the exploration of cortical control of finger movements using electrophysiological mapping were reviewed. The work provided important basic science insights with high relevance to human health and immediately influenced researchers in human neurology, who used the enhanced understanding of cortico-spinal systems in order to make sense of results emerging from functional brain imaging studies of recovery following brain damage in the clinic. This work was highly cited in important journals. Moreover, being situated in an institute which integrated basic and clinical scientific effort and brought together investigators from across the spectrum of fundamental and clinical studies greatly increased the probability of it being used in clinical work.

4.2.12 Another important centre for NHP work had developed strong links between fundamental cognitive neuroscience and clinical applications. NHP models developed in the laboratory were applied to the development of new drugs to enable workers to design clinical trials more effectively. This ensured not only that the science was taken to the clinic, but also that experience in the clinic was fed back to improve the science.

4.2.13 Effective knowledge transfer is a key issue in any area of science, but is arguably even more pressing when the welfare of sentient creatures has been compromised during the search for improvements in understanding. Clearly the publication of science in peer-reviewed journals is a basic and vital step. Publishing the results of work is demonstrably no guarantee that its significance will be spotted and taken up by those in a position to develop concepts towards practical applications. Government concern with horizon-scanning for problems should be supplemented by a process that systematically scans research outputs for practical applications (output-scanning) and facilitates their take-up by private sector applied scientists and engineers.

Advances in the 3Rs

4.2.14 When asked whether their research had led to novel advances in the 3Rs and improvements in animal welfare, some grant-holders simply reported implementing existing 3Rs techniques, such as anaesthesia and analgesia, confusing the necessity of complying with existing moral and legal requirements to apply the principles of the 3Rs with the development of novel ways to replace, reduce and refine animal use. However, a few researchers had developed new 3Rs techniques and published them, so that good practice could be disseminated. These included: improved husbandry practices with regard to marmoset colonies such that the marmosets lived to a greater age and grew to healthier weights; development and testing of a new tissue-friendly head implant for use in awake, behaving monkey studies; and use of an antimitotic compound to reduce the need for dural scrapes and make electrode penetration of the brain easier.

4.2.15 One grant-holder claimed that use of marmosets represented an improvement over use of macaques in terms of welfare. The Panel's view was that this was only the case insofar as the marmosets were kept in family groups or pairs in relatively spacious and enriched surroundings and bred locally in the UK. The Panel's view was that little evidence existed of a differential capacity to suffer and therefore they were not content to assume that marmosets experienced less suffering than a macaque in equivalent circumstances.

Conclusions

4.2.16 In the area of neuroscience, the majority of research grants were well-focused on important areas of either biological or medical concern. The level of welfare challenge imposed on the research animals could be justified by the quality of the science or, in some cases, the actual or potential medical benefits accrued.

4.2.17 In a minority of instances the justification for the use of NHPs, as distinct from work on other species or on humans, was not wholly convincing.

Recommendation 1
The Panel noted that the processes needed to maximise scientific quality and impact are already in place as part of mechanisms for the funding of NHP research, and concluded that each application for funds to support research using NHPs should be subject to rigorous review of the scientific value of the research, the probability of medical or other benefit, the availability of alternative approaches, and the likelihood and extent of animal suffering. In particular, care should be taken to ensure that the review is a dynamic process that keeps pace with and employs best current knowledge concerning animal welfare, scientific advances and changes in public perceptions.

Recommendation 2
In considering research proposals, peer reviewers and panel members should critically examine the justification for the choice of species and whether human subjects could be used as alternatives. Consideration of the potential for alternatives should extend beyond rodent models; the potential of *in vitro* and *in silico* approaches should be considered, and the potential of other species as models should be fully explored before a decision is made to employ NHPs. Care should be taken to ensure that peer reviewers and panel members collectively possess the full breadth of knowledge and experience to assess all the relevant options.

4.2.18 Some evidence was provided of the translation of fundamental science into applied science and practical application, but in many cases too little consideration was given to effective knowledge transfer.

Recommendation 3
It is an ethical imperative that maximum benefit be derived from studies employing NHPs. When considering research proposals, funders should take into account the nature of the organisation to which the researcher is affiliated, with regard to the extent of integration of teams working in different fields and at different points along the spectrum of science from fundamental to applied. They should consider whether any structures or processes are in place to facilitate knowledge transfer or to ensure the exploitation of outcomes of the proposed work. They should also take into account the researcher's plans for knowledge transfer or other exploitation. Funders should encourage data-sharing and should consider creating or supporting online repositories for digitised data which may be made freely available to other researchers.

Recommendation 4
Science policy-makers together with the public sector, private sector and charitable funders of research should commission a working group to develop proposals for a mechanism (output-scanning) to identify research results with potential to deliver improvements to healthcare or other significant benefits to society, and to assess the extent to which the potential benefits are achieved. The stakeholder bodies should develop mechanisms to facilitate exploitation of new knowledge derived from NHP studies for clinical or other benefits to society.

4.2.19 In a minority of cases, the development of advances in the 3Rs, either as a main research focus, or as spin off from other research, was explicit and disseminated by publication. This was applauded by the Panel.

Recommendation 5
The Review Panel applauded the efforts by some of the grant-holders to deliver 3Rs improvements as part of or alongside their major research outcomes, and particularly their willingness to publish the results of such work. The Panel also noted that funders require implementation of the principles embodied in *Responsibility in the use of animals in bioscience research: Expectations of the major research council and charitable funding bodies* as a precondition for receiving funds. In defining research grant terms and conditions, funders should take particular care to encourage, and where appropriate require, the active dissemination of 3Rs improvements through the international research community and should ensure that appropriate monitoring and enforcement procedures are in place to encourage full compliance with all aspects of the *Responsibility* guidance.

4.2.20 It should be noted that these conclusions and recommendations apply equally to other areas of NHP research (see Sections 4.3–4.6).

4.3 Vision

4.3.1 Most research into vision forms a subset of neuroscience, but the number of grants in vision justified separate consideration of non-visual and visual neuroscience, notwithstanding that the division between the two could be considered arbitrary on occasion. Particular focus on this topic area was justified by the relatively large proportion of research grants reviewed in this area. Of the 67 completed questionnaires, 14 were of grants in the area of vision. Of those where information was available on the numbers and species of animals used, the studies were fairly evenly divided between the use of marmosets and the use of macaques. A few used both.

4.3.2 The 14 studies addressed a range of questions relevant to understanding the biological basis of vision including modelling eye movement control and the neural mechanisms involved in processing visual motion, the functional anatomy of the visual cortex, and the processing of colour vision.

4.3.3 The research tools employed included electrophysiology, neuro-anatomical connectivity tracing, MRI, transcranial magnetic stimulation (TMS) and computer modelling. In one case contact lenses were used to explore the effects of blurring the retinal image on juvenile eye growth.

Welfare impact

4.3.4 Of the 14 studies, four were assessed as having imposed a high welfare impact on the subjects, although this assessment must be tempered by the very small numbers of animals used in the studies. Of these, two were of particular concern in that, owing to lack of peer reviewed publications, their scientific and medical impact could only be assessed as low. In one of these cases the work did not appear to have been written up at all. In the other, four papers authored by the grant-holder were submitted but none appeared to be directly relevant to the grant application. Most of the other studies were assessed as of low welfare impact, often because the work had been carried out under terminal anaesthesia.

Medical impact

4.3.5 For a variety of reasons, some of which are explored below but also including the fundamental nature of much of this work, the actual and potential medical impacts of most of these studies were low. This may partly reflect the fact that the majority of the work (75%) was funded by the BBSRC or Wellcome Trust. The BBSRC's remit excludes the funding of research aimed specifically at human medical applications and a high proportion of Wellcome Trust grant calls attract basic science bids. The MRC funded studies tended to be aimed more towards furthering scientific understanding of clinical impairments, such as visual field defects following stroke, and congenital or early developing visual defects in children.

Failure to publish

4.3.6 In total, of the 14 grants in this area, four had failed to produce any published papers without suggestion that this was due to a need to protect intellectual property. This is unacceptable, particularly given the impact of these studies on animal welfare. The scientific community in general and funders in particular must insist on the importance of the publication of results. The Panel recognised that on occasion a failure to publish is due to the intervention of an unforeseeable *force majeure* or that protection of intellectual property can be important when it can lead to patents. In some cases research programmes were seriously disrupted due to departures of trained staff or difficulty in recruitment. Failure to publish may also be due to negative results, but the Panel's unanimous view was that researchers using NHPs should have a moral obligation to publish results even if negative – to prevent work being repeated unnecessarily. Whatever the circumstances, failure to publish is an unsatisfactory state of affairs and funders should review the publication performance of particular individuals or research groups when considering subsequent applications for grants.

Skills of the research team

4.3.7 In two instances the Review Panel noted that the outputs of the research had been relatively poor because the skills range within the team appeared to have been sub-optimal. The problems appeared to include difficulties in the effective training of animals and the choice of behavioural methods.

Knowledge transfer

4.3.8 On a separate but related point, one grant directed at elucidating fundamental properties of the primate visual system which had been carried forward into marmosets from work that had previously been performed by the grant-holder using cats. The citation record was poor for the primate work and it appeared to have existed in a vacuum, with little evidence of follow-up or translation into further work. This case reinforces the point made in relation to non-visual neuroscience, that publication of results alone does not guarantee that they will make their way out into the scientific or clinical mainstream, even when of good scientific quality.

Advancements in the 3Rs

4.3.9 Two of the grants included the development of functional MRI laboratories for monitoring and mapping brain activity in macaque monkeys. These techniques will progressively reduce the need for using microelectrode recording to relate brain activity to visual function, though at the present stage of technological development they cannot replace such methods entirely.

4.3.10 In addition, two of the teams had been developing TMS in NHPs in order to study the effects of temporarily interfering with the activity of specific visual brain areas. TMS provides a new way of establishing the causal role of particular brain areas in visual function, without causing the permanent tissue destruction that has long been the traditional method for investigating such causal links.

Conclusions

4.3.11 In the area of science exploring the biological basis for vision, the studies were mainly addressing fundamental neurobiological questions. The actual and potential impact of much of this science on medicine was judged as low in the short-medium term, though the impact on biological science was generally judged as high.

4.3.12 A minority of the studies posed a high welfare impact; most were assessed as low.

4.3.13 In several cases the publication record was disappointing and in four cases none of the funded work had been published.

Recommendation 6

Researchers using NHPs have a moral obligation to publish results – even if negative – in order to prevent work being repeated unnecessarily. In considering grant applications, funding bodies should take into account the previous publication performance of applicants and their research groups. Where there has been a history of limited dissemination or exploitation, the funders should consider with particular care the likely balance of the animal welfare cost against the potential benefits arising from funding that application.

4.3.14 As has already been pointed out in relation to some of the neuroscience grants, weaknesses in knowledge transfer and the appropriate skilling of research teams were also noted. In two instances the Review Panel noted that the outputs of the research had been relatively poor because the skills range within the teams appeared to have been sub-optimal.

Recommendation 7

Conducting the highest quality NHP research demands a range of skills and resources. Funders should take care to ensure that the teams and infrastructure involved in a funding bid are fully appropriate to the requirements of the intended research.

4.3.15 The Panel accepted that its retrospective analysis could not be compared directly with the prospective judgements made at

the times when funding for the projects were agreed. If the committees making the judgements could have been certain about the outcome of the research programmes, then funding the work would have been pointless. Nonetheless, while acknowledging many examples of well executed and well reported high quality science, the Panel was concerned that a small subset of research programmes using surgically invasive techniques had yielded no discernible scientific, medical or social benefit.

Recommendation 8
Highly invasive and long-term NHP research often carries a high welfare cost. In such cases, funders should take particular care only to fund projects with a very high likelihood of producing scientific, medical or social benefit. Wherever possible, funders should take steps towards encouraging a preferential or complementary use of less invasive techniques such as neuroimaging and transcranial magnetic stimulation.

4.4 Behaviour

4.4.1 Five questionnaires related to studies of the behaviour of NHPs. One involved work with captive chimpanzees (*Pan troglodytes*) in the USA and one with wild populations of chimpanzees. One study involved marmosets, one macaques, and one utilised hair and faeces samples from wild and zoo populations of tamarins (*Saguinus spp.*). In every case the welfare impact was deemed low.

4.4.2 Research objectives included studying cultural transmission and communication in chimpanzees, the functional utility of colour vision in foraging, hormonal determinants of social care in family groups of marmosets, and the ability of macaques to read the intentions of other macaques. How well these objectives were achieved varied from case to case.

4.4.3 It is difficult to generalise from a small number of varied studies, but two areas are worth special mention.

4.4.4 Both the chimpanzee studies were found to score medium to high on the quality of the science with good publication and citation records. Both had been successful in encouraging public engagement and therefore had delivered benefits with regard to the public understanding of science. The medical benefits were low, but the study of cultural transmission was relevant to the conservation of chimpanzees in the wild, particularly as regards the importance of conserving culturally discrete populations. The study conducted on wild populations under field conditions was important in demonstrating what can be achieved from some work in the wild with minimal or no impact on welfare.

4.4.5 In one case a particular study had changed focus as a result both of difficulties in getting a new NHP facility up and running, and a change of principal researcher. The resulting work on parental care in marmosets was sound but some of the work on paternal involvement could have been carried out on hamsters. Furthermore some indirect benefits to marmoset handling and breeding were not published or disseminated. It was felt that the redirected work made reasonable use of the grant, but it was not the reason the grant had originally been made and it was perhaps regrettable that the award had been made before the infrastructure was in place to support the work.

4.4.6 In a second case, the Panel noted that observations of animals in restraining chairs could have been obtained more appropriately if the animals had been studied in social groups.

4.5 Immunology and infectious disease

4.5.1 Seven of the grants were related to work in immunology and infectious disease; four of them concerned with HIV, two with malaria and one with trypanosomiasis. Typically, these studies involved larger numbers of animals than those reported above. Six of the seven used macaques and the sixth (on trypanosomiasis) used vervet monkeys (*Chlorocebus pygerythrus*).

4.5.2 The work on HIV focused on various aspects of the search for an effective vaccine strategy, ranging from assessing potential vaccine candidates, through exploring the role of non-immune vaccine responses and variability in the immune response, to testing the concept of DNA vaccination.

4.5.3 The studies on malaria also sought to identify new active ingredients for pharmacological development and explored vaccination against the pre-erythrocytic stage, while the remaining study looked at the role of nitric oxide in sleeping sickness.

4.5.4 Two of the HIV projects worked with live attenuated vaccine and provided evidence that what was being observed was not an adaptive immune response. The quality of the science was considered good but given that progress in HIV vaccine research has been protracted, the direct translational applicability was not clear. The welfare impact on the macaques was, however, considered medium. The project which explored the possibilities of DNA vaccination found that the concept being tested did not work and the experiment was halted without using all of the animals requested/purchased. The Panel would have liked to have seen this work reported in a peer-reviewed journal given that the hypothesis tested was reasonable and the reporting of the negative result important, not least to prevent someone else repeating the work. The final study of those looking at HIV was exploring how to deal with the variability of the HIV immune response. This work was highly cited and had been taken up in clinical trials.

4.5.5 The work seeking to identify new active ingredients with potential for a single-dose treatment for malaria was also judged to be likely to have a high impact on medical developments. A multi-disciplinary approach had been adopted and a new *in vitro* screen developed. Nothing had been published, probably for reasons of intellectual property protection because company compounds were being tested. It was noted that the new *in vitro* screen might also mean that fewer animals needed to be tested in the future. The other malaria study also failed to generate any publications and was never completed.

4.5.6 In the case of the study on trypanosomiasis, the vervet monkey was found to exhibit an immunological response which was much more similar to the human than the existing rodent model of sleeping sickness. In theory, knowing the time course of inflammatory responses could influence delivery of therapy; even so, a translational benefit was not immediately obvious. Moreover, the Panel considered it possible that similar results could have been obtained from human studies.

4.5.7 In all these studies the impact on welfare was either medium or low, partly depending on how far the disease was allowed to progress before the animal was either treated or euthanised.

Conclusions

4.5.8 It is difficult to draw valid general conclusions from so small a group of studies, but the Panel's views were reinforced on both the benefits of a multidisciplinary approach and the risks of failure to achieve effective knowledge transfer.

4.5.9 Some research programmes yield negative findings that are difficult to publish. This is a general problem that involves the potential waste of resources. If the negative findings are not published, other research workers may undertake the very same work that led nowhere. The problem is especially acute when highly sentient animals have been used. A strong case can be made for ensuring that negative findings are made available to the scientific community.

4.6 Reproductive biology

4.6.1 Seven of the studies reviewed related to work on reproductive biology and these addressed very different areas of scientific interest. Most of the work was conducted on macaques and marmosets, but one used baboons (*Papio sp.*). In each case the justification for use of NHPs was centred around the need to use experimental animals with as close a reproductive function to humans as possible. In general, the published work describing NHP studies appeared in journals with mid to modest impact factors. Two highly cited review articles were included in the bibliographic material.

4.6.2 One questionnaire related to a programme at an MRC unit. The objective was to elucidate the role of angiogenesis in the ovary in normal follicular development and corpus luteum function, and the role of angiogenesis in the uterus and endometriosis. These are subjects where use of NHPs is important given the unique features of primate reproduction.

4.6.3 Three other studies explored the underlying biology of reproduction in order to address a range of health issues including the maintenance of fertility in men treated with gonadotoxic agents, the mechanisms initiating parturition, and the processes of implantation and placentation during pregnancy. One study had been terminated early and the projected work on marmosets was not carried out.

4.6.4 The final three studies were a connected programme of work looking at the impact of a range of environmental factors on testicular development and function.

4.6.5 The impact on welfare across these studies ranged from low to high. It is not possible to generalise across such a small number of very varied projects, but two specific concerns are worthy of note. Two studies involved major surgical interventions including the hysterectomy of pregnant NHPs in which both mother and foetal welfare were compromised. In one case both the scientific value and the medical relevance were deemed to be high and the numbers of animals involved low. However, the second case involved a research training fellowship which involved studies that were mainly repetitive of work published a decade earlier and, although technically sound, confirmed studies previously conducted on human material. Its benefit appeared to be limited to the training of research personnel and therefore the justification for the work on the basis of scientific and medical benefit would appear to have been small. Perhaps the fact that the work was being pursued outside the UK was a factor; but in general work should not be funded outside the UK that would not meet the standards acceptable in the UK.

4.6.6 The second concern related to a lack of detail with regard to the standards of husbandry applied to the NHP subjects in studies conducted in parts of the world which are less well regulated than the UK. Without this detail in both research proposals and reports, it is difficult to see how funders can satisfy themselves that the welfare impact on the animals is ethically justifiable in all the circumstances.

4.6.7 The three linked studies on the impact of environmental factors were a rare example of research using an NHP model to explore the impact of environmental contaminants. The welfare impact of these studies was low and the potential medical benefit was low. However, the potential benefit to the development of public policy and the public understanding of science was high. In general, views and policy relating to the risks of environmental contamination are over-influenced by work on rodents.

The marmoset used in these studies is a far better model of the human response. Findings that they are less sensitive than rodents to contaminants such as phthalates are therefore highly relevant, even though evidence from human epidemiology would also be necessary before environmental policies were changed. Some publications derived from this research were highly cited, although they did not appear in journals with high impact factors.

Conclusions

4.6.8 The Panel recognised that much of the work it had surveyed had been started at a time when standards of animal welfare were lower than they are at present and that techniques that would have obviated the need for use on NHPs had not yet been developed. Many of its observations, therefore, relate to future funding. Nonetheless, in general it is not acceptable knowingly to fund work outside the UK that would not be legally permissible or ethically acceptable in the UK in the light of knowledge current at the time the funding decision is taken.

Recommendation 9

The Panel noted that all funded NHP research, regardless of where it is conducted, should comply with the *Responsibility* guidance and NC3Rs guidelines *Primate accommodation, care and use*, and that the NC3Rs had visited laboratories in the UK and overseas to give advice and to monitor compliance. The Panel's view was that funding bodies should take all necessary steps to satisfy themselves that work on NHPs funded by them outside the UK meets the standards acceptable in the UK.

4.7 Other research – evolutionary biology

4.7.1 Two other studies reviewed were concerned with the genetics of coat colour in NHPs using samples of hair from museum and zoo collections. The welfare impact of the work was therefore deemed low in the context of this review. The Panel did not include an expert in this field, but it was noted that the outputs of this research were published in relevant journals.

Section 5
Cross-cutting issues

5.1 The value of NHP research in the UK

5.1.1 In their 2006 report Sir David Weatherall's working group concluded that "*if non-human primate work is deemed to be important, the skills and capacity to conduct such research should be retained in the UK*". The reasons for this conclusion were listed as:

- retaining the control of welfare standards in accordance with what is widely thought to be the most stringent regulatory framework anywhere in the world;
- research can be carried out according to priorities set by the UK public and scientific community;
- evidence from pharmaceutical companies testifies to the value they place on the strength of academic collaborations with UK NHP researchers.

The view was therefore taken that retaining strength in this area gave the UK a clear research and commercial advantage.

5.1.2 The Panel's general conclusions with regard to the overall value and outputs of the research under review supported this conclusion. It was also noted that the bibliometric data for the studies in the current review, particularly those in neuroscience, showed that the output compared favourably with other research.

5.1.3 Given the benefits, it is of concern that a number of researchers reported difficulties in continuing with NHP research in the UK. These are considered in greater detail below. In addition, anecdotal evidence suggests that a number of researchers have moved overseas as a result.

5.1.4 One specific centre for NHP research closed during the course of this review following an MRC review of directly funded work and an options appraisal that assessed the likely future demand for primate facilities.

Conclusions

5.1.5 In general scientific research carried out in the UK is highly regarded worldwide. The best of the work carried out on NHPs in the UK is as good as the best of the work carried out in other fields. Where it has not occurred already, this NHP work is likely to bring with it benefits to medicine and the public good. Pressure resulting in the movement of work on NHPs from the UK to less well regulated parts of the world may lead to a worsening of welfare as experienced by the subjects, not an improvement.

5.2 Training of researchers

5.2.1 If the pursuit of NHP research delivers a benefit to the UK, then a logical corollary is that the effective training of researchers in the techniques of the science and the humane handling and treatment of the animals is also a benefit. A high proportion of the completed questionnaires made reference to junior researchers continuing in the field and subsequently becoming grant-holders in their own right. However, the Panel also noted an instance where the dubious justification for the research appeared to rest solely on the training element, and a number of instances where failure to write up and publish work means that knowledge transfer opportunities were missed. If high quality NHP research is to be fostered then the training component of research grants requires emphasis, provided that does not become either the sole or even the main justification for carrying out the work.

Conclusion

5.2.2 In order to ensure the propagation of best practice and the continued improvement in the impact of research and the welfare of NHPs, the training component of research grants should be emphasised.

5.3 Regulatory controls and reviews

5.3.1 The questionnaire provided responders with an opportunity to report problems. Given this open invitation, it is perhaps surprising that only five reported significant problems with the mechanics of regulation. However, a common thread emerged in these comments which should be given serious consideration.

5.3.2 All the researchers who commented accepted and embraced the importance of ensuring appropriate animal welfare standards in work on NHPs. However, the

comments of those who had difficulties related not to the regulations, but to how they were administered. Whilst noting that "*Home Office Inspectors were helpful and supportive*", the view was also expressed that adherence to the wording of licences "*took precedence over commonsense*" and that welfare suffered as a result. Other workers reported delays in procedures such as transfer of a licence to a new principal researcher when the original licence-holder suffered from ill health.

5.3.3 While sympathetic to the frustrations of the researchers, the Panel was wholly supportive of the need for appropriate, objective and robust regulation of animal research. While adherence to specific wording on a licence might seem petty to the researcher, the inspector must have a clear specification against which to judge the compliance of the research. However, some responders felt that Home Office inspectors seemed to differ in how they perceived their role. While some inspectors wish to facilitate the pursuance of research which is in full compliance with the regulations and required standards, others were perceived as much more restrictive. If delays are a serious or a common problem for researchers in this field the efficiency of the relevant processes should be reviewed. Some UK Government organisations which provide a service to the public or industry have already obtained accreditation to a relevant International Organisation for Standardisation standard for their delivery processes.

Conclusion

5.3.4 While the processes underpinning the regulation of research involving animals were not the primary objective of this review, the Panel considered that it should take account of issues drawn to its attention by researchers. It concluded that the regulatory standards were necessary and proportionate; but, in accordance with the spirit of the Better Regulation agenda, the Panel believed that there was scope to improve the efficiency of the bureaucratic processes; hence the following recommendation.

Recommendation 10
The Home Office should review its performance with the regard to the operation of the Animals (Scientific Procedures) Act to ensure that inefficiencies of processes or inconsistent advice to researchers do not create unreasonable delays or obstacles to appropriate NHP research. Accreditation of the enforcement processes to the appropriate ISO standard should be considered.

5.3.5 Two researchers also commented on the frequency of reviews. One wrote: "*the major problem with NHP research in the UK [is] not the regulations nor the protestors, but the perception that every aspect, even international best practice has to be re-questioned at a rate that is faster than the research cycle of these complex experiments*."

The understandable complaint was that a range of national reviews (Boyd Group, Weatherall working group, Nuffield Council on Bioethics, House of Lords, etc) had occurred on top of the essential, regular local ethical review process and reviews by grant bodies. All of this takes up a great deal of researchers' time and has to be balanced against other justifiable demands for accountability and progress in animal welfare. No-one who accepts or is reliant on public funding should be surprised to be held to account on issues of fundamental public interest. And no-one interested in pushing the boundaries of scientific knowledge should be surprised that the field of animal welfare also moves forward. However, it also makes no sense that the scarce financial resources available to science should be wasted on the completion of questionnaires or reviews that do not add value. In this field as in any other, care should be taken to learn from earlier reviews or those carried out by other authorities and to avoid needless repetition. The timing of reviews should therefore be carefully considered. However, researchers have to accept that the timing of a particular review will never be perfect for all the studies underway at that time. Of the research projects considered in this review, some had been completed near the beginning of the 10 year window and others

had only just begun towards the end. Due allowance for these issues was made when considering the impact of the research.

Conclusion

5.3.6 Care should be taken with the timing and design of reviews to ensure that they are not repetitive and that they add value proportionate to the demands on researcher time.

5.4 Cost of NHP research in the UK

5.4.1 Around one third of respondents drew attention to the high cost of carrying out NHP work in the UK. The costs of both the animals themselves and of the holding charges were said to have risen 400% to 500% over the five year period from 2003, while costs in the USA and many other centres throughout the world were much lower. Some of these costs were associated with the inimical public attitude to research on animals in the UK. Some were apparently due to Home Office insistence on standardising climatic variables such as humidity that are very expensive to implement, impoverish the environment and are questionable in terms of their scientific or welfare benefits. The Panel understands that funding bodies make every effort to ensure that funding boards/panels are able to focus on the quality of the science rather than the cost when making funding decisions. This is done by separating the costs of the animals and the animal facility from the remaining costs of the research when considering proposals. In so doing, NHP projects are more likely to be considered on a level playing field with other areas. While the Panel applauds this approach, the full economic cost of animal facilities, particularly for NHPs, is widely known and so the playing field is not quite so level as it might first seem. Consequently assessors of applications are usually aware that many rodent studies can be conducted for the cost of one NHP study.

Numbers of animals used

5.4.2 Costs have consequences for key factors related to the ethics of conduct of the research. In general, if research involves high welfare costs, smaller numbers of animals will be used. In any event, the number of animals used should always be the minimum necessary to achieve the scientific objectives. The Panel had some discussion about a study that involved the taking of many measurements on very few animals followed by statistical analysis of the total number of measurements that were not independent of each other. Generalising outcomes from such limited studies can be questionable, although this needs to be considered on a case-by-case basis.

Conclusion

5.4.3 UK researchers using NHPs face difficulties relating to additional costs of animals and facilities and to the activities of the animal rights sector which, unaddressed, may contribute to further moves of science from the UK.

Recommendation 11

The recommendations of the Weatherall Report (Recommendations 13–15) concerned with addressing the impact of both the costs of work in the UK and harassment by activists should be followed up as a matter of urgency. Researchers in the UK using NHPs still experience an unacceptable level of personal risk. The risks and the high costs of NHP research are increasingly perceived as barriers to continued work in the UK.

5.5 Medical relevance

5.5.1 The Weatherall group reported cases where fundamental research had led to major advances in medicine and also discussed cases where search for an understanding of fundamental biological processes proceeded hand-in-hand with clinical research. The group concluded therefore that "*in assessing the importance of biological science for our future well-being, the question of whether a piece of research is fundamental or applied science has become outdated. The study of normal function, as well as being central to our understanding of why we are what we are, is often a vital step in the elucidation of the mechanisms that underlie its breakdown in disease. The central issue is whether a programme of research is directed at an important biological or medical question and is designed in a way*

that has a reasonable chance of answering that question; hence the importance of the case-by-case assessment that forms the basis of UK legislation and practice around animal research." The group also mentioned the well-known paper by Comroe and Dripps[5] who showed how an advance in medicine depended on findings obtained many years beforehand from research conducted without concern for medical benefit.

5.5.2 The present Panel took note of these points and, in making assessments of the medical benefit of a piece of research, recognised that considerable time might elapse before any medical or other significant public benefit emerged. This mattered especially when a piece of funded research had ended only five years before the review was conducted. As has already been noted, the Panel's assessments of medical and other benefits were made with difficulty and often could be no more than informed guesses. This contrasts with the emphatic public statements about the medical benefits of NHP research made by some of the funding bodies and by grant applicants in, for example, lay abstracts.

Recommendation 12
In their public engagement, the funders and researchers should avoid overstating and generalising the medical benefit of NHP research, since this cannot be substantiated in many cases. Instead, the statements should reflect the actual basis for funding decisions, recognising that these are often based on scientific value.

5.6. Technological advances relevant to NHP research

5.6.1 The Weatherall group concluded that it was "*too early to assess the relative roles of molecular and cell biology, non-invasive human investigation and mathematical/ systems approaches, compared with whole animal studies.*" However advances in technology over the last decade have created new opportunities to derive information from the study of NHPs. Some of these, such as imaging technologies, are making an important contribution to the 3Rs. Others raise ethical and welfare concerns.

These advances include:
- imaging technologies;
- DNA sequence technology and the sequencing of non-human primate genomes;
- stem cell biology;
- transgenic technology; and
- development of reagents and platforms for characterisation of cells in gene expression.

Imaging technologies

5.6.2 Neuroscientistists and pharmacologists have been major users of NHPs for research. Over the last decade, advances in brain imaging and non-invasive electrophysiological methods have furthered efforts to refine and replace primate investigations in cognitive neuroscience and pharmacology.

5.6.3 Traditional studies of the functional anatomy of the brain based on correlating behavioural changes with targeted lesions have been improved by the availability of MRI to define lesion anatomy and relate it directly to functional changes in the brain, as well as to behaviour[6], allowing faster progression to the understanding of brain structure-function relationships[7]. Such methods have highlighted the complexity of the effects of even localised lesions, contributing to more refined interpretations of data[8]. Integration of magnetic resonance based structural and functional methods with those for transient inactivation of highly targeted brain regions allows studies to be performed without longer-lasting impairments or disability in the animals[9]. Structural MRI is also being used to more accurately target recording, stimulation, lesioning and transplantation procedures, yielding better quality data[10].

5.6.4 MRI studies of NHPs using diffusion tensor imaging (DTI) have been validated against traditional tracer techniques for plotting the connectivity between different brain areas[11]. Human DTI studies can have a similar degree of validity[12]. Cognitive neuroscience has been revolutionised by the potential to replace psychophysical and electrophysiological studies of the primate with functional MRI studies of humans,

which directly relate measures of brain activity to behaviour[13]. Functional MRI in NHPs is now also developing rapidly, offering a powerful tool for directly refining and replacing electrophysiological studies, and other technologies for non-invasive research will doubtless continue to advance over the coming decade. However, despite the exciting opportunities offered by imaging techniques, they are a long way from being able to replace completely studies in animals. For example, information on the direction of an anatomical connection (anterograde versus retrograde) is unavailable from MRI-based techniques, and it is impossible to infer fine grained connectivities (at the level of individual cells or groups of cells) using these approaches. Functional mapping techniques such as fMRI are limited in recording a haemodynamic signal, rather than the neuronal activity itself. This makes it impossible, for example, to make inferences about the relative timing of events at a fine temporal scale. Techniques such as magnetoencephalography (MEG) can offer greater insights into neuronal timing and do directly reflect the electrical activity of a region, but the MEG signal reflects synchronised activity across populations of cells, rather than the single cell level information that is available from electrophysiological studies in animals.

5.6.5 Methods other than MRI are also contributing. Advances in quantitative methods for positron emission tomography (PET) allow replacement of invasive primate autoradiographic and microdialysis studies with non-invasive human studies[14], which now are being extended to provide simultaneous information of pharmacodynamics, as well as tissue pharmacokinetics[15]. Non-invasive, reversible interference with localised human brain functions using TMS allows mapping of brain structure-behaviour relationships, providing a powerful alternative to NHP lesion studies. However, TMS can only be reliably targeted to structures on the cortical surface; deep brain structures, or medial cortical areas, are inaccessible to this technique yet are important to study because of their role in many neuropsychiatric disorders.

5.6.6 These technologies also have application to the study of important physiological processes such as reproduction and intrauterine development (e.g. placentation and foetal development).

DNA sequencing and NHP genomes

5.6.7 The development of so-called next generation DNA sequencing technology has made possible the sequencing of large and complex human genomes in a short time frame and at rapidly declining cost[16]. This technology is evolving quickly and creating opportunities to determine the sequences of animals and microbes at a pace heretofore unthinkable. It is now possible readily to genotype animals for genotype-phenotype studies, to select animal cohorts that have a similar genetic background for studies in which genetic similarity is an advantage, and to explore important evolutionary aspects of NHP biology[17]. The sequencing of NHP genomes provides the necessary information to produce microarray platforms to monitor global gene expression. Additionally, technology to examine DNA methylation at a global level has advanced and it is now possible to study this epigenetic modification. This is an important advance for investigators wishing to study the effects of the environment on molecular processes.

Stem cell biology

5.6.8 Rhesus macaque embryonic stem cell lines were created in 1995[18]. These cell lines, as well as the newest technology of induced pluripotent stem cell formation by transfer of a small number of genes controlling pluripotency, represent systems to study non-human cells *in vitro*, to create differentiation paradigms that will allow investigators to prepare specific cell types (e.g. neurons, cardiac muscle, germ cells) for *in vitro* studies, and to explore the therapeutic potential of stem cells and stem cell-derived differentiated cells in a NHP model[19].

Transgenesis

5.6.9 The use of transgenic technology with lentiviral vectors now permits the production of NHP models of human disease and this technology has been used to create a rhesus

macaque model of Huntington's disease[20]. Monkey transgenic models potentially offer a means to explore disease prevention in slowly developing genetic disorders like Huntington's disease, or diseases where multiple organs are involved so that *in vitro* models are not adequate to explore therapeutic interventions. However, the significant animal welfare issues, including the end result of creating animals with debilitating disease, and the efficiency of current multi-step technology for producing transgenic animals, as well as the complexity and expense of the current technology, will require careful assessment of the scientific merit and impact of proposals to pursue NHP transgenesis, including consideration of their value over and above rodent transgenic models.

Reagents

5.6.10 The development of new reagents such as microarrays to characterise NHP gene expression and antibodies that can be used in cell sorting experiments to characterise immune cells have made it possible to obtain large amounts of information relevant to cellular and tissue responses[21]. These large data sets, coupled with other physiological or imaging records prepare the way for the application of systems biology to the NHP. They have been particularly important in the realm of SIV/HIV research.

Conclusion

5.6.11 Technological advances are progressing very rapidly in a number of fields including imaging, DNA sequencing, stem cell biology, transgenesis and the development of reagents. It is important that wherever relevant and practical, new technologies should be used actively to deliver 3Rs improvements in the use of NHPs.

5.7 Improvements in animal welfare

5.7.1 Over the last ten years new scientific knowledge about animal welfare, ethical and public acceptability considerations, and legislative and policy change have all driven major advances in the housing and husbandry of laboratory NHPs in the UK, with concomitant improvements in animal welfare. Perhaps most significant among these have been:

- acceptance of social housing as the default housing configuration, including for implanted monkeys[22];
- larger enclosure sizes and the use of adjoining play areas, to provide additional space and environmental enrichment for performance of a broad range of species-typical behaviour patterns[23]; and
- the use of positive reinforcement techniques to socialise and train monkeys for co-operation with husbandry practices[24].

5.7.2 Advances in science and technology have also enabled refinements of scientific procedures and methodologies, particularly within the neurosciences. For example, infrared reflection and video-based systems for tracking eye position/movement have replaced the use of surgically implanted scleral eye coils in many experiments. High resolution anatomical MRI scans are being used to guide the construction of custom-fitted plastic head-holding devices, providing secure, lightweight, stable and healthy implants[25]. Screw-mounted headposts and recording chambers machined from single pieces of titanium have replaced traditional devices using dental acrylic which create greater defects in the scalp, are less biocompatible and must be maintained assiduously to prevent infection[26]; use of antimitotic compounds (e.g. 5-flurouracil) have reduced, and in some cases removed, the need for dural scrapes[27]. Modern anaesthetics, from which the animals recuperate more rapidly, have enabled NHPs to be reintroduced to the social group more quickly, reducing the likelihood of aggression due to disturbance of the group hierarchy[28].

5.7.3 In addition, opportunities to reduce the number of primates used have arisen through a number of techniques including simultaneous recording with multiple electrodes of the activity of many single neurons, permitting a much greater yield of data from each experimental session and from each experimental animal[28].

5.7.4 In 1999, the MRC, Wellcome Trust and Universities of Cambridge and Oxford agreed to establish the Centre for Macaques (CFM), a rhesus macaque breeding facility located at Porton Down. This has ensured a local supply of high health status macaques, well-socialised with humans and raised to best practice standards of animal husbandry. CFM now operates as an MRC unit and scientists funded by the MRC, Wellcome Trust, and BBSRC who use rhesus macaques in research are required by the funders to obtain animals from this centre (NC3Rs 2006).

5.7.5 Dissemination and implementation of these and other refinements in publicly funded research has been accelerated by: the development of the NC3Rs guidelines *Primate accommodation, care and use* and their adoption by the funding bodies as a condition of funding; the involvement of the NC3Rs in the peer review of research grant, fellowship and studentship applications; and through a range of working groups and seminars, in particular the annual NC3Rs Primate Welfare Meeting. It is important that this momentum is maintained through support from the funders and regulatory bodies.

5.8 Public attitudes to research involving animals

5.8.1 As reported and discussed at some length in the Weatherall Report, the debate over the use of animals in research is polarised between those who believe that any form of animal research is completely unjustified and those who believe that it is acceptable provided it is carefully regulated to cause minimal suffering and provided it is directed to alleviating human suffering or for the pursuit of knowledge that in the long term might achieve that end. Opinion polls repeatedly show a high level of concern about the use of NHPs amongst the general public. This concern is driven by a variety of reasons not least the close evolutionary relationship between NHPs and humans. In the UK the extent to which a minority of those who are opposed to such research are willing to embrace illegal means to further their cause seems greater than in most other countries. Roughly a quarter of respondents reported problems with animal rights activists ranging from infiltration of premises to direct intimidation of staff and their families. More reported the inimical atmosphere for such research in the UK as damaging to staff morale and contributing to difficulties recruiting appropriately qualified staff. It was another of the factors reported as contributing to decisions to pursue other areas of science or to move from the UK.

5.9 Challenges and difficulties in undertaking this review

5.9.1 Section 2 has already touched on the challenge of undertaking a systematic review of a relatively small number of studies employing many different methodologies and addressing many different scientific questions, while Section 3 set out the methodology we adopted. In the paragraphs below are recorded the difficulties experienced in obtaining and assessing the relevant data, how we addressed them, and some recommendations for improving the process for the future.

Data collection

5.9.2 The first and major difficulty related to the level of non-responders to the request to participate in the study. Following initial contacts with grant-holders the funding bodies made considerable efforts to improve the participation rate by further approaches to their grant-holders. These contacts resulted in further completed questionnaires and the elucidation of further relevant information about the grant-holders and the studies. For example, two studies involved modelling analyses using data generated by earlier NHP work undertaken elsewhere; some non-responders were no longer active in research and/or were non-contactable.

5.9.3 Table 2 sets out the final participation rates by grant-holders.

5.9.4 Of the three researchers who declined or did not respond, one had retired and one had left the UK. Due to the Wellcome Trust's Data Protection policy they could not provide any information on their system regarding those

Table 2: Participation rates in the survey by number of grant-holders

NO. OF GRANT-HOLDERS					
Funder	**No. of grant-holders identified**	**Participation declined/did not respond**	**Could not be contacted**	**No. of grant-holders who completed questionnaires**	**% who completed questionnaires**
Wellcome Trust	30	2	3	25	83%
MRC	24	1	1	22	92%
BBSRC	10	0	1	9	90%
NC3Rs	1	0	0	1	100%
Total	**65**	**3**	**5**	**57**	**88%**

** 60 grant-holders were identified across all funders. Of this 60, five researchers held grants with more than one organisation throughout the review period 1997–2006.*

two grants. Of the three Wellcome Trust grant-holders that were not contactable, two were deceased and the other had retired and left the UK. All three of those grants were awarded in 1997, before the Trust had introduced grant conditions allowing their information to be used for evaluation, and so consent was needed to release their information to the review. To provide as much information as possible, the Trust supplied the panel with a list of publications for those researchers.

5.9.5 For MRC and BBSRC grants where the grant-holder proved impossible to contact, questionnaires were completed by the funding bodies with information held on file (from the applications and the final reports) and provided to the Review Panel. The Panel was also provided with references for papers published by the grant-holders. However, in most instances these returns were less complete than those provided by grant-holders.

5.9.6 It will be noted that after assiduous chasing, only two grant-holders who were contacted failed to provide completed questionnaires. In the view of the Panel, it is reasonable to expect the recipients of public or charitable funding to be held accountable on issues of public interest and therefore this attitude was regarded as unacceptable. Nor should it be necessary for funding bodies to be obliged to go to such great lengths to elicit a response.

5.9.7 Nonetheless, the Panel recognised that requests to complete questionnaires do impose a cost. Moreover, it was noted that a significant number of respondents had difficulty in providing detailed answers to some questions because they had complied with Home Office advice to destroy records which were more than five years old and were not required for publications. In other instances even the grant-holders appeared to be uncertain about which grants were being reviewed and which published papers related to those grants. References to publications in a number of cases were found to refer to other work, some of which did not involve NHPs at all. In terms of both reducing the additional effort required by grant-holders and improving the quality of data available, we would recommend that as part of their research contracts, funding bodies require grant-holders to provide relevant data, including outcomes and evidence for emerging or realised impact of the work beyond any advances in scientific understanding on a standard template, when they report progress. The Panel noted that the funding bodies had initiated such improvements, but these had not taken effect at the time the research under review was initiated.

5.9.8 The report on bibliometric data provided by Thomson Reuters' Evidence was helpful, although the Panel was also careful to note a number of constraints on its validity. For example, where a paper is published in a limited field, as is the case for much NHP work but particularly for theoretical modelling, then the number of citations will be limited not just by the quality or importance of the work, but also by the limited number of fellow workers in the field. Identifying the paper trail from a discovery in fundamental science and its translation into medical application was also difficult.

Conclusions

5.9.9 The process of collecting historical data on the justification for and impact of research using non-human primates could be streamlined by addressing the feedback and reporting requirements in standard grant terms and conditions.

Recommendation 13
The Panel noted that since the period under review, the funders had made progress in improving the collection of research outputs through standard end of grant templates and, in some cases, through annual data collection. The Panel recommended that a culture of routine output reporting should be embedded in all funded researchers and that provision of such data should be a condition of the grant. In particular, where grants were awarded on the promise of human health benefits, the grant-holders should provide evidence of interest in and use by the medical and biopharmaceutical sectors. Failure to update funders regularly with relevant data should disqualify grant-holders from further funding.

5.9.10 Home Office advice to destroy records after five years is not helpful and should be reconsidered if reviews such as this one are to be repeated in the future.

Recommendation 14
The Home Office should reconsider its advice to research workers to destroy records after five years.

5.9.11 The Panel took note of the improvements in the collection of outcome data which had been introduced by funders subsequent to the commissioning of the research that was considered by the Panel but prior to the completion of this review. Taking into account these improvements, the rapid development of science and techniques that impact on NHP research, the public concern about such work and the views of researchers, the Panel concluded that further comprehensive reviews of the outcomes of NHP research and the contributions made to scientific knowledge, animal and human medicine and other public goods should be carried out at intervals of, say, every 15 years. The reviews should not, however, be so frequent that the difficulties of identifying and measuring impacts are exacerbated.

Recommendation 15
Further reviews of the outcomes, benefits and impact of NHP research should be carried out periodically.

Section 6
Conclusions

6.1 The role of the review was to assess the outcomes of research using NHPs funded by the BBSRC, MRC, Wellcome Trust and NC3Rs between January 1997 and December 2006. In order to judge each piece of research, three separate dimensions were assessed independently: the scientific quality and importance of the research, the probability of medical and public benefit, and the likelihood of animal suffering. These were then brought together to make an overall judgement about whether or not the research project was acceptable and justifiable in all the circumstances.

6.2 The Panel was made aware of a number of developments in procedures which had been initiated but were not in place during the period under review. These included improvements in the rigour of funding decisions, the monitoring of compliance with welfare and legislative requirements and the provision of output data. The Panel applauded these initiatives and made a number of recommendations related to further improvements.

6.3 In the area of neuroscience, which provided the bulk of the material seen by the Panel, the majority of research grants were well-focused on important areas of either neurobiological or medical concern. In specific instances the level of welfare challenge imposed on the research animals could be justified, case by case, on the basis of the quality of the science and the actual and potential medical benefits derived. In a minority of instances the Panel felt that the justification for the use of NHPs, as distinct from work on other species or on humans, was not compelling on the basis of available information. The translation of fundamental science into applied science and practical application was evident in some projects. However, the Panel was concerned that in many cases too little consideration had been given to effective transfer of knowledge. In a minority of cases improvements in the 3Rs (Reduction, Refinement and Replacement) had been developed and disseminated by publication. This was applauded by the Panel.

6.4 In the area of the science exploring the biological basis for vision, the studies mainly addressed fundamental questions. The actual and potential impact of much of this science on medicine was low. A minority of the studies posed a high welfare impact although in these cases the numbers of animals used were low; the remainder were assessed as low welfare impact. In a minority of cases, the publication record was disappointing and in four cases none of the funded work had been published. Weaknesses in knowledge transfer and the appropriate skilling of research teams were also noted. In two instances the Panel suspected that the outputs of the research had been relatively poor because the skills range within the teams appeared to have been sub-optimal. Some progress was noted towards improvements in the 3Rs, particularly in the development of new techniques involving considerably less invasive procedures. These refinements are worthy of encouragement.

6.5 Overall, the Panel agreed that in many cases the use of NHPs was justifiable even in the context of modern understanding of animal welfare and advances in knowledge that might now render some work on living animals unnecessary. However, the Panel was concerned about a number of research programmes in which no scientific, medical or social benefit had emerged. The Panel accepted that its retrospective analysis could not be compared directly with the prospective judgements made at the times when funding for the projects were agreed. If the committees making the judgements could have been certain about the outcome of the research programmes, then funding the work would have been pointless. The outcome of research is always uncertain.

6.6 Some research programmes yield negative findings that are difficult to publish. This is a general problem that involves the potential waste of resources. If the negative findings are not published, other research workers may undertake the very same work that led nowhere. The problem is especially acute when highly sentient animals have been used. A strong case can be made for ensuring that negative findings are made available to the scientific community.

6.7 The Panel recognised that much of the work it had surveyed had been started at a time when standards of animal welfare were lower than they are at present and that techniques that would have obviated the need for use of non-human primates had not yet been developed. Many of its conclusions, therefore, relate to future funding.

6.8 Despite the quality of the work, the sheer expense of working on NHPs in the UK, the degree of harassment experienced by the research workers and the delays involved in administrative procedures has meant that outstanding scientists have left the country or shifted their research to other areas. Where good work on NHPs continues in the UK, it clearly should be supported by proper protection and appropriate funding. Moreover, pressure which results in the movement of work on NHPs from the UK to less well regulated areas of the world will result in a worsening of welfare as experienced by the subjects, not an improvement. At the same time research workers should respond to advances in technology which might lead them to use species other than NHPs. Where use of NHPs is essential, researchers should ensure that their laboratories have implemented improvements in husbandry of NHPs, and their research workers have been properly trained in a range of techniques including those used in training animals.

6.9 In general, scientific research carried out in the UK is highly regarded worldwide. The best of the work carried out on NHPs in the UK is as good as the best of the work carried out in other fields. Where it has not occurred already, this NHP work is likely to bring with it benefits to medicine and the public good.

6.10 Effective knowledge transfer from the research laboratory to areas of wider application is a key issue in many areas of science, but is arguably even more pressing when the welfare of sentient creatures has been compromised during the search for improvements in understanding. The Panel felt that, while publication of science in peer-reviewed journals is a basic and vital step, it is no longer acceptable to regard that as sufficient. Equally, Government commitment to horizon-scanning for problems should be supplemented by a process which systematically scans research outputs for practical applications (output-scanning) and facilitates their take-up by applied scientists and engineers in the public and private sectors.

6.11 The Panel observed that care should be taken with the timing and design of reviews to ensure that they are not repetitive and that they add value proportionate to the demands on researchers' time. The process of collecting historical data on the justification for and impact of research using non-human primates could be streamlined by addressing the feedback and reporting requirements in standard research terms and conditions. Home Office advice to destroy records after five years is not wholly helpful and should be reconsidered. Given the level of public concern about the use of NHP research, periodic reviews are necessary but another should not be repeated for 10–15 years.

6.12 The Panel is aware that its recommendations will not please everybody. In the sharply polarised debate about the use of NHPs in research, it is important to take an evidence-based and systematic approach that carefully considers the case that has been made to support the use of NHPs, the actual benefits arising from this work in practice, and the implications for the animals involved. This was the approach adopted by the Panel in its retrospective review, which makes a unique contribution to the debate. Some of the research considered was scientifically outstanding and, if it has not already benefited medicine, is likely to do so in the future. Some of the findings are of great interest to the public. However, in a few cases the justification for the work was inadequate or insufficient. Moreover, as is the way with any form of exploration, some of the work led nowhere. In this context, an all-or-nothing conclusion on NHP use would have been stupid. Implementation of the Panel's recommendations, already happening in some cases, should lead to the highest standards of animal care in commissioned research and the rapid transfer of findings to the benefit of both humans and other animals.

Section 7
References

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Appendix 1
Questionnaire

BBSRC, MRC and Wellcome Trust 'Post Weatherall' Ten Year Review of Non-human Primate Research

Background to the survey

As part of our response to the Weatherall Report on "*The use of non-human primates in research*" published in December 2006, the Biotechnology and Biological Sciences Research Council, the Medical Research Council and the Wellcome Trust have agreed to undertake a review of all our non-human primate research undertaken over a ten year period.

In order to effectively carry out this review we need to gather information, in addition to that already obtained from end of grant reports, from all our grant holders that were funded for research using non-human primates between the dates of January 1997 and December 2006**. The information that you provide and the views that you hold are critical to ensuring the success of this review, and informing our future strategies on non-human primate research.**

The Questionnaire

This questionnaire refers to **one specific grant only**, which will be clearly indicated in Section A overleaf. If you have received multiple grants during 1997-2006 from the BBSRC, MRC and Wellcome Trust within this research area then you will receive a separate form for each grant. Please attempt to allocate research outcomes to the different grants as accurately as possible.

This questionnaire has been populated as far as possible with information already held on record by the funders, **please check that this information is correct**. Rather that filling out all of the questionnaire yourself, we have commissioned an independent consultant to undertake an interview with you to gather the remaining information. **Brian Jamieson & Associates will contact you shortly to arrange an interview -** to be carried out, at your preference, by phone or face to face.

Therefore, please do not complete and send the questionnaire back to the funder, Brian Jamieson & Associates will collect all the remaining information at the interview.

We appreciate that some grants may have finished some time ago, in which case please look through the questionnaire and consider questions that will be asked during the interview. We hope this will enable you to provide as much information as possible during the interview process. **Please give as much detail as possible as these answers are extremely useful.**

Responses from the questionnaires will be analysed, anonymised and forwarded to an independent review panel that has been convened by the funding bodies. Please note that no information regarding named individuals will be made publicly available.

The information that you provide and your views will be essential for ensuring the success of the review and for informing our future strategies on the use of non-human primates in bio-medical research.

Thank you for your assistance in this important review.

SECTION A: BACKGROUND INFORMATION

Details of Grant	
Name of Grant Holder	
Project Title	
Funding Organisation(s)	
Grant Number	

Non-human primates used

Please provide details of the type(s) and numbers of non-human primates used in this research.

Species	Number requested	Number used	Source *(please put an 'X' in the relevant box)*		Cost per animal
			UK	Overseas	

Location of animal work

Was the research involving the animals conducted in the UK or overseas? *Please put an 'X' in the relevant box.*

		UK
		Overseas – *please provide details in the space provided below*
		Both – *please provide details in the space provided below*

Home Office licence

Was a Home Office licence required for this research? *Please put an 'X' in the relevant box.*

		Yes - *Please indicate the severity band for the research*	Mild:
			Moderate:
			Substantial:
			Unclassified:
		No - *Please provide further details in the space below*	

SECTION B: ANIMAL USE IN RESEARCH

Procedures

Please list the procedures undertaken on the non-human primates as part of the research.

Re-use of animals

Were the non-human primates re-used? *Please put an 'X' in the relevant box.*

		Yes – *Please provide details below.*
		No – *if not, what was the fate of the animals?*

Euthanasia

Were the animals euthanized at the end of the research? *Please put an 'X' in the relevant box.*

		Yes
		No – *Please explain what happened to the animals using the space below.*

Rationale for use of non-human primates

Please provide details of the scientific basis for why non-human primates were required for the research.

Research using other models

Did your research involve the use of animals other than non-human primates?

Did your research involve the use of human participants?

Relevance of the research
Please explain how the research is relevant to human and/or animal health, 3Rs or another agenda.

Specific problems		
Were any specific problems concerning the use of non-human primates experienced during the research? Please indicate, by putting an 'X' in the relevant box(es), if you encountered any problems in the following areas, and give details in the space below.		
	Animal rights activists	
	Training of staff	
	Cost	
	None	
	Other – *Please specify*	

SECTION C: OUTPUTS AND OUTCOMES

Key achievements

To what extent did the research undertaken on this grant meet the proposed objectives? What would you describe as the key achievements of this research? *Please use no more than 350 words.*

Intellectual Property

Please tell us if any intellectual property has arisen wholly or partly as a result of research carried out. *Please put an 'X' in the relevant box(es) and provide details in the space provided below.*

Software/database development	
Patents filed	
Product licences	
Other – *please specify*	

Communication / Public engagement activities

Please tell us if you have carried out any communication/public engagement activities with the research/research outcomes. *Please put an 'X' in the relevant box(es) and provide details in the space provided below.*

Academic workshop/conference presentations	
Communication with non-academic audiences (including schools); Presentations/ posters/ electronic medium	
Feedback to research participants and related communities	
Meetings or discussions with policy makers/healthcare professionals	
Media coverage	
Other – *please specify*	

Collaborations

Please tell us if the research has resulted in any of the following types of collaboration. *Please put an 'X' in the relevant box(es) and provide details in the space provided below.*

Collaborations with commercial partners	
Collaborations with academic groups outside of this award	
Other – *please specify*	

Professional development of staff

Please provide details of any training or professional development activities (including career progression) for any staff employed during this research.

Follow-on funding

Did the research lead to the award of any further funding? *Please put an 'X' in the relevant box.*

		Yes – *Please provide details (i.e. funder, date, type of award, etc.) in the space below.*
		No

Impact on research field

1. Has your research been influenced by, or built significantly on, the research of others? *Please provide details below.*
2. Are you aware of whether your research has been referred to in the work of other researchers. *Please provide details in the space provided below.*

Impacts on human/animal health or other agenda

Please tell us if the research has had any impacts on human and/or animal health. *Please indicate, by putting an 'X' in the relevant box(es), if there have been impacts in any of the following areas, and give details in the space below.*

	Human	Animal
Vaccines		
Clinical trials		
Policy and practice		
Other – *please specify*		

Impact on animal welfare and the 3Rs

Please tell us if the research has resulted in any specific output or wider impact related to animal welfare and the 3Rs (replacement, reduction and refinement) including any technological developments. *Please put an 'X' in the relevant box(es) and provide details in the space provided below.*

Welfare	
Reduction and replacement	
Dissemination of these outputs	
Other – *please specify*	

[A list of publications was also requested]

Appendix 2

Timeline of relevant activities regarding NHPs used in research

1997

Start of review period for the *Review of Research using Non-Human Primates*

1999

A decision to establish the Centre for Macaques (CFM) is taken by the MRC, Wellcome Trust, and the Universities of Oxford and Cambridge

2003

CFM starts supplying rhesus macaques to researchers supported by the funders

2004

NC3Rs is established, providing expertise to the Funders to ensure the 3Rs are implemented in the research that they support, for example by peer reviewing all grants requesting NHPs

2006

Publication of *The use of non-human primates in research*[2] from the working group chaired by Sir David Weatherall.

The NC3Rs and the Funders publish guidelines on *Primate accommodation, care and use*[3]

2006

The MRC and Wellcome Trust publish *Primates in Medical Research*[1] - an introduction to issues raised by NHP research

Wellcome Trust incentivises grant-holders to complete end of grant forms by retaining 10% of funding

End of review period for the *Review of Research using Non-Human Primates*

2007

Working with the NC3Rs, the Funders expand and harmonise the questions on animal use in their grant application forms to support the peer review process

2008

The NC3Rs and the Funders publish guidelines on *Responsibility in the Use of Animals in Bioscience Research*[4]. All funded researchers are required to implement its principles

2009

MRC introduces eVal – a compulsory system to gather data about the outputs and outcomes of MRC-funded research[5]

2010

NC3Rs publish working group report on refining the use of food and fluid control[6]

2010

EU Directive 2010/63/EU on the protection of animals used in scientific procedures is passed in European Parliament

NC3Rs initiates visits to UK NHP laboratories to monitor compliance with the NC3Rs guidelines, attended by BBSRC and Wellcome Trust

2011

BBSRC introducing a Research Outcomes System. Wellcome Trust introducing an online progress tracking tool for some major awards

1. www.wellcome.ac.uk/stellent/groups/corporatesite/@msh_publishing_group/documents/resources/wtx041908.pdf
2. www.acmedsci.ac.uk/images/project/nhpdownl.pdf
3. www.nc3rs.org.uk/primatesguidelines
4. www.wellcome.ac.uk/stellent/groups/corporatesite/@policy_communications/documents/web_document/wtd040017.pdf
5. www.mrc.ac.uk/Achievementsimpact/Outputsoutcomes/e-Val/index.htm
6. www.nc3rs.org.uk/Foodandfluidcontrol

Appendix 3

Methods of assessment

1. For the purposes of judging the overall acceptability of a piece of research, three separate dimensions need to be assessed independently: the scientific importance of the research, the likelihood of medical benefit and the degree of animal suffering. These may be brought together to make an overall judgement about whether or not the research project is acceptable. Figure 2 illustrates the principle but the height of the columns indicating what is unacceptable represents just one point of view and did not necessarily represent the views of the Panel.

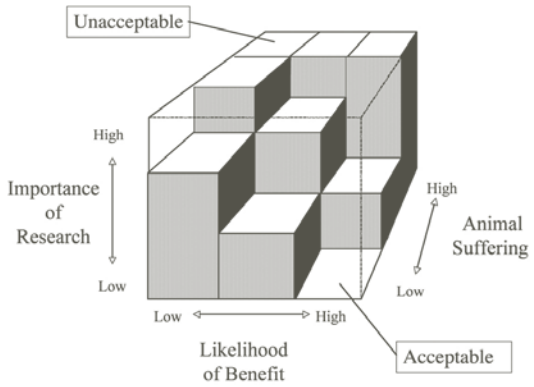

Figure 2. A decision cube for representing one case of rules about whether a scientific research project should be allowed to proceed. Three independent assessments are made. The first assessment is of the maximum suffering that the animals are likely to endure in the course of the project, the second is of the overall scientific importance of the project and the third is of the likelihood of medical or social benefit. If the three assessments fall into the solid part of the cube, the project would be deemed unacceptable according to one view, otherwise it would be deemed acceptable.

2. The general principle is that a much lower amount of animal suffering would be tolerated in scientific research if the work were not regarded as being of high quality and the medical or social benefit was deemed unlikely. Conversely a high standard of science with high medical or social benefit would justify more suffering. Animal suffering should be tolerated only when both the importance of the research and the probability of benefit are assessed as being high. It is all the more important therefore that claims for benefit are well-justified at the time of application for research funding and shown retrospectively to have been successful. Moreover, certain levels of animal suffering would generally be unacceptable regardless of the quality of the research or its probable benefit. The decision rules used would permit research of high importance involving little or no animal suffering – even if the work had no obvious potential benefit to humans. This feature takes note of the concern of scientists who want to understand phenomena that have no immediate and obvious clinical relevance. This is seen as worthy in itself even though an indirect but unforeseeable benefit might be an advance in medicine or public understanding.

3. The scientific approach to the problems of assessing suffering in animals has to be evidence-based and collecting evidence requires orderly methods. Many debates about what should and should not be measured in welfare studies suggest that a variety of approaches are more likely to improve understanding than a single approach. All of the following approaches contribute to an assessment of adverse welfare: (a) measurements of physical damage to the animal; (b) measurements of the extent to which it has been required chronically to operate homeostatic mechanisms that would normally operate acutely; (c) measurements of physiological states that would be found in suffering humans; (d) measurement of the animal's preferences; and (e) considerations of the ecological conditions to which the animal is adapted, its normal social structure and the ways in which it maximises its reproductive success.

4. The decision cube is emphatically not a cost-benefit piece of accountancy since it does not depend on a common currency or on balancing mathematically incommensurable properties. It is a set of pragmatic rules that has proved helpful in determining whether or not a particular piece of research was acceptable. The positions of the lines between acceptability and non-acceptability represent a consensus acceptable to the majority of the public. All the evidence suggests that in highly developed countries the consensus has been moving towards a more restrictive view of what is acceptable. However, it might well change in the opposite direction were human populations to be afflicted by a new and terrible plague and vaccines could only be developed on animals very similar to humans.

5. The suffering of every individual matters. A problem arises when attempting to equate a small number of animals suffering a lot versus a large number suffering a little because the numbers of animals used is not commensurate with the degree of suffering that each individual suffers. A mathematical combination of the two dimensions is impossible. Here again, though, the problem can be overcome by application of the rule that use of a larger number of animals may be tolerated if the welfare costs to the animals are lower. The overall index of suffering which can be fed into the decision cube shown in Figure 2 is shown in Figure 3. Here again the lines that separate the overall degrees of suffering are reached by consensus.

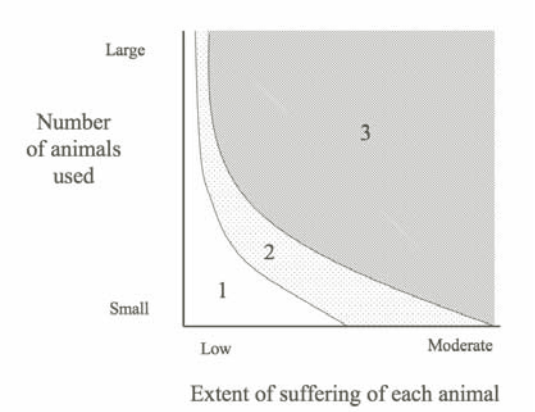

Figure 3. The number of animals used in a research programme is plotted against the suffering that each animal is likely to endure in the programme. The overall amount of suffering is given by the numbers that refer to the severity bands used in Figure 2 where low=1, medium=2 and high=3.

Appendix 4

Panel members

Chairman

Professor Sir Patrick Bateson ScD FRS

Patrick Bateson is a behavioural biologist at the University of Cambridge. He was Provost of King's College, Cambridge (1988–2003). He is President of the Zoological Society of London. He was elected a Fellow of the Royal Society of London in 1983 and was its Biological Secretary and Vice-President from 1998 to 2003. He was knighted in 2003. His research is on the behavioural development of animals, and much of his scientific career has been concerned with bridging the gap between the studies of behaviour and those of underlying mechanisms, focusing on the process of imprinting in birds. He has written more than 290 scientific papers and book chapters on imprinting in birds, the development and evolution of behaviour, neural mechanisms of learning, and the conceptual and methodological issues in the study of behaviour and animal welfare. He has edited 15 books, chaired two reports on aspects of animal welfare and is co-author (with Paul Martin) of *Measuring Behaviour* (3rd edition, 2007) and *Design for a Life: How Behaviour Develops* (1999); he is also co-author (with Peter Gluckman) of *Plasticity, Robustness, Development and Evolution* (2011).

Members

Dr Heidi Johansen-Berg DPhil

Heidi Johansen-Berg is a Wellcome Trust Senior Research Fellow and Reader in Clinical Neurology at the University of Oxford. Her research concerns how the brain changes with learning and recovery from damage. Her group studies these questions mainly using brain imaging and stimulation methods in human volunteers and in people who have suffered strokes. They are now applying what has been learnt to development of new rehabilitation strategies for stroke. In addition to studies in human volunteers, her group carries out studies in rodents to understand the cellular changes that underlie effects seen with imaging. Dr Johansen-Berg has developed and applied new approaches for using non-invasive brain imaging technology to study anatomical connections in the brain. She is currently serving as President of the Organisation for Human Brain Mapping, the primary international organisation dedicated to neuroimaging research.

Professor Derek K Jones PhD, Dip IPSM

Derek Jones is an MRI physicist and Director of CUBRIC (Cardiff University Brain Research Imaging Centre, School of Psychology, Cardiff University, UK) – a centre dedicated to multimodal imaging of the human brain. He is Deputy Editor of *Magnetic Resonance in Medicine*, sits on the Board of Trustees of the International Society for Magnetic Resonance Medicine (ISMRM), has served on the Neuroscience and Mental Health Funding Committee of the Wellcome Trust and currently sits on the Expert Review Group for the Wellcome Trust. He has held several positions of office in the ISMRM (Education Co-ordinator, Chairman of Diffusion/ Perfusion Study Group) and has served on the Editorial Boards of *NeuroImage* and *MAGMA*. His research focus is on the non-invasive quantification of tissue microstructure in the human brain, particularly in white matter, and how this impacts on behaviour, cognition and electrophysiology.

Professor Eric Barrington (Barry) Keverne ScD, FRS, FMedSci

Barry Keverne is a behavioural neuroscientist. His research is on mechanisms of behaviour (neural, hormonal) with social groups of primates (rhesus monkey, talapoin monkey). His primary interests are in mother-infant relationships and how the neural reward mechanisms, which evolved in this context, also subserve social bonding and cohesion of the monkey group. Parallel work on sheep gathered more detailed knowledge on the electrophysiological changes and *in vivo* microdialysis of neurotransmitter changes which occur during mother-infant bonding in sheep. He has also studied neural and behavioural basis of olfactory communication in mice and how recognition memory is sustained and is affected by pheromones themselves. He is currently investigating genomic imprinting in brain and placenta development and the significance of this for maternalism and the co-adaptive evolution of brain and placenta.

Professor Paul M Matthews OBE, MD, DPhil, FRCP

Paul Matthews is Professor of Clinical Neurosciences at Imperial College London, Vice-President for Imaging in GlaxoSmithKline and founding Head of the GSK Clinical Imaging Centre at Hammersmith Hospital. He received his undergraduate degree in chemistry and his DPhil in biochemistry from the University of Oxford and an MD from Stanford University before completing his specialist training in neurology at the Montreal Neurological Institute of McGill University. After a brief appointment as an MRC (Canada) Clinician Scientist and Assistant Professor of Neurology and Medical Genetics at McGill, he returned to Oxford to establish and direct the Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB) in the Department of Clinical Neurology as an MRC Clinical Research Reader and then Professor. He stepped down from his roles as Director of the FMRIB Centre and Head of the Department of Clinical Neurology to move to Imperial College and GSK in 2005. He currently is a Fellow by Special Election of St Edmund Hall, Oxford and holds honorary Professorships in the University of Oxford, University College London and McGill University, Canada. He practices neurology as an Hon. Consultant Neurologist at the Hammersmith Hospital and the John Radcliffe Hospital, Oxford. Prof. Matthews' research focuses on experimental medicine for new therapeutics development and has made particular use of non-invasive clinical imaging with MRI, magnetic resonance spectroscopy and positron emission tomography (PET). He was made an OBE in 2008 for services to neuroscience.

Professor Arthur David Milner PhD, FRSE, FRS
David Milner is Emeritus Professor of Cognitive Neuroscience at the University of Durham. He received his undergraduate degree in psychology, philosophy and physiology from the University of Oxford, and his PhD from the University of London. After working for almost 30 years at the University of St Andrews, he moved to Durham in 2000. His research interests lie principally in the workings of the brain's cortical visual system. His investigations have been carried out chiefly, though not entirely, with human subjects – especially neurological patients with relatively circumscribed brain damage. The work has focused on the underpinnings of visual perception, visual attention, and visually guided behaviour. His work over the past 20 years has been concerned with two main themes: (a) the division between the brain systems respectively devoted to visual perception and visuomotor control; and (b) unravelling the nature of the puzzling and complex clinical condition of visuospatial neglect. He has published over 170 scientific papers and book chapters, has co-written two books (with Prof. M A Goodale), and has edited or co-edited four further books in his area of research. He was elected a Fellow of the Royal Society of Edinburgh in 1992 and of the Royal Society of London in 2011.

Dr Mark Prescott PhD
Mark Prescott leads the animal welfare and peer review programmes at the National Centre for the Replacement, Refinement and Reduction of Animals in Research (NC3Rs). His main research interest is the welfare of animals used in scientific procedures, principally non-human primates. He graduated in zoology from the University of Edinburgh. During his PhD in psychology at the University of Stirling he studied the behaviour and ecology of New World monkeys in captivity and in the field. He is an Honorary Research Fellow of the Scottish Primate Research Group. Prior to the NC3Rs he worked as a Lecturer in Animal Management and Primate Conservation, and as Senior Scientific Officer in the Research Animals Department of the RSPCA. He serves on the Animal Procedures Committee, the Advisory Board and Ethical Review Process of the Centre for Macaques, and the Captive Care Committees of the Primate Society of Great Britain and International Primatological Society.

Dr Ian Ragan PhD
Ian Ragan is a neuropharmacologist and an independent consultant in the biomedical sector. He spent nearly 20 years in the pharmaceutical industry, most recently with Eli Lilly as Executive Director, Neuroscience Research, Europe, and Executive Director, European Scientific Affairs. He was the Lilly representative on the Research Directors' Group of the European Federation of Pharmaceutical Industries and Associations and one of the originators of the Innovative Medicines Initiative. He has been chair of the R&D Committee of the Association of the British Pharmaceutical Industry, a member of the Council of BBSRC and the Executive Director of the European Brain Council. He has been a board member or scientific advisor to a number of companies including Evotec AG, Capsant Neurotechnologies, Biovail and Psynova Neurotech. He is Project Co-ordinator for the European Partnership for Alternatives to Animal Testing, and a board member of the NC3Rs, for whom he chairs the Biologicals Expert Working Group looking into the use of non-human primates in the development of monoclonal antibodies. He is a member of the Independent Scientific Committee on Drugs, chairing a working group on cognition enhancers, and a Trustee of the research charity Autistica.

Professor Robin Shattock PhD
Robin Shattock is Professor of Cellular and Molecular Infection in the Department of Cellular and Molecular Medicine, St George's Hospital Medical School, University of London. He directs a research group working on the pathogenesis and transmission of HIV infection, with a particular emphasis on the development of prevention strategies applicable to the developing world. His research group has been instrumental in elucidating the early mechanism of HIV transmission, which is being used in a translational fashion to develop safe and effective vaginal microbicides and to explore novel HIV vaccination strategies. Prof. Shattock's group receives funding from the Wellcome Trust, the Bill & Melinda Gates Foundation, the European Commission, the US National Institutes of Health and IPM. He coordinates the European Vaccines and Microbicides Enterprise network of Europrise, leads the Mucosal Discovery Team of Center for HIV Vaccine Immunology (CHAVI), and co-coordinates the scientific direction of the European Microbicides Program on Combined Highly Active Antiretroviral Microbicides (CHAARM).

Professor Jerome (Jerry) Strauss III MD, PhD
Jerry Strauss is Professor of Obstetrics and Gynecology and Dean of the Virginia Commonwealth University School of Medicine and Executive Vice President for Medical Affairs of the VCU Health System. He serves on the External Advisory Board of the Wisconsin National Primate Research Center and is a former member and chair of the External Advisory Board of the Oregon National Primate Research Center. He served as a member of the National Advisory Child Health and Human Development Council of the National Institutes of Health, and currently sits on its Board of Scientific Counselors. He is a member of the Board of Directors of the Burroughs Wellcome Fund, of which he is the current Chairman. Professor Strauss was elected to membership of the Institute of Medicine of the United States and the National Academy of Sciences in 1994. Professor Strauss's research interests include the regulation of steroid hormone biosynthesis, control of ovarian and placental function, the genetics of polycystic ovary syndrome, preeclampsia, the genetic basis of preterm birth, and the control of germ cell function. He has authored over 275 original scientific articles, and holds 11 issued US patents for discoveries in diagnostics and therapeutics.

Rapporteur
Heather Peck BSc (Hons) FCIPD
Heather Peck was Deputy Director at the Department for Environment Food and Rural Affairs with particular responsibility for animal welfare policies up to March 2008. Between 2005 and 2008 she was also Regional Operations Director for four outbreaks of avian flu, one of Newcastle disease and part of the 2007 foot and mouth outbreak. Since then she has worked as a consultant in areas involving animal welfare and agricultural policy. She chaired the 2010 Oxford Farming Conference and currently chairs the HGCA's Wheat Committee which selects new varieties of wheat for the UK Recommended List. She is Vice Chairman of Cambridgeshire Community Services NHS Trust. She was secretary to the Independent Inquiry into Dog Breeding and is now secretary to the independent Advisory Council on the Welfare Issues of Dog Breeding.

Appendix 5
Assesment template

BBSRC, MRC and Wellcome Trust 'Post Weatherall' Ten Year Review of Non-human Primate Research

Lead Discussant Assessment Template	
Lead Discussant 1	
Lead Discussant 2	

Your comments will assist the drafting of the Review Committee Report. Please complete the templates with brief bullet points on each of the criteria below or indicate where this is not possible based on the information provided.

Details of Grant	
Agenda number/ Name of Grant Holder/ Title	
Funding Organisation(s)	

What was the scientific value of the work?

What is the evidence from the bibliometric analysis (where available)?
To what extent was the research directed at an important medical or biological question?
How effective was the design/methodology in answering the research questions posed?
How innovative was the research in the context of when it was carried out?
Please indicate whether the Scientific Value was High/Medium/Low.

What were the benefits of the research?
To what extent did the work deliver its aims?
To what extent did the research yield results that were of immediate importance?
What benefits did it deliver (e.g. for health services, for research methods, and/or industry or for scientific knowledge)?

What are the likely (or possible) long-term impacts?
Please indicate whether the Overall Benefits (incorporating benefit to animals and moving scientific knowledge along the trajectory towards tangible benefit) were High/Medium/Low. Please note where the benefit lies.

What was the welfare impact of the research? Noting the use, number and species of animal involved:-
What were the alternative routes to answering the question, if any?
What advances were there in the 3Rs and welfare?
Indicate the Animal Welfare Impact (takings into account the numbers of animals as well as severity per animal) High/Medium/Low.

Name of Lead	
Discussant	
Date	

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