The ASC
Animals in Science Committee

# Review of harm-benefit analysis in the use of animals in research

Report of the Animals in Science Committee Harm-Benefit Analysis Sub-Group chaired by Professor Gail Davies

November 2017

# Foreword

As Chair of the Animals in Science Committee, it is my pleasure to introduce this review of the use of harm-benefit analysis (HBA) in animal-based research and testing, which has been produced by a sub-group of the committee under the leadership of Professor Gail Davies. The importance of the topic is thrown into sharp relief by a few numbers. In 1871 a woman's life expectancy at birth in England and Wales was only 45 years. A century later it stood at 75 and by 2011 it had reached 83. Many factors contributed to this improvement, but progress in medicine and the life sciences played a major role and today these sectors contribute substantially to Gross Domestic Product growth, exports and job-creation across the UK. But if scientific and technological progress has benefited health and wealth, it has also brought hazards in its train. Newly-synthesised molecules may pose risks to health and the environment and innovative medicines may prove ineffective or have harmful side effects that outweigh any advantages they may bring.

The volume of regulatory testing has thus expanded in parallel with research in medicine and the life sciences. Both of these research activities rely heavily on the use of laboratory animals. Currently, some two million animal procedures are performed annually – around a quarter of them in regulatory testing – whilst similar numbers are accounted for in the breeding of genetically modified animals. The use of animals may – given our current state of knowledge – be unavoidable, but it comes at a price. Some 80% of animal procedures are currently assessed as involving suffering and some 6% as involving severe suffering.

Animal suffering has long been a matter of concern to British public opinion and legislation to protect animals was placed on the statute book in Victorian times. Few now would condone the killing or mutilation of animals merely to entertain spectators, but the use of animals in research attracts a wide spectrum of opinion. At one extreme lies the belief that our ethical commitment to humanity should override any concern for non-human species, whilst at the other is the attribution of natural rights to animals which would prohibit their use in any procedure on the basis that they are unable to give informed consent. The weight of public opinion, however, holds the use of animals to be acceptable if and only if: the reasonably-foreseeable benefits outweigh the welfare costs (or 'harms') unavoidably imposed on the animals; there is no other way in which these benefits can be obtained; and the work is undertaken to the highest practicable welfare standards.

This, essentially utilitarian, HBA calculus is embodied in the Animals (Scientific Procedures) Act that governs animal-based research in the UK. As Professor Davies and her colleagues point out, whilst HBA constitutes an essential stage in the scrutiny of project licence applications under the Act, it does not end here. The HBA should be seen as an ongoing process, which continues throughout the life of the licence and the work carried out under it.

Professor Davies' group have carried out an ambitious analysis of the underpinnings and implementation of HBA. Much of their work is concerned with the problem of animal suffering – particularly that characterised as 'severe' under the Act – and with identifying, endorsing and promoting best practice in this respect. They also raise questions which have not always received the attention they deserve and require to be debated in the context of future policy formulation, for instance, how should societal concerns attaching to some novel procedures be identified and addressed? Of particular interest, however, are the questions raised in respect of the hitherto under-examined area of allowable 'benefits'. Should, for example, this category be expanded to include public engagement with and understanding of, science? How should we weigh the proposed benefits of research in basic science which may only be fully realised long after the conclusion of the project itself? Similarly, in the case of regulatory safety testing – which accounts for most of the procedures involving 'severe' suffering – the substances tested are treated equally regardless of their nature and purpose (except for those such as tobacco products and cosmetics where animal testing is forbidden). Is it really appropriate to equate the benefits of a new food colouring to those of a potentially life-saving pharmaceutical?

The importance of the HBA process to the conduct of animal-based research and testing cannot be overstated and I am grateful to Professor Davies and her colleagues for their far-reaching analysis of its bases and their pointers to the way forward. These will be of interest to all those concerned with this vital issue, on whatever side of the debate they may find themselves.

**Dr John Landers,**
Chair of the Animals in Science Committee

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# Executive Summary

This report sets out the Animals in Science Committee (ASC) review of the processes of harm-benefit analysis (HBA) carried out under the UK Animals (Scientific Procedures) Act 1986 (A(SP)A). The A(SP)A requires the HBA of a programme of work to assess whether the harm that would be caused to protected animals, in terms of suffering, pain, distress and lasting harm, can be justified by the expected outcome, taking into account ethical considerations and the expected benefit to human beings, animals, or the environment.

The UK Home Office Inspectorate, part of the Animals in Science Regulation Unit (ASRU), undertakes HBA as part of the evaluation of project licence applications to use animals in research and testing. ASRU produced an Advisory Note (ASRU, 2015) explaining how the HBA process is applied to new project licence applications.

This ASC report was subsequently commissioned to make recommendations on how current arrangements for performing a HBA might be improved. It draws on:

- international policy discussions on HBA
- recent academic literature on key aspects of HBA
- a review of past project licence applications
- new ASC research on the identification and assessment of benefits

The ASC report concludes that HBA remains a legitimate ethical framework for evaluating the use of animals in research and testing.

HBA continues to be the cornerstone of project licence evaluation, in which a decision is made determining if the overall harm that will occur is justified by the benefits that are likely to be delivered.

HBA continues to be the cornerstone of project licence evaluation, in which a decision is made determining if the overall harm that will occur is justified by the benefits that are likely to be delivered. The processes of HBA are also important throughout the life of a project. They can be used to direct efforts to reduce harms and maximise benefits during research. They can also help recognise at what point a project, procedure, animal 'model' or research trajectory can no longer be ethically justified.

However, the operational processes of HBA require regular dialogue and ongoing review to ensure that they remain robust, effective and transparent in realising these objectives.

The ASC identified the following opportunities to enhance the implementation and review of HBA.

- **Understandings of harms and benefits are not fixed in time.** There are novel scientific techniques and frameworks to help to recognise and mitigate harms, including around cumulative and severe severity. There are also new mechanisms for evaluating research design and research impact, which can be used to assess and improve the likelihood of benefits.
- **There are new resources for learning and review.** HBA has been primarily thought of as a prospective evaluation of the likely harms to animals and potential benefits of a programme of research. Requirements, since 2014, to return data on actual severity and the growing documentation of research impact are enhancing capacities for learning and review.
- **Realising these opportunities requires enhanced dialogue.** Further improvements to the HBA will be supported by increasing communication between the different HBA processes. This includes engaging with changing societal views around how seriously certain types of harms are regarded and whether some kinds of benefits resulting from animal research can be justified.

Following review of these resources and opportunities, this report concludes with recommendations for improving good practice, learning and dialogue across the processes of HBA, both in and outside of the regulatory framework implemented by the Home Office.

# Glossary

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| **3Rs** | The replacement, refinement and reduction of the use of animals in research. This is the framework for the humane use of animals in scientific research. The 3Rs are embedded in national and international legislation regulating the use of animals. |
| **ACHM** | Animals containing human material. |
| **AMS** | Academy of Medical Sciences, an independent UK learned society representing medical science. The mission of the AMS is to advance biomedical and health research and translate this into benefits for society. The AMS has conducted work on scientific good practice and integrity, including a public dialogue on ACHM (see above). |
| **APC** | Animal Procedures Committee (now replaced by the ASC, see below). |
| **ARRIVE guidelines** | Animal Research: Reporting of In Vivo Experiments (ARRIVE) guidelines, produced by the NC3Rs in consultation with the scientific community. ARRIVE aims to improve the reporting of research using animals – maximising the information published and minimising irreproducibility of research. |
| **ASC** | Animals in Science Committee, an advisory non-departmental public body of the Home Office. The ASC was established by the Animals (Scientific Procedures) Act 1986 (see below) to oversee the protection of animals used for scientific purposes. The ASC is responsible for providing impartial, balanced and objective advice to the Secretary of State, to animal welfare bodies and to partners within the European Union. |
| **A(SP)A** | The Animals (Scientific Procedures) Act 1986. The A(SP)A regulates procedures that are carried out on protected animals for scientific or educational purposes that may cause pain, suffering, distress or lasting harm. The Act also regulates the breeding and supply of certain species of animals for use in regulated procedures or for the scientific use of their organs or tissues. |
| **ASRU** | Animals in Science Regulation Unit, Home Office. ASRU is responsible for regulating the operation of the A(SP)A. The activities of ASRU include the development of policy, regulation of licensing, inspections and investigations of non-compliance. |
| **AWAG** | Animal welfare assessment grid. Open source software tool for use in implementing a quantitative matrix-based animal welfare assessment system. |
| **AWERB** | Animal Welfare and Ethical Review Body. AWERBs are required at all establishments breeding or using animals for scientific procedures in the UK. AWERBs are responsible for the ethical review of new programmes of work, amendments to these programmes and the assessment of outcomes. |

**Concordat on Openness in Animal Research**

The Concordat was launched by Understanding Animal Research in May 2014 and by 2017 had 112 signatories. They have agreed to be more open about their use of animals in research and to abide by four commitments (Understanding Animal Research, 2014):

- to be clear about when, how and why they use animals in research
- to enhance communications with the media and the public about their research using animals
- to be proactive in providing opportunities for the public to find out about research using animals
- to report on progress annually and share experiences

**Contingent harms**

The inherent and inescapable harms arising from the experimental or scientific use of an animal. Examples include:

- being housed in a cage (as opposed to being able to range freely in the wild)
- inability to express a wide range of the natural behaviours
- handling or transport stress
- olfactory exposure to a large number of conspecifics (in the case of laboratory rodents housed in conventional caging) (ASRU, 2015)

**Cumulative effects**

The ASRU advice note defines cumulative effects as the net impacts of all the events (procedurally and husbandry-based) and effects that affect adversely, positively and by way of amelioration, the welfare of an animal over its lifetime. They include likely habituation, potentiation and/or sensitisation and any temporal element in which recovery between events and memory of them and/or their consequences is likely to be affected.

**Cumulative severity**

The assignment of a severity category in legislation (see below) needs to take into account the potential for the intensity, duration, frequency and multiplicity of techniques to negatively affect the welfare of an animal over its lifetime ie to contribute to cumulative severity. Both the Home Office Inspectorate and the EU Directive 2010/63 consider cumulative suffering within a procedure as a key issue in assigning severity categories.

**HBA**

Harm-Benefit Analysis, in which the likely adverse effects (harms to animals) in a procedure within a project are weighed against the potential benefits of the project for people, animals, or the environment (Home Office, 2014).

**HEFCE**

The Higher Education Funding Council for England. HEFCE funds and regulates universities and colleges in England, distributing public money to support university research through mechanisms like the REF.

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| **Lower threshold** | The lower threshold of pain caused to an animal in a procedure (see Procedure and Severity categories below). |
| **NC3Rs** | The National Centre for Replacement, Refinement and Reduction of Animals in Research (the 3Rs, see above). The NC3Rs was launched in 2004 to increase the focus on the 3Rs across the UK. The NC3Rs funds research and early career scientists, supports the development of new technology, provides evidence for policy makers and promotes knowledge dissemination to the public. |
| **Permissible Purposes** | Purposes for which a Personal Project Licence (see below) will be granted. Purposes include: basic research, translational or applied research, drug development, protection of the natural environment, species preservation, training and forensic enquiries. |
| **PPL** | Personal project licence, required for all individuals carrying out procedures on animals. |
| **Procedure** | An act of commission, deliberate omission or permission applied to, or having any effect on, an animal (Home Office, 2014). A procedure is regulated if it is carried out on a protected animal for a scientific or educational purpose and may cause that animal a level of pain, suffering, distress, or lasting harm equivalent to, or higher than, that caused by inserting a hypodermic needle according to good veterinary practice. This is referred to as the 'lower threshold' (see Severity categories below). |
| **Project-related harms** | Harms to animals directly caused by the procedures within a project, compared with contingent harms, (see above (ASRU, 2015)). |
| **Protocol** | A procedure or series of procedures carried out for a particular purpose as part of an authorised project. |
| **RCUK** | Research Councils UK (RCUK) is the strategic partnership of the UK's seven Research Councils. Research Councils distribute public funds to research projects across the full spectrum of academic disciplines, from the medical and biological science to the arts and humanities, informed by peer review. |
| **REF** | The Research Excellence Framework (REF) is the system for assessing the quality of research in UK higher education institutions. It is run by HEFCE and partner bodies in Scotland, Wales and Northern Ireland, every six to seven years. The results of the 2014 REF were published in December 2014. |
| **Severity** | The intensity of pain, suffering, distress or lasting harm experienced by an animal during a procedure. |

**Severity categories**

There are five levels of severity used to classify harms caused by scientific procedures:

- **sub-threshold** – procedures that are not regulated, because their severity is below the 'lower threshold' – see Procedures above for further explanation
- **non-recovery** – procedures that are performed entirely under general anaesthesia from which the animal shall not recover consciousness
- **mild** – procedures that are likely to cause animals to experience short-term mild pain, suffering or distress, as well as procedures with no significant impairment of the well-being or general condition of the animals
- **moderate** – procedures that are likely to cause animals to experience short-term moderate pain, suffering or distress, or long-lasting mild pain, suffering or distress, as well as procedures that are likely to cause moderate impairment of the well-being or general condition of the animals
- **severe** – procedures that are likely to cause animals to experience severe pain, suffering or distress, or long-lasting moderate pain, suffering or distress, as well as procedures that are likely to cause severe impairment (Home Office, 2014)

**Severity classification**

The process of assigning a severity category to a protocol. It may be sub-threshold, non-recovery, mild, moderate, or severe (see 'Severity categories' above). It is based upon the greatest degree of pain, suffering, distress, or lasting harm likely to be experienced by any animal within that protocol after applying all appropriate refinement techniques (Home Office, 2014).

**Severity limit**

The highest level of pain, suffering, distress, or lasting harm that may be experienced by any animal undergoing an authorised procedure (or series of procedures). It should normally be expressed as a humane end-point in relation to an adverse effect that may be expected to occur. Hence a procedure may have a number of severity limits, which apply at different times in relation to different adverse effects (Home Office, 2014).

# CHAPTER 1

# INTRODUCTION

Photo Credit: Understanding Animal Research

# 1. Introduction

## 1.1. ANIMALS IN SCIENCE COMMITTEE HARM-BENEFIT REVIEW

The Animals (Scientific Procedures) Act 1986 (A(SP)A) requires a harm-benefit analysis (HBA) of a programme of scientific work to assess whether the harm that is caused to protected animals in terms of suffering, pain and distress is justified by the expected outcomes, taking into account ethical considerations and the expected benefit to human beings, animals, or the environment.

This review of HBAs in the use of animals in research was carried out in response to the commissioning letter received from the then Home Office Minister, Norman Baker, in August 2014 (see Appendix A). The letter asked the Animals in Science Committee (ASC) for advice on the current arrangements for performing a HBA and consideration of whether these might be improved. It also asked the ASC to produce advice that particularly considers the most severe procedures and, relevant to particular types or values of benefit, assist in determining where the level of harm lies above which licences should not be approved.

The Animals in Science Regulation Unit (ASRU) Inspectorate has undertaken HBA as part of the evaluation of project licence applications to use animals in research and testing since A(SP)A was implemented in 1987. Following transposition of the European Directive 2010/63/EU in 2013, ASRU has produced a series of advisory notes, including a document explaining how the HBA process is applied operationally to new project licence applications (ASRU, 2015). This supplements guidance on HBA of project licence applications within the Home Office guidance (Home Office, 2014, see Appendix I) and draws upon the European Commission's working document on project evaluation and retrospective assessment (European Commission, 2013).

The HBA advice note (ASRU, 2015) aims to show in detail how Home Office inspectors carry out HBAs during the evaluation of project licence applications and how the outcomes of these analyses are used to determine whether a project licence will be granted or refused. The focus is on how new project licence applications are evaluated. It is acknowledged that HBA should not be viewed as a one-off event and should be appropriately reviewed throughout every licence.

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The ASRU advice note has been placed in the public domain to advise practitioners and assist public understanding of how animal research is regulated, in line with the government's policy on openness and transparency.

This ASC review provides reflection and additional comment on this advice note. It draws on academic and policy reviews of the processes of HBAs, as well as new research on the identification and assessment of harms and benefits, in order to make recommendations on how current arrangements for performing a HBA might be improved.

## 1.2. MEMBERS AND METHODS

The ASC Harm-Benefit Analysis subgroup was established in autumn 2014. Its members are: Professor Gail Davies (ASC, Chair of the subgroup); Huw Golledge (ASC); Penny Hawkins (ASC); Anna Rowland (ASC); Sarah Wolfensohn (ASC); Jane Smith (Boyd Group, advice and report drafting); and Dominic Wells (Animals in Science Group at the Royal Society of Biology, advisory input).

Advice, input and access to past project licences was provided by members of ASRU. Gabrielle King contributed to research on the evaluation of benefits at the University of Exeter. The subgroup was generously supported throughout their work by Dr Jo Wallace and Caroline Wheeler from the Home Office Science Secretariat.

**This review aims to encompass all the stages of assessing and weighing harms and benefits in HBA. These can be summarised as three key steps:**

- **decision** – developing and approving the project licence application
- **implementation** – reducing harms and maximising benefits throughout the life of the project licence
- **reflection** – recognising when a project or procedure can no longer be justified

**Work on harms completed by members of the ASC includes:**

- consideration of **factors involved in the assessment of harms**, including contingent effects relating to husbandry, care and transportation practices
- review of recent academic work on **identifying and assessing cumulative effects**
- discussion within the ASC of routes towards **reducing the use of severe procedures** and
- reflection on **societal concerns relating to harms** and how they might affect the HBA

**Work on benefits completed by members of the ASC includes:**

- consideration of **current advice on assessing and weighing benefits**, informed by the HBA advice note (ASRU, 2015) and ASC discussion
- interviews with scientists and inspectors about **how the assessment of benefits might be improved**
- analysis of relevant **impact case studies from the 2014 Research Excellence Framework**, which documents the impact of animal research in higher education institutions (see methods in Appendix D)
- discussion of **findings and recommendations from this research** at meetings with the ASC, ASRU and Higher Education Funding Council for England (HEFCE)

The final report was considered and approved by the ASC in summer 2017 and a small working group set up to inform the implementation of recommendations with further assistance from members of ASRU.

## 1.3. SCOPE AND AIMS OF THE REPORT

The ASC review seeks to contribute to an ongoing and open dialogue around the development of HBA in animal research and testing. Robust HBA depends on the availability and application of:

- current evidence for harms to animals
- current evidence for potential benefits
- a process of evaluation that is legitimate, effective, accountable, transparent and inclusive of a variety of perspectives, including societal concerns

The review draws on progress in the assessment of harms and benefits to make specific recommendations for improvements to these aspects of the HBA. These recommendations aim to ensure processes of HBA are responsive to new data and changing societal concerns. The review also explores how new techniques, sharing good practice and increasing transparency might be used to improve decision-making and further development of a well-informed, well-judged and inclusive HBA.

The ASC recognises that HBA is situated at the heart of regulations on the use of animals in research and testing and represents an ethical dilemma that cannot be fully resolved. For this reason, HBA must be an ongoing, dynamic process that is responsive to developments in regulatory, scientific, societal and animal welfare domains.

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The outcomes of HBA will be provisional judgements that are likely to change over time, as new ways of thinking and working evolve.

The ASC considers carefully the Minster's request for advice on a level of harm, above which licences should not be approved. For this reason, the ASC reviews in detail:

- measures to assess and reduce cumulative severity
- triggers for additional scrutiny around severe procedures
- moves to eliminate severe suffering
- processes used to identify societal concerns in the HBA

However, the ASC does not specify a level of harm above which licences should not be granted. It notes that recent experience has seen issues move from additional scrutiny, formal review and subsequent exclusion through the application of HBA (for example, the use of great apes, testing for cosmetics and household products). The ASC suggests that a static cut-off is not helpful; weighing harms and benefits will always require people to make judgements informed by current science and societal concerns. However, the ASC does identify additional opportunities for transparency, dialogue and learning that could be used to enhance HBA processes around this issue in the future.

This report is aimed at anyone with an interest in the use of animals in scientific procedures, both nationally and internationally. This includes those who regulate, influence and implement HBAs locally, nationally and internationally, Members of Parliament and relevant committees and, importantly, members of the public.

The specific recommendations to the Minister from the ASC on how current arrangements for performing a HBA might be improved will be published as a separate short advice note written with members of ASRU. This advice note will draw on the principles and opportunities identified in this report, to enable the prioritisation, implementation and evaluation of these recommendations within ASRU.

# CHAPTER 2

# REVIEWING HARM-BENEFIT ANALYSIS

# 2. Reviewing Harm-Benefit Analysis

## 2.1. RECENT DEVELOPMENTS

The Animal Procedures Committee (APC) *Review of Cost-Benefit Assessment in the Use of Animals in Research* (APC, 2003) laid out the ethical basis for the HBA. It drew on consultation with stakeholders to explore how such processes were being understood and used. Many respondents to this consultation believed that HBA had contributed to animal welfare, but many were also uncertain how the assessment operated in practice. The APC review explained the decision-making framework for HBA and set out suggestions for 'moving thinking on'. It was a valuable summation and discussion document and remains an important resource for understanding the ethical principles of HBA on which the Animals in Science Committee (ASC), the successor to the APC, seeks to build.

Since the 2003 APC review, there have been significant changes in the regulation of animal use. The term 'cost' has been replaced by 'harm', which is regarded as more descriptive of the core ethical issues and less likely to be misinterpreted. Both the European Directive 2010/63/EU (European Commission, 2010) and UK legislation regulating animal procedures have been revised (Animals (Scientific Procedures) Act, 1985, revised≈2013), with the production of new guidelines, revised codes of practice and amended bodies for delivering HBAs.

The ASRU remains the key regulatory body for HBA and, as noted in Section 1.1, recently published an account of "*the current processes used by the Home Office to conduct a harm-benefit analysis during the evaluation of a project licence application*" (ASRU, 2015). However, the Ethical Review Process (ERP) has become the Animal Welfare and Ethical Review Body (AWERB) and the independent government scrutiny provided by the APC has been replaced by the ASC.

Many international organisations now require animal research to comply with agreed ethical principles that include HBA. The need to perform an HBA is reflected in legislation and guidelines produced for:

- animal research carried out in Europe under the Directive 2010/63/EU (European Commission, 2013)
- the Office International des Epizooties (OIE) Terrestrial Animal Health Code (OIE, 2016, Chapter 7.8)
- the Council for International Organizations of Medical Sciences and the International Council for Laboratory Animal Science (CIOMS-ICLAS, 2012)

Since the 2003 review, there have also been changes in the recognition of the causes of animal suffering and developments in the assessment of benefits. Research around animal suffering and well-being has been significantly expanded from a focus on procedures in the original HBA to encompass the impact of housing and animal care, as well as the effects of cumulative procedures on the life-time experience of animals.

The requirement to record actual levels of animal suffering since 2014 offers the potential to develop retrospective reviews of HBAs and make prospective assessments more accurate.

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In addition, a growing 'impact agenda' in science and increasingly critical questions around experimental design, reproducibility and rigour in science have resulted in more research on how the benefits from animal research may be enhanced.

There have additionally been significant moves towards public openness with respect to animal research and testing, alongside movements towards open science. Many academic and commercial establishments and other bodies, have signed up to the Concordat on Openness on Animal Research (Understanding Animal Research, 2014). ASRU is making more information about the scope and scale of regulation on the use of animals in research available to the public. In addition to annual reports on species and procedures, ASRU provides information on non-compliance issues and the actual severity of procedures being reported. There are also growing moves to make data derived from animal research more widely accessible through initiatives in open science, open data and data sharing. There are proposals by some non-governmental organisations that increasing openness could and should be matched by further democratic input into the weighing of these harms and benefits in HBA (Lyons, 2014).

This report from the ASC is thus part of an evolving process of developing and reviewing HBA (see also Brønstad et al., 2016; Laber et al., 2016). It builds on the clarification of ethical frameworks by the APC (2003), indicating how subsequent developments in scientific knowledge and practice, changing societal concerns and growing expectations of transparency in regulation may offer further opportunities to enhance the HBA.

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## 2.2. ETHICAL FRAMEWORKS

HBA in the UK operates as a set of interlocking social and ethical frameworks. It requires decision-making based on utilitarian principles, but also includes limits to experimentation on animals through recognition of some intrinsic animal rights. It is implemented in a regulatory context that considers the importance of a culture of care, requires diligence from everyone involved to operate effectively and engages a range of wider societal concerns.

It is implemented in a regulatory context that considers the importance of a culture of care, requires diligence from everyone involved to operate effectively and engages a range of wider societal concerns.

This relationship between different ethical frameworks can be considered a strength of HBA as it operates in the UK context. It may be one reason the framework has proved enduring and adaptable over time. However, it also gives rise to complexities, particularly around limits, as divergent ethical reasoning and societal concerns may be mobilised in assessing applications and making judgements about when licences should not be approved. These different elements are outlined as follows.

- **Utilitarian ethics:** HBA is a form of decision-making that uses moral reasoning based on utilitarianism; i.e. aiming for the **maximum balance of benefits over harms for all affected.** The application of HBA to animal research makes two further moral assumptions: that animals have moral status given their capacity for suffering and that potential harms and benefits can be legitimately 'traded-off', such that greater harms to animals can be justified by greater benefits from research.
- **Deontological ethics:** There are significant exceptions to any expectation that all harms and benefits can be traded off in the use of HBA in UK animal research and testing. Research that involves certain types of harms and benefits is now widely agreed to be **intrinsically wrong.** There are effective restrictions on the use of certain species and the generation of certain types of harm. For example, the use of great apes in the UK has been forbidden since 1998 and no great apes have been used in the UK since at least 1987 when the UK Animals (Scientific Procedures) Act 1986 (A(SP)A) was implemented. Causing animals to experience severe pain, suffering and distress, which is likely to be long-lasting

and cannot be ameliorated, is not normally permitted under the A(SP)A. In addition, there are certain kinds of benefits that are no longer considered acceptable, regardless of the levels of harm, such as policy bans on the use of animals in testing cosmetics products and ingredients and in tobacco and alcohol product development.

- **Ethics of care:** In the UK, HBA also operates within a regulatory framework that requires the application of the **3Rs** (the replacement, refinement and reduction of the use of animals in research), incorporating legal commitments to mitigate harm to animals, independent of benefits. Regulation operates through seeking to facilitate local cultures of care that enhances the welfare of research animals and supports staff who provide care for animals.
- **Virtue ethics:** Finally, the APC (2003) review notes that the quality of judgements relevant to HBA also depends largely on the **diligence** of those who make them and their understanding and awareness of the issues. Much thus rests on the integrity of those involved across HBA processes and how conscientiously they assume these responsibilities and make judgements in practice.

This combination of ethical frameworks can foster a robust and flexible process, but it also produces tensions and practical complexities, notably concerning the distribution of responsibilities within the different stages of HBA and the wider processes for identifying limits. These require regular review, both inside and outside of the HBA undertaken by ASRU, as part of processes for continuing improvement of HBA.

## 2.3. SOCIETAL CONCERNS

There is a further requirement to engage a wide range of perspectives in relation to the incorporation of societal or social concerns in HBA. "*Important animal welfare or ethical concerns, novel or contentious issues, or societal concerns*" are mentioned several times in the guidance on A(SP)A (Home Office, 2014) and are also listed as criteria for deciding whether retrospective assessments will be required (ibid, Section 5.17). Criteria for determining whether a licence application should be referred to the ASC includes "*projects of any kind raising novel or contentious issues, or giving rise to serious societal concerns*" (Section 13.5). This includes animals containing human material (ACHM) (Section 5.18.2), which "*may raise significant ethical issues and societal concerns*".

The social concerns associated with animal research are varied and may develop with respect to a range of issues such as animal welfare, the use of genetically modified organisms in food production, climate change and trade liberalisation (Tothova, 2009; Batie and Schweikhardt, 2010). Concerns also differ across society and species (Ormandy and Schuppli, 2014) and vary with geography. They can both reflect deeply held ethical positions and be expressed in ways that vary according to the kinds of animal use proposed and the methods used to elicit public views. Societal concerns around animals are important, but these complexities mean they can be a challenge to incorporate into HBA. Societal concerns are often left undefined in legislation and the processes for engaging them left open in the guidance or advisory note on HBA (Home Office, 2014; ASRU, 2015).

In his 2016 Paget Lecture, Mark Walport suggests that animal research presents challenges for both science and democracy. Its "*complexity means that animal research is a topic where the institutions of science meet the institutions of democracy fairly and squarely. It is an area where the arguments will continue and the opposing cases will need to be made and remade. We live in a plural democratic society, where different citizens hold different views based on differing moral precepts*." This complexity and plurality means that many questions around animal research are highly resistant to resolution and some arguments maybe never be resolved. Nevertheless, he concludes "*it is for democratic governments to decide on the acceptability and conditions under which research on animals is undertaken*" (Walport, 2016).

There is a significant policy literature on how to address these challenges across both science and democracy, from the identification of so-called "*wicked problems*" for policy (Rittel and Webber, 1973) to work on post-normal science (Funtowicz and Ravetz, 1993). The policy arenas considered and terminology used varies in this research, with discussion across planning, economics and healthcare. However, all agree that policy issues

characterised by complex systems, scientific uncertainty and plural values should not be treated in the same way as policy questions typified by low uncertainty and low conflict.

Instead, what is emphasised across these approaches is the importance of acknowledging complexity, engaging widely and working collaboratively to understand the implications of different solutions. For example, in its public policy perspective paper, the Australian government supports the Organisation for Economic Co-operation and Development (OECD) approach of creating shared understanding about such matters by promoting stakeholder and citizen engagement, including providing information and facilitating active engagement (Australian government, 2012).

Applying such approaches to understand and engage societal concerns around animal use may have the potential to improve the implementation of HBA and allow this to reflect shifts in prevailing public opinion and societal concerns.

Applying such approaches to understand and engage societal concerns around animal use may have the potential to improve the implementation of HBA and allow this to reflect shifts in prevailing public opinion and societal concerns.

## 2.4. ITERATIVE PROCESSES

HBA has long been a cornerstone for ethical evaluation of animal research in the UK, forming the basis of the prospective assessment framework for evaluation of project licence applications. The HBA advisory note (ASRU, 2015) is one of the most comprehensive explanations of the way HBA is implemented in a regulatory context. This document:

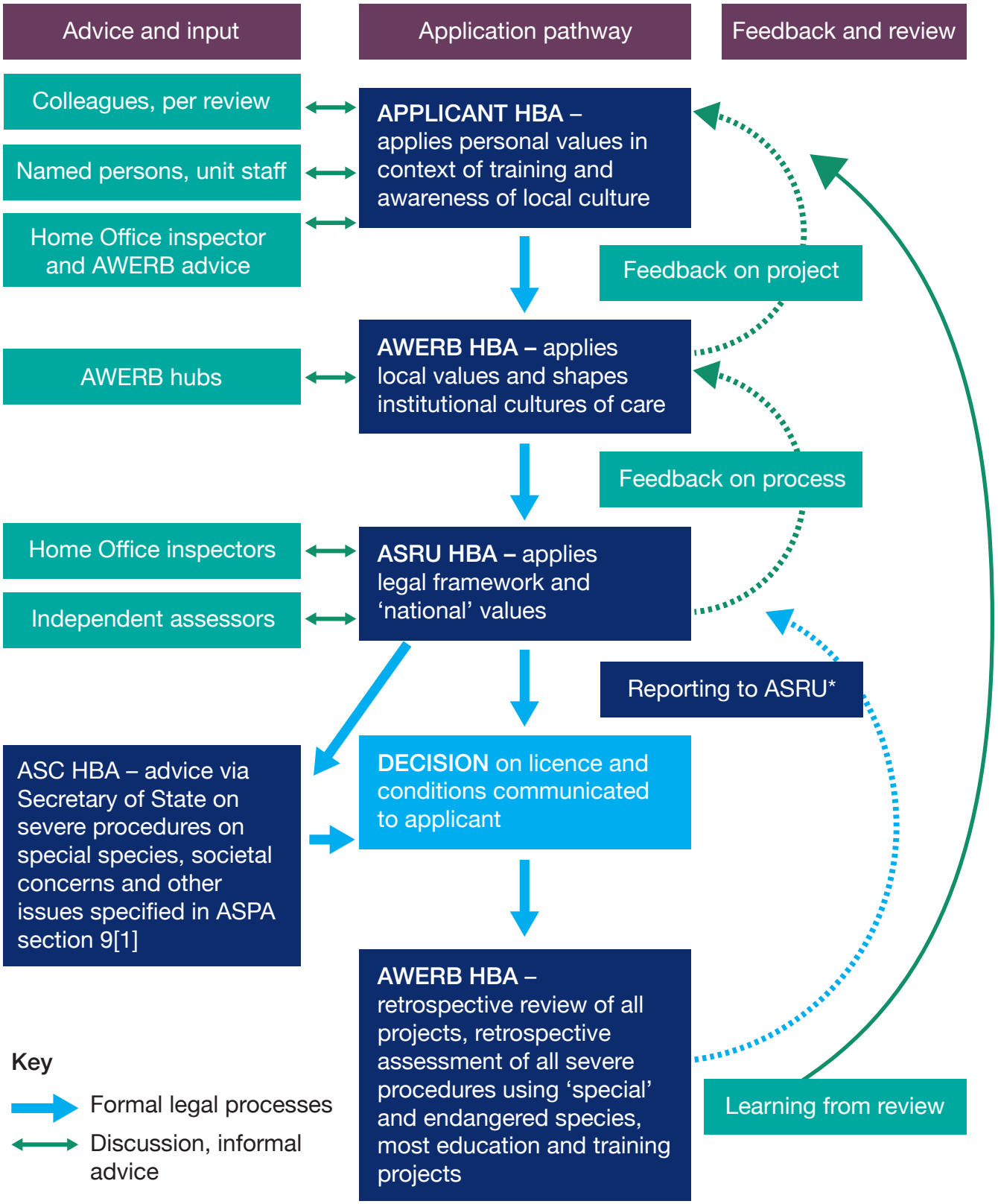
- divides the implementation of HBA into a sequence of assessments
- provides details of how Home Office inspectors identify and weight harms and benefits
- provides details how they weigh the benefits against the harms

These steps are brought together in a flowchart (see Appendix B) to illustrate ASRU's perspective on the sequence of events in the HBA. ASRU's flowchart is largely linear, representing its route for assessing project licence applications. It does not emphasise HBA processes in other contexts or before and after the ASRU HBA. Some of these additional elements are provided by ASRU itself. Ongoing reviews of HBA are offered through inspection, notifications required in standard conditions for project licences (Home Office, 2014) and assessment of project licence amendments. These all have the potential to contribute to the development of HBA as a continuous process.

However, it is important to recognise that the HBA conducted by ASRU is not the only one applied to a project. Harms and benefits should be carefully considered by the researchers, the local establishment AWERB and by referral to the ASC if the project has certain features (see Appendix C), in addition to the Home Office Inspectorate.

In this report, the ASC seeks to place the HBA advice note (ASRU, 2015) on the formal regulatory processes of HBA (ASRU, 2015) within the wider context of advice, informal discussions and feedback that inform it. The operation of and relations between different processes of HBAs was identified as a priority for further research in a recent exercise developing a collaborative agenda for humanities and social scientific research on laboratory animal science and welfare (Davies et al., 2016).

**Figure 1:** *Harm-benefit analysis, advice and feedback processes for project licence applications*




**When retrospective assessment is required in licence conditions*

Here the ASC proposes an alternative flowchart, which:

- illustrates the HBA processes that operate before and after licensing decisions
- identifies the range of personal local and national values that inform these judgements
- demonstrates the feedback processes which offer further points to review the HBA

Figure 1 (see p19) puts the applicant at the start of the HBA process. Researchers are responsible for the design and conduct of research using animals, in conjunction with associated named veterinary and animal care staff. They have specific legal obligations and are responsible for applying good practice principles around the 3Rs, research reporting and the development of appropriate mechanisms for realising the benefits from animal use and testing.

Many funding bodies require researchers to make the ethical case for the use of animals in grant proposals. Funders and the peer review process also have an important role in assessing the validity, necessity and justification of the proposed research. The most recent *Responsibility in the use of animals in bioscience research* (NC3Rs et al., 2017) provides guidance to researchers, AWERBs and others about the expectations of a wide range of bodies who fund the use of animals in research[1]. It refers to the responsibilities of those involved in funding for deciding *"whether the potential benefit justifies the possible adverse effects to the animals"* (ibid p11). These are generally structured around harms and benefits, but individuals and bodies may have different views on HBA, dependent on their perspectives and priorities and will not necessarily employ the same criteria.

The AWERB should be recognised as a lynchpin within the HBA process, as it brings together a wide variety of relevant perspectives and operates within the establishment, enabling it to take account of local expertise and knowledge that might impact on the HBA. Guidance for HBA is available for AWERBs (European Commission, 2014; Home Office, 2014, for example, p48, Chapter 10 and Appendix I, p125; Jennings and Smith, 2015; RSPCA/LASA, 2015).

Aside from HBA per se, AWERBs also have responsibility for other relevant tasks, such as:

- advising on animal welfare and the application of the 3Rs
- retrospective assessment, which follows the development and outcome of projects
- providing a forum for discussion and development of ethical advice to the establishment licence holder (Hawkins and Hobson-West, 2017)
- The development of a network of AWERB hubs has the potential to strengthen the role of AWERBs in relation to HBA, by providing opportunities for exchange

The ASC also plays a role in this process, in its review of those licence applications which are referred to it.

This ASC report seeks to contribute to developing a robust, inclusive and iterative HBA process by introducing new developments in the assessment of harms and benefits, exploring ways of engaging societal concerns and enhancing learning across these different processes.

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1 *This includes including The National Centre for the Replacement, Refinement and Reduction of Animals in Research (NC3Rs), Biotechnology and Biological Sciences Research Council (BBSRC), Department for Environment, Food & Rural Affairs (Defra), Engineering and Physical Sciences Research Council (EPSRC), Medical Research Council (MRC), Natural Environment Research Council (NERC), Wellcome Trust and other Association of Medical Research Charities (AMRC) charities.*

# CHAPTER 3

# ASSESSING AND REDUCING HARMS

# 3. Assessing and Reducing Harms

## 3.1. INTRODUCTION

Predicting harms and assessing the actual harms experienced by animals used for scientific purposes is a critical part of the process of HBA. In this chapter, the ASC addresses three key areas relating to harms:

- reviewing the processes of identifying and assessing harms
- examining ways of incorporating cumulative effects in the HBA
- identifying strategies for minimising and potentially eliminating severe suffering

All three of these areas are vitally important in ensuring that the potential harms to an animal are fully identified, minimised as far as possible and then evaluated, so that they can be weighed against the project licence applicant's assessment of potential benefits in the HBA process.

The ASC make a series of recommendations around the assessment and reduction of harms in the HBA in this chapter. Some of these may be considered foundational to the assessment of the harms involved in animal research and testing and are reflected in the HBA advice note (ASRU, 2015). The critical importance of considering harms from the animals' perspective means these responsibilities are restated here as principles for all processes of HBA. Others are medium- and longer-term recommendations for developing new scientific techniques and institutional opportunities for measuring, assessing and reducing the harms experienced by animals used for scientific purposes.

## 3.2. IDENTIFYING AND ASSESSING HARMS

Since the implementation of the UK Animals (Scientific Procedures) Act 1986 (A(SP)A) and the Animal Procedures Committee (APC) report 2003 there have been significant advances in animal welfare science.

A great deal more is now known about:

- the impacts of many procedures on animal welfare
- the amelioration of the impacts by refinement or clinical intervention
- the positive and negative effects of different housing, husbandry and care protocols

Additional techniques have been developed and employed to assess welfare impacts on animals, including:

- behavioural and other indicators of pain and suffering (European Commission, 2013; Sneddon et al., 2014)
- physiological markers of stress, for example, hormonal or other parameters (Lane, 2006) or distress such as stereotypies (Mason and Latham, 2004)
- tests of motivation to avoid potentially stressful situations (Dawkins, 1990; see also Dawkins, 2012)
- most recently, integrative markers of lifetime stress such as changes in telomere length (Bateson, 2016) or changes in specific brain areas such as the hippocampus (Mahar, 2014)

Such methods can be used to inform prospective and ongoing assessments of harm and assist with retrospective assessments of actual harms.

Animal welfare assessment is a growing area of development but there are also many knowledge gaps, such as the interpretation of some behavioural signs that may indicate the onset of either cumulative suffering or habituation. Further research to generate, evaluate and critically integrate data on acute and chronic harms to animals will contribute to strengthening evidence around harms for the HBA.

**Recommendation 1**

Data on animal welfare, including cumulative suffering, should be systematically collected in a format that allows comparison with other studies of a similar nature. Ideally, common reporting standards should be developed to facilitate such comparisons, for example, through publication, data repositories and the AWERB hubs.

There is also a place for the use of cautious anthropomorphism whereby, when evidence is lacking, it is reasonable to give animals the 'benefit of the doubt', by assuming that a procedure that causes pain, suffering, distress, or lasting harm to humans may also cause similar welfare problems in non-human animals, unless and until evidence to the contrary emerges.

### 3.2.1. IDENTIFYING HARMS EXPERIENCED BY ANIMALS

The ASRU HBA advice note (2015) explains that applicants for project licences are "*asked how they will minimise suffering whilst achieving their objectives*" and must define specific, practical strategies for implementation of the 3Rs (the replacement, refinement and reduction of the use of animals in research). Applicants are also required to define humane end-points that "*serve as absolute upper limits (or caps) to the nature and level of suffering that an animal will experience*".

The prior Animal Procedures Committee (APC) review suggests that assessments should consider what the harms actually mean for the animals in practice – for example, they should identify "*social and psychological effects such as fear, anxiety … confusion and boredom, as well as more overt physical harms*" (APC, 2003).

The HBA advice note (ASRU, 2015, pp14-16) also emphasises that the assessment and reduction of harms should cover all relevant impacts on the animals and should cover:

- **project-related harms**, ie those specific to the regulated procedures
- **contingent harms**, which include "*husbandry and care practices and transportation*" (Home Office, 2014, p128)
- **cumulative effects**, ie the net impact on animals of all the events and effects due to both procedures and husbandry, which requires further explanation of how such effects can be identified, assessed and taken into account within HBA.

See the **Glossary** for fuller definitions.

It is also generally accepted that minimising the suffering of individual animals should take precedence over minimising the number of animals used, ie in circumstances where reducing the number of animals would cause each individual to suffer more severely (for example, if more invasive procedures were required to obtain equivalent data).[2]

**Recommendation 2**

Realistic estimation of the harms likely to be experienced by individual animals undergoing licensed procedures is critical throughout the different processes of HBA. Harms arising from all sources (not just procedures, as it is not significant to animals where the harms come from) should be taken into account by researchers, reflected on by AWERBs as part of their responsibilities for the application of the 3Rs and considered in the HBA.

### 3.2.2. SPECIES AND EVIDENCE IN THE ASSESSMENT OF HARMS

Assessments of and efforts to avoid harms should always be based upon welfare data relating to the particular species involved. Within the text of the A(SP)A, there is an implied hierarchy between species at certain points, including when those applying for licences must ensure that the procedures; "*involve animals with the lowest capacity to experience pain, suffering, distress, or lasting harm*" (Part 3, 181[b]).

2 *The guidance on the operation of the Animals (Scientific Procedures) Act 1986 (A(SP)A) suggests that "on occasions it may be necessary to use a greater number of animals than the absolute minimum scientifically justifiable if each individual animal will suffer less as a consequence of the greater number being used" (Home Office, 2014, p13).*

In addition, the A(SP)A explicitly offers additional protection to some species (cats, dogs, Equidae and non-human primates).[3]

The ASC suggests that it cannot be assumed that the severity experienced by these species is greater than that experienced by any other species covered by the A(SP)A. Social science research on the implementation of this aspect of the A(SP)A (Hobson-West and Davies, 2017) suggests, instead, there is more 'societal sentience' around these animals. This includes recognition of close cultural relationships with companion species and awareness of the potential for greater societal harms in the use of these animals. Recent science also suggests humans may be more responsive to the suffering of certain species due to the recent co-evolutionary histories of domesticated species (Nagasawa et al., 2015).

The capacities of species, the affordances provided to animals by laboratory environments and the close cultural relationships which humans have with certain animals do suggest that some species may have needs that could be more easily met in laboratory settings, with harms more readily ameliorated and for which there are fewer societal concerns.

However, the ASC suggests that neither phylogenetic proximity to humans, close cultural relationships nor neurophysiological complexity necessarily mean that a given species will suffer more than any other species when undergoing a given procedure. Judgements about the relative severity of a given procedure for a given species can only be made where there is clear comparative scientific evidence that a procedure is more or less severe for one species than another.

**Recommendation 3**

Scientists should accept their responsibilities to research and obtain expert advice on factors affecting the welfare of their study species, recognising the impact on science as well as animal welfare. Wherever possible the HBA should be based on recent scientific evidence regarding harms. Where these data are not available, efforts should be made to obtain data through sharing across organisations, for example, via AWERB hubs and identifying priorities and funding for future research, for example, via the NC3RS.

### 3.2.3. PROSPECTIVE ASSESSMENT OF SEVERITY CATEGORIES

The term 'severity' represents *"the intensity of pain, suffering, distress or lasting harm experienced by an animal during a procedure"* (Home Office, 2014, p8). For the purposes of HBA, prospective assessments of the potential harms to animals are required to determine a **severity category** for each protocol within a project licence. The assessments are based on 'worst case scenarios', which each define an upper limit to the suffering that an animal may experience in a given protocol (ASRU, 2015, pp16, 18). There is a detailed definition of '**severity limits'** in the Glossary of this report.

Severity limits for regulated procedures are classified according to one of four categories:

- non-recovery
- mild
- moderate
- severe

Each category is fully defined under **severity categories** in the Glossary.

However, as the HBA advice note (ASRU, 2015, p14) points out, determining a severity limit is not sufficient to assess harms fully and *"information regarding the nature, incidence or duration of the harms or the percentage of animals affected also has to be taken into account"*, along with details of each protocol, which will help determine *"the different levels of severity likely to be experienced within that protocol"*.

3 *These protections are outlined in the guidance on the operation of the A(SP)A (Home Office 2014). Permissions to use these species are only given if the purpose of the work specified in the licence can be achieved only by their use; or where it is not practicable to obtain other suitable animals. Projects involving these species are subject to retrospective review and proposals for procedures causing severe suffering in these species is subject to further review by the ASC. Funders of research intending to use these species may also require additional review of research proposal by the NC3Rs.*

### 3.2.4. RETROSPECTIVE (ACTUAL) ASSESSMENT OF SEVERITY

Since 2014 actual severity assessments have also been required. These take place after the procedures are completed and reflect the actual harms caused to each individual animal in a given procedure, disregarding contingent harms. The evaluations are based on ongoing observations of each animal during day-to-day welfare assessments and record the highest level of suffering experienced by an individual animal during a procedure, taking account of any cumulative effects on suffering (ibid).

The categories are the same as for prospective classification, with the addition of 'sub-threshold', which is used when actual severity turns out to be lower than the threshold for regulation of animal procedures (for example, below the level of pain, suffering, distress, or lasting harm caused by a skilled insertion of a hypodermic needle). Severe retrospective assessments encompass a variety of situations. Sometimes the suffering is well known in accordance with the legislation. Other times, severe is used as a principle of precaution when animals are 'found dead' in unknown circumstances, as the level of suffering they have experienced is unclear and could well have been severe.

Actual severity should be carefully and accurately recorded wherever possible. Actual severity assessments should be discussed at AWERBs and are returned annually to the Home Office.

The recording of retrospective severity data presents a new opportunity for researchers, AWERBs and ASRU to refine the definition of severity categories for procedures, to develop strategies to reduce suffering within establishments and across procedures and to inform the overall HBA.

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**Recommendation 4**

Retrospective severity assessments should be used by researchers, AWERBs and ASRU to inform HBAs for future applications that employ the same or similar procedures. Information gleaned from these assessments should offer opportunities for establishment AWERBs to reflect on their own retrospective severity data and to highlight areas for refinement to reduce suffering, whether it be mild, moderate, or severe.

## 3.3. INTEGRATING CUMULATIVE EFFECTS

The ASRU advice note on the HBA process lists "*cumulative effects*" as a harm, which is defined as: "*The net impacts of all the events (procedurally and husbandry-based) and effects that affect adversely, positively and by way of amelioration, the welfare of an animal over its lifetime. They include likely habituation, potentiation and/or sensitisation and any temporal element in which recovery between events and memory of them and/or their consequences is likely to be affected*." (ibid)

This is broader than the definition of "*cumulative effect*" in the guidance to A(SP)A (Home Office, 2014). This was defined as "*the effect which occurs where, in a series of procedures, a second or subsequent procedure has a compound effect, which may be positive or negative, in terms of causing pain, suffering, distress or lasting harm*." The HBA advice note (ASRU, 2015) is correct to include not only cumulative effects due to procedures, but also the net impact of all life events – that is, the lifetime, or cumulative, experience of the animal.

This is a sound principle but as it acknowledges, experiences influence an animal's perceptions of subsequent events for better or worse. For example, while animals can habituate to procedures, they can also become sensitised and less able to tolerate them. Whether cumulative effects are experienced as a cumulative increase in the severity of harms, that is cumulative suffering or cumulative severity, depends on a range of factors.

These include:

- the species
- characteristics of the individual animal
- the procedures
- housing, husbandry and care
- whether animals can be (and are) trained to co-operate with procedures
- the empathy of handlers

The ASC suggests that the concept of cumulative effects is essential.

For ethical and animal welfare reasons, it is right to consider the animal's lifetime experience and it is widely recognised that each intervention applied to an animal should not be considered in isolation.

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**Recommendation 5**

Consideration should be given by researchers, establishments and the regulator to the harms experienced over the whole lifetime experience of the animal, recognising the risks of considering the animal's experiences in isolation and being aware of all potential sources of harm.

As indicated, this attention to cumulative effects is present in the HBA advice note (ibid), but the ASC restates this again as an important principle to underpin all processes of HBA.

However, the ASC also notes that it is difficult to predict and recognise cumulative effects objectively and reliably. This is especially the case where these are negative, with implications for what may be experienced as cumulative severity or suffering. This can result in inappropriate assumptions about an animal's ability to habituate, or become sensitised to, scientific and other procedures. Thinking of cumulative severity as harms 'stacking up' until a severity threshold is reached is over-simplistic and the likely scenario in practice is much more complex. The ASC thus follows this recommendation with further discussion of research on and recommendations for predicting, measuring and recording cumulative severity.

These address the key question: How can cumulative severity be best understood, predicted and recognised and then factored into the HBA? For example, when might repeated or chronic mild severity interventions cross the threshold to become moderate? Might non-A(SP)A studies involving repeated or chronic sub-threshold harms result in a cumulative level of severity that is above the threshold, without this being recognised or alleviated? Or is there a risk that some procedures may go beyond their severity limits, including beyond severe, due to lack of recognition of cumulative severity? Answers to questions like these are essential if HBA is to be properly and rigorously applied.

### 3.3.1. PREDICTING AN ANIMAL'S CUMULATIVE EXPERIENCES

If the concept of cumulative effects is to be robustly applied, understanding and assessing the net impact of life as a research animal will require thoughtful and informed consideration of the kinds of 'life events' and interventions that may affect the animal (either positively or negatively), their short- and long-term impacts and how these will affect the animal's perceptions of subsequent events and interventions.

This cannot be achieved without understanding what an 'adverse effect' means from an animal's point of view, yet consideration of the animal's actual experiences is not universal. For example, in the experience of ASC working group members, researchers often mistakenly think of unexpected adverse effects only, or regard adverse effects as what they wish to do to an animal, for example, a 'needle stick'. To a laboratory mouse, the needle stick is but one event in a sequence that includes stressful capture, particularly if caught by the tail (Hurst and West, 2010), restraint, the pain of the needle stick, possible painful tissue distension, potential after-effects of the substance injected or its vehicle and a recovery period after return to the cage. If this happens multiple times, the animal will learn what is about to happen and may even predict this if injections are regular, which could add further stress and anxiety. This is far from trivial for the animal and represents much more than 'just a needle stick'.

Thinking about harms in this way will help to answer the essential questions:

- will the animal habituate or become sensitised
- if the animal becomes sensitised, at what point will severity limits be approached
- might the harm-benefit balance be altered so that the procedure is no longer justifiable?

In addition to direct harms caused by procedures and their after-effects, contingent suffering must also be considered. Russell and Burch (1959) first described this as the incidental harms caused by suboptimal animal husbandry or concurrent pathologies not related to study objectives. The HBA advice note (ASRU, 2015) cites contingent harms, giving examples of:

- being housed in a cage (as opposed to ranging freely in the wild)
- inability to express a wide range of natural behaviours
- handling or transport stress
- olfactory exposure to a large number of conspecifics (in the case of laboratory rodents housed in conventional caging)

These and other factors will also affect the animal's experience of experimental and other interventions. There are different frameworks that can be used to assist in the identification of contingent suffering and their impacts on quality of life. These have also been revised following the APC (2003) review, with implications for the assessment of cumulative effects and severity.

The HBA advice note cites the 'Five Freedoms', developed by the Farm Animal Welfare Council (FAWC) from the Brambell Report (1965), suggesting that any compromises of these could also be used to help to identify contingent suffering. These were originally listed as:

- Freedom from hunger or thirst
- Freedom from discomfort
- Freedom from pain, injury, or disease
- Freedom to express normal behaviour
- Freedom from fear and distress

The Five Freedoms concept has been reviewed, principally because the original formulation related to avoiding negatives rather than promoting positives. FAWC (2009) more recently defined welfare in terms of the promotion of positives and suggested that one should consider positive feelings (what an animal likes) and the resources that they are motivated to obtain (what an animal wants).

FAWC and others have subsequently defined categories of welfare that relate to an animal's quality of life and total lifetime experience as:

- a 'good life'
- a 'life worth living'
- a 'life worth avoiding'
- a 'life not worth living'

A more recent development in thinking is the 'Five Domains' model of welfare (Mellor, 2016), which comprises:

- nutrition/hydration
- environment
- health/functional status
- behaviour
- mental state

A paper by Littlewood and Mellor (2016) describes how the 'Five Domains' approach can be used to grade negative and positive states in a fictitious scenario following a working dog before, during and after an injury, through to rehoming as a companion animal. Although this is not an example in a research setting, it is useful in demonstrating how animal welfare science and a quality of life assessment model can be used to predict how an animal may be feeling and make judgements over time.

**Recommendation 6**

Consideration of cumulative effects should be used by establishments to provide a focus for increasing the animal's positive experiences. Any assumptions about an animal's ability to habituate to procedures, or conversely to become sensitised, should be critically scrutinised, by researchers, AWERBs and regulator. Suggestions that an animal habituates should be verified with empirical, objective evidence.

### 3.3.2. DETECTING AND ASSESSING CUMULATIVE SUFFERING

The following sections focus on assessing cumulative suffering, on the basis that in the context of animal experimentation it is usual to prioritise detecting and ameliorating negative cumulative effects, as opposed to detecting positive effects. However, cumulative suffering will continue to be an abstract concept unless more reliable ways are developed to detect and assess it. For example, indicators are needed to detect:

- when an animal has become sensitised to repeated procedures
- when an animal is no longer coping with life in the laboratory and all that this entails

For the first, this could be indicated by exaggerated physiological and/or behavioural responses to a 'routine' procedure, whereas the second instance will involve chronic stress. The latter may be evidenced by stereotypic behaviour and/or apparent depressive symptoms, but more sensitive early indicators should prevent the animal's welfare state falling to these levels.

Ideally, an effective, comprehensive and properly implemented welfare assessment protocol would be able to detect when acute responses to procedures are heightened. Further research would be required to evaluate whether it is being, or could be, achieved. At the time of writing (August 2017), the ASC HBA subgroup was not aware of any objective indicators that have been developed and validated for chronic stress.

An attempt was made to assess the potential for cumulative severity in non-human primates used in neuroscience research by the APC primate subcommittee. This found 'little evidence' for adverse cumulative severity. However, the 'Pickard Report' relied to a large extent on qualitative data (in the form of the views from self-selected practitioners) and did not include objective indicators of animal welfare apart from body weight and 'willingness' to perform behavioural tests (APC Primate Subcommittee Working Group, 2013).

The ASC raised the lack of objective indicators in a response to the APC primate subcommittee's report (ASC, 2014), further pointing out that:

- there is debate as to whether 'willingness' to perform tests can be used as a welfare indicator
- the practitioners who participated were a self-selecting sample
- there is a need for further work based on larger, more meaningful datasets derived from systematic sampling

Although the ASC is not aware of current systematic studies of cumulative severity using data from significant numbers of animals (of any species), some novel approaches to defining and evaluating indicators are in development. It is hoped that these will be able to indicate the long-term experience of an animal and be useful 'measures' of cumulative severity.

Some novel approaches to defining and evaluating indicators are in development. It is hoped that these will be able to indicate the long-term experience of an animal and be useful 'measures' of cumulative severity.

One example is telomere attrition, in which telomeres (repeated sequences of DNA at the ends of each chromosome, which have a protective function and naturally shorten with age) become significantly reduced in length because of chronic stress. This can be evaluated by analysing blood or cheek cell samples. Studies are ongoing in a number of species including humans (Bateson 2016).

Another potential measure is the volume of grey matter in the hippocampus, which has been evaluated using magnetic resonance imaging (MRI) in the rat (Lee et al., 2009), extensively in humans and, in an ongoing project, the macaque.[4]

4 See: https://nc3rs.org.uk/assessing-cumulative-severity-macaques-used-neuroscience-research (last accessed 8/9/2017)

Both telomere attrition and hippocampal volume loss appear to be reversible. This could make them especially useful tools for understanding harms to animals and assessing potential refinements, if correlations with cumulative severity levels are demonstrated and evaluated.

Both approaches can also be measured repeatedly during the animal's lifetime, allowing for longitudinal assessments. The equipment and analysis required would preclude widespread and routine use of these techniques and there may be harms imposed by multiple bouts of anaesthesia. However, they may be helpful for understanding the welfare impact of chronic protocols, or those involving repeated technical acts, with the aim of improving the accuracy of severity classifications, evaluating refinements and defining more humane end-points.

This is an area that requires more research and there is a need for large, meaningful datasets and systematic sampling of procedures, plus quantitative data on a range of parameters obtained via detailed, longitudinal studies.

**Recommendation 7**

Funders, including the NC3Rs, should consider further funding research into behavioural and physiological indicators of cumulative severity and into assessing the affective states of animals in research. Researchers should explore if this can be done by obtaining valid data from animals already undergoing regulated procedures, to avoid causing additional harms.

### 3.3.3. RECORDING AND REVIEWING INDICATORS OF CUMULATIVE SUFFERING

In order to be alleviated and considered in HBA, cumulative suffering has to be effectively monitored and reviewed. With respect to chronic, negative cumulative effects, some animals have adaptive capacities that allow them to withstand the negative effects of certain conditions, whereas others undergo sensitisation such that adverse effects may be potentiated.

However, for all animals there will be a 'tipping point' when their welfare will become unacceptably compromised and an ideal recording and reviewing system would help to predict, or at least rapidly detect, when this point occurs.

Concurrent with the development of research on behavioural and other signs that may indicate the onset of either cumulative suffering or habituation, the ASC suggests that recording techniques are used during to both monitor animals and carry out further research on cumulative severity.

**Recommendation 8**

AWERBs should be encouraged to engage with new research tools for recognising and recording cumulative severity. These could be used to assist and develop the HBA by advising the establishment licence holder whether to support project proposals, following the development and outcome (retrospective review) of projects and providing a forum for discussion and development of ethical advice, including via AWERB hubs.

The following example is based on work by HBA subgroup member, Professor Wolfensohn (Honess and Wolfensohn, 2010; Wolfensohn et al., 2015).

## The animal welfare assessment grid

One example of a recording system that takes into consideration the impact of direct suffering (due to scientific procedures) and contingent suffering is the animal welfare assessment grid (AWAG).

This has been developed in a collaboration between Public Health England (PHE) and Surrey University Veterinary School. Technical and download information for the current AWAG software system is available at their **website (https://github.com/PublicHealthEngland/animal-welfare-assessment-grid/wiki).** There is further background and some examples of the grid being used in research available via the NC3Rs **website (https://crackit.org.uk/improving-animal-welfare-using-animal-welfare-assessment-grid-awag).**

This tool can be used to evaluate and monitor the animal's clinical condition and behavioural deviations, in the context of scientific procedures and the animal's living environment. It provides graphic illustrations of an animal's likely quality of life, at a single point and over time.

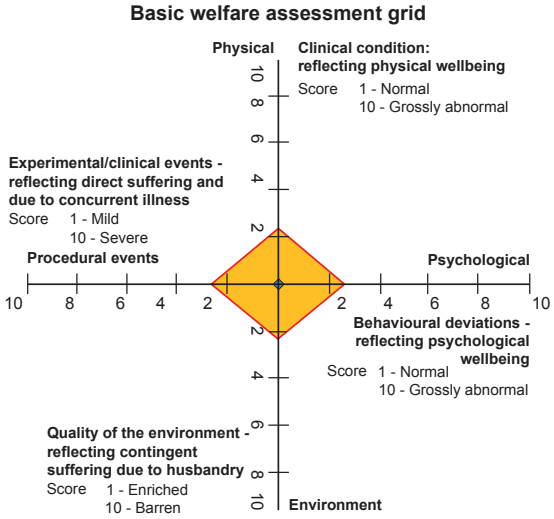


Figure 2: An animal welfare assessment grid at a single point in time (Source: Dennis et al., 2015)

The size and shape of the central box of the chart will vary according to the severity of each of the four factors:

- experimental/clinical events, reflecting suffering
- clinical condition, reflecting physical well-being
- behavioural deviations, reflecting psychological well-being
- quality of the environment, reflecting contingent suffering due to husbandry

This approach provides an immediate and straightforward way of visualising the extent of the harms across all four domains, to highlight the key factors that are having the most detrimental effect. This enables refinement to be closely targeted and improvements in welfare and reductions in suffering to be maximised.

Comparing consecutive AWAG assessments is particularly helpful in assessing cumulative suffering, as it shows the peaks and troughs of the harms caused to the animals over time.

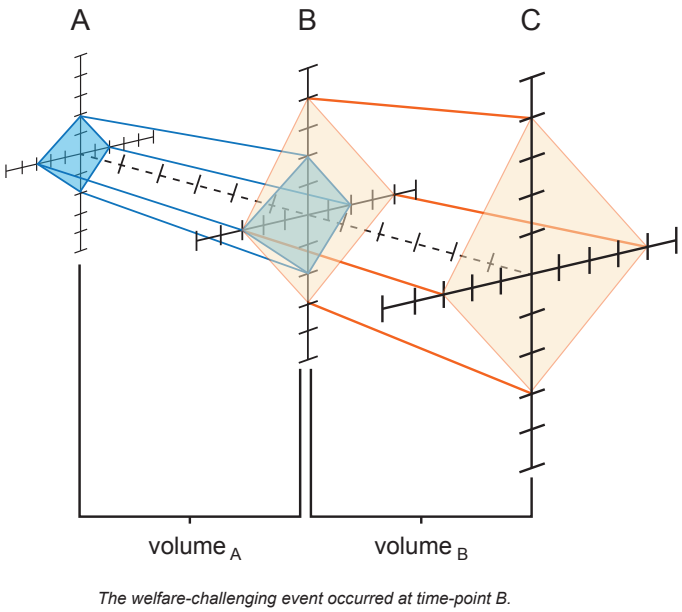


Figure 3: Illustration showing changes in the animal welfare assessment grid resulting from a welfare-challenging event *(Sources: Honess and Wolfensohn, 2010)*

A system like the AWAG could be used for project planning and both interim and retrospective reviews of an animal's welfare status (Honess and Wolfensohn, 2010; Wolfensohn et al., 2015). It also offers the opportunity to consider ways of reducing cumulative severity, for example, in assessing whether leaving a longer time between procedures is an advantage for the animal by allowing more time for adaptation and habituation, or whether it adds to the overall severity, for example, by increasing the time the animal must spend in a less than ideal environment.

## 3.3.4. EVALUATION AND NEXT STEPS

It is an essential acknowledgement of the facts that repeated scientific procedures conducted on an animal cannot be considered in isolation. An animal's other, non-procedural (ie contingent) life experiences can have a significant influence on the intensity and nature of suffering due to procedures. The temporal impacts of both chronic procedures and life in the laboratory in general, are also fundamental to the concept of cumulative severity.

Understanding cumulative severity requires consideration of the animal's lifetime experience, including sourcing, husbandry and care issues, study design and methodology, interventions to minimise adverse effects, end-points and humane killing.

Understanding cumulative severity requires consideration of the animal's lifetime experience, including sourcing, husbandry and care issues, study design and methodology, interventions to minimise adverse effects, end-points and humane killing.

However, validated indicators of chronic stress, such that an animal is beginning to lose the ability to cope with life in the laboratory, are lacking. Systems that will enable longitudinal recording of welfare indicators and inputs (for example, husbandry refinements), such as the AWAG, are being successfully developed. These may help to identify both chronic stress per se and sensitisation, indicated by increased responses to 'routine' procedures.

Until more work has been done to develop and validate objective indicators of long-term cumulative suffering and to ensure that sensitisation is being effectively detected, factoring cumulative suffering into HBA will continue to be subjective and assumptions will be made that may or may not be appropriate. Our recommendations focus on the opportunities for research, exchange and review to develop frameworks to further the knowledge and assessment of cumulative effects.

## 3.4. MINIMISING SEVERE SUFFERING

Any type and degree of suffering caused to an animal should be taken seriously and minimised as far as possible. However, as would be expected, there is particular concern about procedures that cause severe suffering, in which animals are likely to experience "*severe pain, suffering or distress, or long-lasting moderate pain, suffering or distress, as well as procedures that are likely to cause severe impairment*" (Home Office, 2014).

In relation to upper limits of severity, procedures that may cause an animal "*severe pain, suffering or distress that is likely to be long-lasting and cannot be ameliorated*" are prohibited by UK project licence Standard Condition 7 (Home Office, 2014). This is also reflected in Article 15(2) of Directive 2010/63/EU, but can be subject to the use of the so-called 'safeguard' clause in Article 55, whereby if there are exceptional scientifically justifiable reasons a provisional measure can be adopted to allow the procedure.

However, in this case the European Commission and other EU Member States must immediately be informed and within 30 days the Commission will either authorise or revoke the provisional measure.

In this section, the ASC discusses strategies for reducing severe suffering, with the goal of eliminating it altogether. First it examines the levels of severe suffering actually experienced by laboratory animals.

### 3.4.1. RETROSPECTIVE DATA ON SEVERE SUFFERING

Since 2014, the annual publication of data on actual (retrospective) severity of procedures, as reported by licence holders, has provided information on the extent of severe procedures, including by species and purpose of the procedure. Table 1 below shows total retrospective, ie actual, severity assessments for 2014, 2015 and 2016. The table shows that, overall, 114,000 animals experienced severe suffering in 2016 (6% of all animals used).

There are some questions around the comparability of these data. However, it appears to indicate that actual numbers of experimental procedures recorded as causing severe suffering went down between 2014 and 2016. Conversely, the number of procedures retrospectively identified as causing moderate suffering has increased. Moderate suffering is a wide category band, which is explored in Section 3.4.4.

Table 1: Actual severity of suffering recorded in experimental procedures on animals, 2014-2016

| | 2014 data | | 2015 data | | 2016 data | |
|---|---|---|---|---|---|---|
| Actual severity category | Number of procedures | % | Number of procedures | % | Number of procedures | % |
| Sub-threshold | 180,121 | 9 | 268,455 | 13 | 235,000 | 12 |
| Non-recovery | 132,770 | 7 | 123,079 | 6 | 154,000 | 8 |
| Mild | 975,513 | 51 | 1,063,585 | 51 | 938,000 | 46 |
| Moderate | 483,262 | 25 | 501,620 | 24 | 581,000 | 29 |
| Severe | 149,917 | 8 | 123,231 | 6 | 114,000 | 6 |
| Total | 1,925,583 | 100 | 2,079,970 | 100 | 2,022,000 | 100 |

Source: Home Office (2015b, 2016, 2017)

Table 1 excludes data for the creation and breeding of genetically altered animals (1.91 million in 2016, of which 67% were assessed as sub-threshold, 29% mild, 3% moderate and 2% severe).

Table 2 below shows the number of procedures recorded as causing severe suffering, broken down by species. The largest group experiencing severe suffering were mice: with a total of 101,494 procedures (8% of all those on mice) retrospectively classified as having caused severe suffering.

Table 2: Actual severe suffering recorded in experimental procedures, by species, 2015

| Species | Number of procedures retrospectively classified as severe procedures | Total number of procedures | % of severe procedures |
|---|---|---|---|
| Mouse | 101,494 | 1,264,501 | 8.0 |
| Rat | 3,358 | 257,665 | 1.3 |
| Guinea pig | 2,004 | 21,831 | 9.1 |
| Other rodent | 105 | 3541 | 2.9 |
| Rabbit | 180 | 14,155 | 1.2 |
| Dog | 3 | 4,643 | 0.06 |
| Ferret | 1 | 626 | 0.16 |
| Pig | 14 | 2,895 | 0.4 |
| Other ungulate | 12 | 40,387 | 0.03 |
| Other mammal | 12 | 871 | 1.4 |
| Primate | 28 | 3,612 | 0.8 |
| Bird | 1,466 | 140,724 | 1.0 |
| Amphibian | 1,863 | 10,333 | 1.8 |
| Fish | 12,633 | 293,558 | 4.3% |
| **TOTAL** | **123,231** | **2,079,970** | **5.9%** |

Source: Home Office (2016)[5]

The number of animals experiencing severe suffering also varied according to the procedure involved. As shown in Table 3, regulatory testing was the most common cause of severe suffering, both numerically and proportionally (see section 4.3.5).

5 *No cats or horses experienced severe suffering; there were no procedures on reptiles or cephalopods in 2015.*

Table 3: Actual severe suffering recorded in experimental procedures, by purpose, 2015

| Purpose of procedure | Basic Research | Translation/ Applied | Protection of natural environment | Preservation of species | Higher education or training | Forensic enquiries | Regulatory | Total |
|---|---|---|---|---|---|---|---|---|
| Number of animals experiencing severe suffering | 23,202 | 11,647 | 344 | 0 | 0 | 0 | 88,038 | 123,231 |
| Total number of procedures | 1,102,096 | 401,811 | 17,741 | 757 | 1,845 | 0 | 555,720 | 2,079,970 |
| Percentage of total that were severe | 2.1 | 2.9 | 1.9 | 0.0 | 0.0 | 0.0 | 15.8 | 5.9 |

Source: Home Office (2016)

Given the extent of severe suffering, there is clearly a need to consider additional levels of scrutiny for the most severe procedures and investigate ways of refining severe suffering, with the aim of eliminating it altogether.

### 3.4.2. SCRUTINY OF THE USE OF SEVERE PROCEDURES

When considering the use of severe procedures, the first step should be to refine the procedures as fully as possible to reduce their severity.

When considering the use of severe procedures, the first step should be to refine the procedures as fully as possible to reduce their severity.

This should include consideration of whether, after application of the 3Rs, the level of harm caused to the animals will be so high that it cannot be justified, whatever the benefits might be.

In some instances, applications to use severe procedures are referred to the ASC, alongside other potentially contentious projects. Specific circumstances in which projects might or must be reviewed by the ASC are listed below.

**Published criteria for referral to the ASC**

Severe (as well as complex and/or contentious) projects and procedures are scrutinised within a referral framework. This may involve inspectors with relevant specialist training, inspector review and case discussion panels and independent assessors. In addition, the Secretary of State may refer project licence applications to the ASC for advice, especially applications involving use of:

- wild-caught non-human primates
- cats, dogs, Equidae or non-human primates in severe procedures
- endangered species
- admixed embryos (under certain circumstances)

- any of the 'safeguard clauses' in Directive 2010/63/EU with respect to the purpose of primate use, proposals for the use of a great ape, or proposals to cause long-lasting pain, suffering, or distress that cannot be ameliorated[6]
- projects with major animal welfare or ethical implications
- raising novel or contentious issues, or giving rise to serious societal concerns.

Whether or not applications to carry out severe procedures are referred to the ASC, steps can be taken to enhance the assessment and amelioration of harms.

- **Pre-approval scrutiny** of procedures can be used to determine the conditions under which the licence might (or not) be approved. For example, a licence may be granted for a short initial period to allow for pilot studies, with clearly defined humane end-points, to assess the actual effects of the procedures and where possible mitigate them. Similarly, where novel studies are concerned, there should be an early review of potential issues of concern to identify opportunities for refinement. Ideally, the findings of any such studies would contribute to the research dataset, to avoid using any additional animals.
- **Post-approval scrutiny** by the researchers and the institutional AWERB should clarify the severity actually experienced by the animals, the effectiveness of attempts to mitigate severity and the balance of realised benefits versus harms. This should demonstrate clear progress in reducing harms, based on presentation and discussion of relevant data and the dissemination of knowledge about actual severity in such circumstances. This stage review should enable further refinement of the techniques and prevent the use of severe procedures wherever possible.

Where severe suffering is unavoidable, there should be an exceptionally high level of benefit and likelihood of achievement.

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Whenever procedures are carried out, their classification must be kept under review, so that issues affecting severity arising during a procedure can be re-evaluated and if necessary reclassified – for example, with experience of the work, a moderate procedure may be reclassified as severe (or vice versa).

Throughout the above scrutiny processes, the option 'just to say no' must remain on the table and be employed whenever there is sufficient concern about the severity of harms and/or the balance of benefits over harms.

The ASC identifies two recommendations to support the challenge provided by projects involving severe procedures prior to submission to ASRU by the researcher and AWERB: and to draw attention to the opportunities for scrutiny post-approval, including in subsequent reporting and publication.

**Recommendation 9**

Researchers and AWERBs involved in developing and/or reviewing project licence applications prior to submission should always provide a robust, constructive challenge to the scientific need and the ethical justification for using a severe model or procedure . Support for this might be provided through additional components in existing training for AWERB members and exchange via AWERB hubs.

**Recommendation 10**

Projects that may cause severe suffering should be given intensive scrutiny at every stage of their design, in the ethical review process and in subsequent reporting and publishing. This should not only include scrutiny by the researchers involved, the AWERB, the Home Office inspector and in some cases the ASC – but also, where relevant, funding bodies and journal editors who publish research involving animals.

6 *If any such exemptions were supported, it would require legislative amendment in the Houses of Parliament.*

### 3.4.3. STRATEGIES FOR MINIMISING AND ELIMINATING SEVERE SUFFERING

This section examines ways of mitigating, minimising and avoiding procedures classified as severe under the definition above and in the Glossary. Finding new ways of working to avoid severe suffering is a challenge in which every establishment should participate, sharing strategies, obstacles and successes with each other wherever possible.

The Research Animals Department of the Royal Society for the Prevention of Cruelty to Animals (RSPCA) is working towards the ending of severe suffering and has developed a 'Road Map' strategy to help establishments to achieve that goal. The Road Map sets out a systematic approach, available as a paper and poster (Lilley et al., 2014a; 2014b). Key elements of this are summarised below.

**Summary of key points in the Royal Society for the Prevention of Cruelty to Animals' Road Map towards ending severe suffering**

The central premise of the Road Map is that *"every establishment should ensure there is a process to achieve the following for severe 'models' or procedures"*, by acting on the following five key elements.

**1. Culture.** Establish and maintain a progressive, open-minded and caring research culture. An institutional 'culture of care' is a prerequisite for effective implementation of the Road Map.

**2. Analysis.** Establish to what extent severe suffering occurs. Perform an in-house 'severity audit' of all protocols, procedures and 'models'. Establish where there is potential for severe suffering and what actual severity is experienced by individual animals.

**3. Evaluation.** Look at why severe suffering occurs and what current approaches are used to avoid it by considering the following questions.

- Why is the procedure used and what factors contribute to it being severe?
- Is severe suffering really necessary to achieve the scientific objective?
- What proportion of animals in each protocol, procedure or 'model' experienced severe suffering?
- What refinements are already in place, how effective are these and is there potential for further application of the 3Rs?

**4. Define obstacles.** Establish what the impact of ending severe suffering would be. What are the scientific obstacles to ending severe suffering? Set these out clearly and assess the genuine impact of stopping severe protocols, procedures or 'models'.

**5. Overcome obstacles.** Set out a plan to end severe suffering.

- Take an alternative approach. For example: Use a non-severe model. Re-frame the research question to avoid a severe model. Use a mechanism-based approach rather than a disease-model approach.
- Apply refinement. For example: Refine every element of the lifetime experience of the animal. Establish, validate and implement humane endpoints.

The RSPCA approach offers opportunities for AWERBs in relation to this goal:

- to consider the idea of ending severe suffering caused to animals within the establishment (and beyond)
- to think creatively and share strategies, obstacles and successes with each other wherever possible
- to dedicate time and resources towards achieving that goal

**Recommendation 11**

Finding new ways of working to avoid and eliminate severe suffering is a challenge in which every establishment and its AWERB should participate. As projects progress and at their conclusion, feedback on successful refinements and ongoing concerns should be provided to all those within and across establishments (for example, via AWERBs and AWERB hubs) who have been involved in addressing severe suffering. The RSPCA's Road Map offers a systematic approach and opportunity to address questions in the broader research community, such as whether severe procedures currently in use are necessary and whether and by how much a 'ban' on severe suffering would impact on research and testing.

### 3.4.4. WIDER CONSIDERATIONS REGARDING SEVERITY THRESHOLDS

It is important to acknowledge that harm categorisations, while useful in helping to ensure a consistent approach to regulation and compliance, are blunt instruments when dealing with the suffering of individual sentient animals. In EU legislation, the examples of severe procedures are a narrow subset that lies at the highest end of the severity classification. This means that:

- the moderate classification includes a wide range of procedures, some of which many may regard as severe
- similarly, the mild category will also include a spectrum of procedures that range from just within the threshold for inclusion in the regulatory framework up to those that fall immediately below the threshold for the moderate category

For that reason, those undertaking HBA need always to recognise the likely and/or actual experience of the animals involved and remember that each category of severity (mild, moderate and severe) includes a variety of procedures that differ (sometimes widely) in the level of their adverse effects.

The length of time that an animal is subjected to mild and/or moderate levels of suffering is also a critical point and can cause severity to cross the threshold from mild to moderate or from moderate to severe. Duration of suffering is a key element in consideration of cumulative suffering, which has been discussed in section 3.3 above.

The European Commission's report (2012) on severity classification emphasises that determining severity classifications requires a team approach, which has several knock-on benefits, including:

- increased opportunities to apply the 3Rs and improve animal welfare and, as a result, improve scientific data
- enhanced transparency and communication between those using, caring for and monitoring animals
- increased understanding of how to assess severity, leading to greater consistency and provision of evidence-based information to help inform future severity categorisation

The above report also provides a sample 'scoring scheme' to assist with consistency in severity classification and inform humane end-points.

It is also important to remember that each individual animal's suffering is their own and that the number of other animals experiencing suffering makes no impact on the experience of the individual. Even if just one animal suffers at any level, efforts should always be made to avoid and mitigate that suffering.

Moreover, for all procedures, regardless of their severity, the benefits that accrue from the work should be as high as possible. However, those procedures that lie at the upper end of the severity classification must be subject to intensive scrutiny, taking into account a wide range of views and a balanced, thoughtful approach to HBA.

**Recommendation 12**

It is important that researchers, establishments, AWERBs and inspectors all understand that each category of severity includes a range of adverse effects and that the moderate category includes a particularly wide range of procedures, some of which other people might regard as severe. Severity categories alone are blunt instruments for HBA and at all times the likely and actual experiences of the animals should be used as the measure of harms in the ethical weighing process. There is a legal requirement for the project licence holder to notify the Secretary of State if the severity limits or other controls are, or are likely to be, breached. When approaching the upper limit of any severity classification, there should be particular scrutiny by researchers and establishments of the duration of suffering , as long-lasting moderate suffering can cross from moderate into severe and similarly, long-lasting mild suffering can become moderate.

## 3.5. CONCLUSION

This section has suggested the HBA cannot be properly conducted unless it takes account of all the harmful effects of scientific procedures, including contingent as well as direct project-related harms and the cumulative effects of all the different impacts on animals over time. This has direct implications for methods of assessing animal suffering, implementing refinements, factoring in lifetime experiences and justifying procedures and research projects.

There are opportunities to learn from new assessment methods and emerging data on animal welfare and to refine the prospective assessment of harms from the recording of actual severity. Licence applicants and AWERBs play a key role in identifying, assessing and minimising harms and should seek opportunities to engage new tools and learn from other processes of HBA.

There should be a specific focus on steps that can be taken to minimise severe suffering, with an ultimate goal of eliminating severe suffering altogether. AWERBs should take the idea of ending severe suffering caused to any animal within the establishment (and beyond) seriously, think creatively and dedicate time and resources towards achieving that goal.

One key intended outcome of this report is to help and encourage those who use and evaluate the use of animals in research to do things differently and better when identifying an animal's suffering and other experiences (whether positive, neutral, or negative). Some recent changes to practice have come about from modifications to regulation, revised guidelines and public pressure. However, it is also important that mechanisms are available to initiate and support change emerging from voluntary "on the ground" improvement in relation to animal use among the scientific community

**Recommendation 13**

Applicants and AWERBs play a key role in driving and implementing change and should seek opportunities to improve. ASRU already provides feedback to the licence applicant following decisions on project licences. There should additionally be feedback to and when necessary review by, AWERBs when an inspector, or the ASC, identifies ethical or welfare concerns that the AWERB and the applicant have not identified or sought to address.

# CHAPTER 4

# ASSESSING AND WEIGHING BENEFITS

# 4. Assessing and Weighing Benefits

## 4.1. INTRODUCTION

Under the UK Animals (Scientific Procedures) Act 1986 (A(SP)A) , project licences may only be granted for specified, permissible purposes listed in Section 5 of the Act (see Glossary) and only when:

- there is no suitable alternative that would avoid the use of animals
- the number of animals to be used is optimised and suffering is minimised as far as possible
- the likely harms caused to the animals have been 'weighed' against the potential and likely benefits

While research on laboratory animal welfare has made considerable contributions to the assessment and minimisation of harms, direct research on the evaluation and enhancement of benefits from animal research has been more limited (though see Pound et al., 2004).

Nevertheless, new ways of collecting and evaluating data on research benefits are becoming available. There is a growing international translational agenda within the life sciences, which seeks to facilitate the transfer of laboratory discoveries about disease mechanisms to clinical applications (Hobin et al., 2012). There are increasing demands from national funders and government for accountability, using metrics and processes such as the Research Excellence Framework (REF)[7] to evaluate the investments made in research and understand the most effective pathways to impact. There is also increasing attention, led by learned societies like the Academy of Medical Sciences (AMS, 2015), on scientific good practice, with the aim of understanding how research cultures and credit structures may hinder or enhance the reliability, reproducibility and integrity of scientific research.

In addition, there is now more emphasis on public transparency. For example, the opening commitment of the Concordat on Openness on Animal Research in the UK (Understanding Animal Research, 2014, p6) requires signatories to "*provide accurate descriptions of the benefits, harms and limitations of such research, [and] be realistic about the potential outputs of such research*".

These and other initiatives can be used to help assess potential benefits and weigh potential benefits against harms from animal research in HBA. However, they also indicate the challenges; ongoing debates around research integrity and outcomes suggest that the life sciences are not currently (as at August 2017) realising the expected benefits to human and animal health and the environment (Van der Worp et al., 2010; Garner, 2014).

In this chapter, the ASC considers the opportunities to improve the assessment and weighing of benefits in HBA. In Section 4.2 it reviews the Animals in Science Regulation Unit (ASRU) advice on assessing benefits and discusses some common challenges across the evaluation of all benefits.

In Section 4.3, the ASC then considers these opportunities to enhance the evaluation and realisation of benefits in HBA through:

- the use of systematic review
- attention to experimental design
- identifying benefits from basic research
- considering different pathways to translational research
- collaboratively evaluating the benefits associated with regulatory research and testing

Chapter 5 explores further issues around incorporating societal concerns around the benefits from animal research.

7 *http://www.ref.ac.uk/ (last accessed 8/9/2017)*

## 4.2. CHALLENGES IN ASSESSING AND WEIGHING BENEFITS

The 2003 Animal Procedures Committee (APC) review concluded that the *"evaluation of benefits and harms can be based only on potential, likely and probable, not certain, outcomes"* (APC, 2003, p35) and that the weighing of harms and benefits is not a quantitative process – rather, it is a matter of judgement, which is always contestable (Smith and Boyd [eds], 1991). This fundamental challenge has not changed and this is acknowledged in the HBA advice note (ASRU, 2015).

Whilst there are challenges in assessing and weighing both harms and benefits, the ASC suggests that there are additional issues in the evaluation of prospective benefits. The assessment of harms can be informed by previous experience of the outcomes of similar procedures, alongside the animal welfare science literature, enabling predictions about adverse effects and evaluation of how they might affect the animal in advance. Researcher experiences of and literatures around the realisation of benefits have yet to be organised in a similar way, with competitive pressures making this exchange less likely.

Furthermore, the overall harms associated with a procedure or study can be assessed at one-time point after the study has ended, making to easier to check whether the prospective assessment of harms was accurate.

Furthermore, the overall harms associated with a procedure or study can be assessed at one-time point after the study has ended, making to easier to check whether the prospective assessment of harms was accurate.

In contrast, only short-term benefits and interim steps towards longer term outcomes can be checked in an analogous manner at the end of a project, with other elements of research benefits remaining open. The implications of these and other challenges are reviewed below, with particular attention to issues around cultures of science, timescales, checklists and ongoing reviews.

### 4.2.1. THE ANIMALS IN SCIENCE REGULATION UNIT ADVICE NOTE

The HBA advice note (ibid) explains that "*the benefits considered during the HBA are the specific, expected beneficial outcomes of the objectives of the project*". These include direct project-related benefits and indirect benefits to the wider research field or the 3Rs (the replacement, refinement and reduction of the use of animals in research), but exclude *"the non-specific benefits of the area of research in general"*.

**The Animals in Science Regulation Unit advice note review of benefits**

The HBA advice note lists the following questions (pp17-18) that are asked during the review of benefits.

- **What will be the benefits of the work?** For example, what data may be acquired, what drugs may be developed, what scientific questions may be answered, what knowledge gaps might be filled and what is the project's output?
- **Who and how many will benefit from the work?** For example, other researchers? Human or veterinary patients? A relatively small set of patients, for example, people with a rare genetic disease? Potentially millions, for example, a vaccine candidate for malaria? The environment?
- **How will the benefits accrue?** For example, improved scientific knowledge/understanding? New or more efficacious therapies? Cheaper therapies? An impact on patients' quality of life?
- **When will the benefits be achieved?** This can range from within the lifespan of the PPL (for example, toxicological safety testing) to decades in the future (for example, basic research into malarial immunology that may eventually contribute to the development of an efficacious vaccine).
- **What benefits are not allowed?** For example, there are prohibitions on developing or testing offensive weapons, testing alcohol or tobacco products and testing cosmetics. (Ibid)

The ASRU HBA note further explains (p19) that benefits are qualitatively weighted[8] within HBA to reflect their likely value, including in terms of:

- the seriousness of a human disease
- the number of patients affected
- the overall societal impact
- filling a knowledge gap in basic science
- regulatory requirements

Benefits are also qualitatively weighted within HBA to reflect their likely success. These reflect:

- the clarity of objectives
- the research establishment's track record
- the provision of detailed information
- the application of the 3Rs (ibid, p20)

The weighing of harms against benefits is then carried out. This is the process of determining if the overall harm that will occur is justified by the benefits that are likely to be delivered.

The HBA advice note acknowledgest that inspectors are required to make value-laden judgements (ibid, p17), but advises that these judgements are expected to be balanced, rational and consistent across project licence applications (p19) and based on the information provided in the application and other relevant sources. The HBA advice note outlines that ASRU makes use of referrals, the scientific literature and discussion to evaluate benefits fully and consistently.

Nevertheless, there remain multiple sources of uncertainty in evaluating benefits, from the inherently open-ended nature of scientific research, to the variability of value accorded to different kinds of benefit. In addition, in-depth personal knowledge about the science relating to each project application and access to the relevant scientific literature, may not always be available to individual ASRU inspectors and it is not clear how much time and resource is available for such consultation.

For these reasons, much rests on whether the scientists' claims about the potential benefits in project applications are clear and persuasive (ibid, p20),

> and whether there is trust and confidence in their establishments' cultures of care

and capacity to support delivery of the promised benefits. Other research also suggests that confidence, rather than evidence may be key to the authorisation of animal experiments (Vogt et al., 2016).

### 4.2.2. CHANGING CULTURES OF SCIENTIFIC PRACTICE

The APC review (2003, p29) emphasises that only scientifically valid projects should move on to HBA. Determination of scientific validity should cover factors such as:

- the validity of the scientific approach
- experimental design
- statistical analysis
- choice of animal models
- experience of the research team in the particular field
- sufficiency of resources, including staff time, funding and quality of the facilities (see also Jennings and Smith, 2015)

All the above assessments should be critically evaluated over time, encouraging researchers and their AWERBs to "*consider whether and how far they engage in sufficient innovative, creative, flexible and challenging thinking when choosing methods and models*" (APC, 2003, p80).

In the period following the APC report, questions around research integrity, reliability, reproducibility and misconduct have received considerable attention from learned societies, most recently in the research integrity inquiry (House of Commons Science and Technology Committee, 2017). These reports have sought to support behaviours and values that result in high quality, ethical and valuable research concerns and

8 *The ASRU (2015) HBA advice note uses the specific local terminology of weighting benefits to refer to the likelihood and value of those benefits and weighing to reflect the way that they are balanced against harms. This report uses the ASRU terminology of weighing in the same way, but uses the more general terms of assessing or evaluating benefits instead of weighting benefits.*

understand the ways in which individual incentives and competitive research cultures (for example, 'publish or perish' demands) may impede the realisation of good practice.

Researchers' career progressions and economic benefits[9] are not permissible purposes under the A(SP)A. They are indirect outcomes of a successful project authorised under one of the permissible research purposes, rather than benefits in their own right. Nevertheless, it is important to recognise that research and credit structures in science have become more competitive and commercialised in general. These motivations for carrying out animal research and testing cannot be critically evaluated as part of the full assessments of benefits. However, these aspects of research culture have contributed to concerns about research practice and integrity, so it is important to be aware of how they may shape the experimental practices, publishing behaviours and narratives of potential research impact in the HBA.

As the ASC outlined in its 2017 response to the Science and Technology Committee consultation on Research Integrity (ASC, 2017; see also Würbel, 2017), research integrity is an ethical consideration fundamental to the realisation of the benefits of research using animals and demands attention at all levels of the research process from individual experiments to institutional factors.

Research integrity is an ethical consideration fundamental to the realisation of the benefits of research using animals and demands attention at all levels of the research process from individual experiments to institutional factors.

### 4.2.3. SPECIFYING MEANINGFUL TIMESCALES

While short-term benefits may be measurable, medium-term benefits (for example, contributing towards a greater understanding of a physiological system of interest) and long-term benefits (for example, providing information that has led to a new therapy for a specific disorder) become progressively more difficult to assess.

It is not clear how and to what extent longer term benefits are considered by the regulator, institutions (including AWERBs) or indeed funding bodies. The response to the question "*When will the benefits be achieved?*" (ASRU, 2015, see 4.2.1 above) includes the phrase "*decades in the future*". Research may have benefits realised over these timescales and stating these ambitions may help to underline and deliver on project objectives. However, the ASC suggests that these are currently difficult to evaluate in a rigorous way within the prospective HBA of an individual project and could be used to signal general aspirations rather than likely benefits.

There is now more research retrospectively tracking research benefits, which the ASC explores below. This includes reporting on research completed up to 20 years before 'impact' is recorded. Whilst it remains difficult to predict potential or prospective benefits over these timescales, these reports could be used to help break down such aspirations into the discrete activities and short-term milestones that increase accountability and the likelihood of delivering on longer term objectives.

Given that open-ended assertions of benefits can potentially be used to justify any procedure on animals, the ASC suggests that assertions that projects may to lead to long-term gains should be carefully scrutinised and not given undue weight in the HBA. Given this, the ASC suggests that the phrase "decades in the future" is not an appropriate terminology to use in the prospective evaluation of likely future benefits. The ASC would encourage researchers, AWERBs and the regulator to focus on identifying the processes (and if possible probabilities) that can be used to demonstrate and evaluate steps taken towards longer term project objectives, including using checklists and milestones.

### 4.2.4. USING CHECKLISTS, INDICATORS AND MILESTONES

As 'weighing' is a matter that requires judgement, there are no easy-to-follow rules for assessing or quantifying when the likely benefits justified the overall harms. The HBA advice note describes the process of weighing benefits and harms as follows:

9 *The HBA advice note (ASRU, 2015, p19) does indicate the economic benefits of a new chemical.*

*"Having considered the aspects of the harms and the benefits in detail, an overall judgement is made regarding the severity of the harms and the value and likelihood of delivery of the benefits, ie both harms and benefits are weighted. In order to determine whether or not a project should be granted, the harms are then weighed against the benefits. The weighing of harms against benefits can be considered to be the process of determining if the overall harm that will occur is justified by the benefits that are likely to be delivered. Since there are no agreed quantitative units for either harm or benefit, this is not a quantitative analysis."* (ibid, p18, point 17.)

However, there are methods available to support this process and ensure that HBA is as transparent, rigorous and legitimate as possible. Many of these have been developed by local AWERBs. They include a mix of lists and models, as indicated below.

**Decision support tools**

- **Published guidelines:** These include: Prentice et al., (1990); Smith and Boyd (eds) (1991); de Cock Buning and Theunen (1994); Delpire et al., (1999); APC (2003); Smith et al., (2007); European Commission (2013); Home Office (2014, especially Appendix I); Jennings and Smith (2015); Laberet al., (2016).

- **Local lists**: Many AWERBs will have drawn up lists of factors for consideration for themselves, to help to guide the evaluation of harms and benefits and to offer some insights regarding weighing.

- **Visualisations:** Bateson's cube (Bateson, 1986) offers a visual guide or heuristic to weighing harms and benefits, based on three criteria: animal suffering; probability of benefit; and the quality of the research. Each are graded as 'low', 'medium' or 'high'.

- **Scoring schemes:** (for example, Porter, 1992; Boisvert and Porter, 1995; Stafleu et al., 1999) may offer some insights. However, these are not otherwise favoured, as it is widely agreed that ethical weighing cannot be a quantitative process.

Using such tools can help to ensure that the weighing process is as comprehensive as possible. They can highlight areas of concern that, in turn, can lead to further discussion, reflection and negotiation – for example, with individual researchers, via the AWERB, with wider stakeholders and public and/or in dialogue with the Home Office Inspectorate. The outcomes of these discussions might be to explore alternatives, reduce harms and/or enhance benefits – or in some instances, just to say 'no'.

Most commonly used are lists of factors that can help to identify and assess potential benefits in the different stages of the evaluation process. These may allow for some rough categorisations of possible outcomes – for example, 'low', 'medium' or 'high' potential benefits. Some factors also act as proxies for certain attributes of quality in the absence of quantifiable aspects of research benefits.

The HBA advice note includes reference to the list of factors and information sources used by ASRU to evaluate the range and likelihood of benefits (ASRU, 2015, pp16-18). These prompts are used to enhance the coverage and consistency of reviews across project licences and inspectors.

Other lists have been developed by individual establishments; these can help to ensure that the factors are directly relevant to the establishment's own specific areas of animal research. Institutional AWERBs play a vital role in discussion, assessment and enhancement of benefits. They are well placed to consider the impact of local, institutional factors such as *"access to information about the 3Rs, standards of animal care and accommodation, management of animal use and expertise and competence of staff"* on the likelihood of achieving benefits (Jennings and Smith, 2015).

Many lists focus on the identification of direct benefits. This is important, but there is scope to consider additional information that is relevant to the realisation of benefits and the potential for indirect benefits. This might include information about the research team's objectives with respect to maximising the benefits of the research, such as plans for publications, liaison with other research groups (including clinicians, where relevant) and public and patient engagement. Commitments to

promulgate information about the application of the 3Rs and the enhancement of benefits would also be helpful, provided that these are realised in practice.

Given the growing role and diversity of lists used to weigh harms and benefits, there is scope to engage in debate with others involved in HBA and widen the discussions around the use of these checklists and their associated milestones.

### Recommendation 14

Researchers and AWERBs should support the rigour, transparency and legitimacy of HBA by ensuring that research objectives and project milestones for realising research benefits are realistic, clear and accountable in advance. These should be reviewed over the lifetime of project licences and opportunities sought to enhance benefits. These processes may be facilitated by sharing checklists developed by local AWERBs and using other appropriate decision support tools.

Sometimes the use of proxy indicators, such as impact factors to signify project licence applicants' scientific credentials, may be considered in the evaluation of benefits. However, the San Francisco Declaration on Research Assessment (2013)[10] has criticised impact factors for being:

- opaque
- lacking predictive capabilities
- contributing to unhelpful publishing behaviours

Debates about research reproducibility and integrity have been particularly critical of how indicators of research quality, like impact factors, may be encouraging grant and publishing behaviours in which "*no-one is incentivised to be right*" and where "*scientists too often sculpt data to fit their preferred theory*" (Horton, 2015, p1380). The ASC recommends that impact factors are not used in HBA as this would unjustifiably accentuate their importance.

### Recommendation 15

Whilst targeted checklists and project-specific milestones may be valuable for evaluating the likelihood of success for the HBA, key information on animal research is often missing from highly ranked journals. This suggests that journal impact factors should not be used as a proxy for quality criteria around the likelihood of success when assessing individual project licence applications.

After a project licence has been granted, there should be planned, defined and measurable milestones to trigger reviews of progress, including an ongoing assessment of the likelihood that the potential benefits will be achieved and steps to ensure that the impacts of the work will be maximised. These milestones can apply to short-term benefits and the interim stages en route to medium- and long-term benefits, which are otherwise more difficult to predict.

The potential for additional or longer term benefits may also be enhanced if researchers include in their milestones appropriate proposals for curating, archiving and providing access to their research data.

### Recommendation 16

Not all benefits can be anticipated in advance, but the potential for realising unforeseen and additional benefits can be enhanced. Researchers and establishments should be encouraged to be responsive to opportunities to enhance emerging benefits (for example, through cross-project and AWERB hub collaborations) and should implement the most appropriate proposals for curating, archiving and providing access to their research data, to inform and enhance long-term benefits.

10 *The San Francisco Declaration on Research Assessment (DORA) was initiated in 2012 by the American Society for Cell Biology (ASCB) to improve the ways in which the outputs of all scientific research are evaluated. For more information see http://www.ascb.org/dora/ (last accessed 22/08/201)*

### 4.2.5. DIVERSITY AND REVIEW IN HARM-BENEFIT ANALYSIS

The outcomes of the weighing process in HBA may vary between projects, as well as between Home Office inspectors and across other ethical reviews, including AWERBs and the ASC. The HBA advice note (ASRU, 2015) suggests processes that can help to "*ensure that significant inconsistency is avoided*", including:

- referral to inspectors with specialist expertise
- use of inspector panels, case discussion groups and/or independent assessors
- referral to the ASC
- engagement with external stakeholders who share disparate views

However, differences of opinion will continue to arise and should be expected. AWERBs coming to different conclusions around HBA can reasonably result from each applying their own unique or different 'local' perspectives and values.

For these reasons, HBA should be a dynamic ongoing process, not a one-off event (APC, 1997, p50, point 1.2) that is re-evaluated at appropriate intervals throughout the lifetime of a project, from the initial idea through to the publication of findings. HBA should take account of any changes to the levels of harm, how these might be ameliorated and the degree and likelihood of benefits being realised. It should also be constantly alert to new developments in scientific methods and knowledge about animal welfare that could be used to alter the balance of likely benefits and harms in a project.

## 4.3. IMPROVING THE EVALUATION AND REALISATION OF BENEFITS

All project licences aim to generate worthwhile, lasting benefits – whether they relate to:

- the basic science that might underpin future scientific advances
- research directed towards clinical applications
- testing that meets regulatory requirements to help to safeguard human and animal health and the environment

Applicants for a licence to use animals in research are asked to identify these proposed benefits when filling in the project licence application

Sometimes, animal-based studies lead to direct, highly beneficial outcomes – but more often the benefits are indirect, in that they form a small part of a jigsaw of scientific findings that together might contribute to a breakthrough.

Here, the ASC discusses ways in which the realisation of hoped-for benefits can be supported and facilitated through:

- systematic review
- experimental design
- translational research
- regulatory testing

Not all these steps will be relevant to all projects and some efforts to assess the pathways to benefits are still in the early stages of development. However, engagement with these will help to embed review and learning across the processes of HBA.

### 4.3.1. SYSTEMATICALLY REVIEWING CURRENT EVIDENCE

In establishing the potential for benefit, it is important to review the current evidence base before deciding if animal use is justified. This can prevent the unnecessary use of animals, for instance:

- where there is already sufficient evidence to support scientific claims and replication is not necessary
- where there is clear evidence that an approach will not work

The current 'gold standard' approach to reviewing existing scientific evidence is a systematic review of the published literature followed by meta-analysis, if feasible, of the relevant studies. A systematic review is used to identify all relevant published literature by searching appropriate databases. These are then filtered to identify the papers that are relevant and contain evidence of acceptable quality. Subsequent meta-analysis of the relevant papers can be used to assess the quality of evidence in a research area and to identify potential issues with the evidence-base, such as publication bias, which may skew the results.

Together, these methods can help to ensure that a researcher's choice of animal methods is appropriate and capable of yielding the anticipated benefits (Hooijmans and Ritskes-Hoitinga, 2013; van Luijk et al., 2014) and that the licensing decisions are fully informed.

A range of tools is now available (as at August 2017) to facilitate the performance of systematic reviews of animal studies and subsequent meta-analysis. A selection of these are listed below (links were active in August 2017).

- CAMARADES-NC3Rs Preclinical Systematic Review & Meta-analysis Facility (SyRF) http://syrf.org.uk/
- SYstematic Review Center for Laboratory animal Experimentation (SYRCLE) https://www.radboudumc.nl/en/research/technology-centers/animal-research-facility/systematic-review-center-for-laboratory-animal-experimentation
- Canadian Council on Animal Care http://3rs.ccac.ca/en/research/systematic-reviews.html
- The Critical Appraisal Skills Programme (CASP) checklist http://www.casp-uk.net/casp-tools-checklists

**Recommendation 17**

An explanation of the potential benefits of animal research in the project licence is justified through locating the research in the current relevant field and knowledge. As techniques become more refined and widely available, researchers are encouraged to supplement these with relevant reference to tools for systematic review and meta-analysis.

The systematic improvement of and learning from the outcomes of animal research requires the publication of valid data from the range of animal studies carried out, whether or not they support the original research hypothesis. The value of a systematic review of evidence requires that the published literature is an accurate representation of the current knowledge base.

HBA for animal research is also ethically problematic if data are not made available, as animals harmed in unpublished research cannot contribute potential benefits.

HBA for animal research is also ethically problematic if data are not made available, as animals harmed in unpublished research cannot contribute potential benefits.

**Recommendation 18**

Researchers should strive to publish all the valid data that have resulted from animal research in an appropriate and accessible format, whether or not they support the original hypothesis.

### 4.3.2. ENSURING RESEARCH INTEGRITY AND GOOD EXPERIMENTAL DESIGN

The ASC considers that 'research integrity' includes ensuring that research using animals both seeks to minimise harm and maximise benefit (ASC, 2017). The realisation of any potentially beneficial data from animal research depends upon good experimental design, suitable experimental practice and valid statistical analysis. This is the shared responsibility of funders, researchers, professional societies, AWERBs, establishment licence holders and inspectors.

Ensuring research integrity and good experimental design is an ongoing area of strategic discussion across the animal research and biomedical research community. It is a particular challenge in universities, where research may be diverse and expertise widely distributed. Funders, publishers and educators all have a role to play in supporting the development and promulgation of good practice. There is currently (August 2017) considerable attention being paid to this issue.

The Research Council UK (RCUK) has updated its online guidance for funding applications involving animal research in 2015[11]. This now requires that: *"All proposals using animals should explain not only the need to use animals and the ethical implications of the planned experiments, but also clearly describe how the planned experimental design is appropriate to give robust results."*

11 http://www.rcuk.ac.uk/media/news/150415/ (last accessed 23/08/2017)

The review of investments in in vivo education via the British Pharmacological Society (BPS) (Lowe et al., 2016) outlines the value of roles like the 'experimental officer' – a centrally supported source of advice and review for experimental design and data analysis. The BPS has commenced working with educators and employers in the in vivo community to develop clear core learning objectives, including around experimental design, statistics, animal welfare, cultures of care, ethics and the 3Rs.

The Animal Research: Reporting of In Vivo Experiments (ARRIVE) guidelines (Kilkenny et al., 2010) were developed in consultation with the scientific community to improve standards of reporting of research using animals. They are intended to improve the reporting of experiments, ensure key information about the use of animals in studies are available and minimise unnecessary research.

However, the 2016/17 consultation on research integrity (House of Commons Science and Technology Committee (2017)), the identification of inadequate methodologies used in animal research (Bara and Joffe, 2014) and the continued gaps in reporting of animal research (Macleod et al., 2015; Carbone and Austin, 2016) suggest that there are still considerable improvements required in experimental practice and the evaluation of experimental design and statistical power to realise the benefits proposed in the HBA.

Benefits from all research will be enhanced by further critical attention to the following elements of HBA:

- the validity of the procedure as a means of fulfilling the research objectives
- the rigour of the experimental design
- the statistical validity of the number of animals used
- the reliability of experimental findings
- the planned reporting of research practice and outcomes

The demonstration of benefit might reasonably be judged not against achieving an arbitrary level of statistical significance but rather a strength of evidence (a positive predictive value) reached after the completion of the experiment. This allows users of research to have certainty in the findings presented (Mogil and Macleod, 2017).

There are now resources available to researchers, AWERBs and others to assist in the development of appropriate experimental design and reporting of data. Current tools (with links active in August 2017) include:

- The NC3Rs Experimental Design Assistant – https://www.nc3rs.org.uk/experimental-design-assistant-eda
- The NC3Rs ARRIVE (Animal Research: Reporting of In Vivo Experiments) guidelines – https://www.nc3rs.org.uk/arrive-guidelines

**Recommendation 19**

Researchers, establishments, AWERBs, funders and regulators should work to support researchers in meeting current quality criteria for experimental design and reporting relevant to their disciplinary area. This should include facilitating informed discussions around methods for selecting appropriate sample size, mitigating bias, incorporating randomisation and the blinding of outcomes.

### 4.3.3. IDENTIFYING BENEFITS FROM ORIENTED BASIC RESEARCH

As for all research and testing involving animals, basic or fundamental research must be deemed sufficiently important and necessary to justify the use of animal procedures. The potential benefits of the work must be weighed against the harms caused to the animals; to achieve a positive HBA outcome, there must be an appropriate balance between the two.

There are additional challenges in evaluating the benefits from basic research. In part, this reflects the specialised nature of the potential benefits from basic research, which need to be specified in the HBA[12], but may be less accessible to and/or accepted by the range of perspectives around animal research. It also reflects the changing position and definition of basic research itself[13]. Much research can be placed on a spectrum that spans from basic to applied research; with basic research always being conceived with a strategic research development in mind. Researchers are increasingly encouraged to present their work to funders in ways that highlight its translational nature and potential benefits, so applications that may have been seen as basic in the past are now identified as both basic and translational research.

There are dangers in both overstating translational research applications (in exaggerating research and raising unrealistic expectations, resulting in an inappropriate HBA) and in undermining the potential benefits of more basic research (in not identifying and engaging other potential research users and communities to realise benefits). It is essential for the proposed benefits to be transparently and honestly set out for all research and to recognise that there may be implications for the HBA if the potential benefits change along the spectrum between basic and applied as research develops.

The OECD (2013) defines **basic research** as *"experimental or theoretical work undertaken primarily to acquire new knowledge of the underlying foundations of phenomena and observable facts, without any particular application or use in view"* [ASC's emphasis]. The ASC views the OECD (2013) definition of **oriented basic research** as a more accurate and appropriate characterisation of most contemporary animal research. This is defined as "*research carried out with the expectation that it will produce a broad base of knowledge likely to form the background to the solution of recognised or expected current or future problems or possibilities*".

This definition recognises the indistinct boundary between basic and applied research and acknowledges the expectation (whether realised or not) that knowledge gained through the research may support future advances that could help bring benefits to humans, animals and/or the environment. Recognising the oriented basic nature of most contemporary research should help to subject studies to appropriate HBA at the outset and to review these as research develops.

In the ASC's view, the likelihood that a piece of research could lead, directly or indirectly, to human or veterinary medical and/or environmental benefit can have a bearing on the level of harm that is deemed permissible.

In the ASC's view, the likelihood that a piece of research could lead, directly or indirectly, to human or veterinary medical and/or environmental benefit can have a bearing on the level of harm that is deemed permissible.

For example, if a study that is initially presented as likely to be translatable soon is discussed in depth and, as a result, is 'reclassified' as being further away from likely application (and angled towards basic research), the level of harm that would be acceptable to achieve the scientific objectives may well be reduced, directly impacting on HBA.

Here the ASC restates the applicability of recommendation 14 for all oriented basic research and translational research.

### 4.3.4. DEVELOPING PATHWAYS FOR TRANSLATION OF RESEARCH

In recent years funding bodies and policymakers have invested considerable resources to support the translation of laboratory animal research into clinical applications for human and animal health. Early policy identified different stages of research, from bench to clinic, to help to understand

12 *Whilst it can be argued there is always the potential for a piece of research to lead, directly or indirectly, to human or veterinary or environmental benefits, such a claim is so broad as to be meaningless for the HBA.*

13 *Calvert and Martin (2001) suggest that there is no clear-cut boundary between basic and applied science. Moreover, they show how the definition of basic research has changed historically and is more often used as a marker of intention rather than an accurate description of scientific practice. They outline how the idea of 'basic science' developed alongside the growing involvement of the military and industry in science. Basic science was used in the post-war period to identify an ethical ideal of science furthering knowledge for its own sake and a particular type of scientist who was autonomous and curiosity-driven. The subsequent shift to so-called Mode 2 knowledge production, has seen a return to science that is valued for being context-driven, problem-focused and interdisciplinary (Gibbons et al., 1994).*

barriers to translation (see, for example, Khoury et al., 2007; Westfall et al., 2007; Dougherty and Conway, 2008).

At the same time, work mapping the complexity of networks involved in translation (Cambrosio et al., 2006) demonstrated the nonlinear nature of much translational research and the value of interactions between laboratory researchers and clinicians (Fudge et al., 2016). Recognition of the complexity of the process of translating research from the laboratory to clinical application is an important counter to the linear and at times overstated claims made about the likely benefits of single projects.

Preclinical research (animal) and clinical applications (for both human and animal) can sometimes vary widely and the extent to which researchers liaise to understand clinical contexts or commercial viability is not always evident. More opportunities for dialogue between basic and clinical scientists can facilitate and enhance this process – especially when laboratory researchers are able to work alongside clinicians and others at an early stage in the research process. This may enable the better alignment of animal models and clinical contexts – and, later, the publication of findings in journals that are read by clinical communities or the engagement of commercial developers.

To assist inspectors and others involved in the evaluation of research benefits, the ASC has drawn on analysis of the REF2014 Impact Case Studies.[14] These case studies report the impacts of biomedical research carried out in UK higher education institutions (HEIs).

The analysis covers six main pathways through which research in HEIs is judged to have a demonstrable impact on human and veterinary medicine through:

- Drug discovery and development
- Implementing platform technologies
- Developing translational devices
- Breakthroughs in experimental medicine
- Changing health and welfare practices
- Informing public debate and policy

These are elaborated and illustrated with active links to case studies in Table 4; the methods are explained in Appendix D.

14 *This currently unpublished research was carried out by Professor Gail Davies and Gabrielle King at University of Exeter in 2016 for the purposes of this report. All links to REF2014 case studies last accessed 8/9/2017.*

Table 4: Indicative pathways to impact from animal research reported in REF2014 Impact Case Studies *(http://impact.ref.ac.uk/CaseStudies/)*

| Pathway | Drug discovery and development | Implementing platform technologies | Developing translational devices |
|---|---|---|---|
| Key features | 43% of impact case studies report new understandings of disease mechanisms; testing in clinical trials; or implementing new drugs, vaccines, or diagnostics in clinical contexts. | 27% of impact case studies refer to the development of new platform technologies, often via spin out companies, used within research and drug development processes. | 8% of submitted case studies report the development of new devices to facilitate translation between animal studies and clinical practice. |
| Titles of indicative REF2014 Impact Case Studies | Prospect of a cure for Rett syndrome has driven the formation of a charity and underpins clinical trials<br><br>A new pharmacological approach for treating ADHD<br><br>BRCA genes in cancer improved screening regimes and novel therapies<br><br>The Development of Vaccines for Porcine Circovirus Diseases. | Improved efficiency for derivation of mouse embryonic stem cells: reducing use of animals and saving costs in life sciences<br><br>Everest Biotech Ltd: providing high quality reagents for research<br><br>Oxford BioMedica: effective tools for gene therapy<br><br>Asterion, a Start-Up Company Delivering Third Generation Biopharmaceuticals. | Advancing clinical assessment of acute pain in companion animals<br><br>Establishing effective doses of analgesics in animal research through a behaviour-based pain scoring system<br><br>Touch screen based cognitive testing for rats and mice<br><br>Developing tools to restore fertility in dairy cows. |
| Pathway to impact | Drug discovery and development is the most fully characterised and regulated pathway to translational research. However, research rarely progresses linearly through animal studies, preclinical and clinical research. It can be enhanced by communication and exchange across multidisciplinary teams, supported by organisational cultures of collaboration and institutional infrastructures (for example, bioinformatics). | These are associated with the involvement of large multinationals and international research collaborations. Reported impacts focus on immediate economic gains around patents, licensing and spin out companies. Many health benefits are still more speculative, but platform technologies may have extensive impacts through their transformation of practices across a wide field of research (for example, biopharmaceuticals). | Here, collaborations are facilitated by strong alignment between interests of researchers and companies involved in application. Research reach is enabled by simple behavioural technologies, which can be easily embedded in new settings, such as pain scoring sheets, standardised cognitive assays, or genetic tools. With shared understandings and complementary incentives studies appear to have strong potential for research impact or benefit. |
| Issues for the harm-benefit analysis | Past experience of multidisciplinary collaboration and institutional support for collaborative work are likely to be key criteria for assessing these studies. Trochim et al., (2011) suggest that translation may be enhanced by using easily operationalised markers to enable collaborators to review progress towards translation on a regular basis. These may differ across the different stages of research, including biomarkers for preclinical animal studies and agreed milestone dates to progress work through the later stages of translation, for example, publication, trial, patents and inclusion in reviews. | These projects may have far-reaching implications on future research practice and animal use, through platforms with the potential to deliver new routes to therapeutic research, whilst either reducing (in the case of validating alternatives) or increasing animal use (in the case of new research areas). The former is an important opportunity to demonstrate the 3Rs as direct benefits. For the latter, given that HBA cannot include contingent 'harms' of increasing future animal use, there is scope to consider how new platforms may seek to maximise the 3Rs at an early stage as indirect benefits of research. | Pain studies involve complex evaluations around the HBA as procedures on animals may be severe, but would be expected to achieve significant benefits. Studies that offer new knowledge around refinements, may also increase the numbers of animals undergoing procedures. If the outcomes are primarily about achieving outcomes in policy and practice, there is scope to consider whether similar benefits might be achieved through processes that involve lower harms to animals, for example, by meta-analysis, systematic review, training, culture change and guidelines. |

| | Breakthroughs in experimental medicine | Changing health and welfare practices | Informing public debate and policy |
|---|---|---|---|
| Key features | 4% (5 studies) recorded research impacts around novel experimental medical techniques with direct clinical potential application. | 13% of the case studies claim the direct impact of animal research on wider practices relevant to healthcare and animal welfare. | 5% of the case studies reviewed made claims for research involving animals that had impacts on policy and public engagement. |
| Titles of indicative REF2014 Impact Case Studies | A new form of deep brain stimulation alleviates severe 'freezing' and loss of balance in advanced Parkinson's disease<br><br>Health benefits, increased public awareness and changes in national policy result from the successful implantation of the first tissue-engineered trachea, created utilising the patient's own stem cells<br><br>Therapeutic hypothermia saves thousands of babies each year across the developed world from severe disability or death. | Pain research improves welfare of fish<br><br>Animal welfare policy and practice improved internationally as a result of research into poultry-stunning prior to slaughter<br><br>Transforming instrument decontamination in dental practice<br><br>Providing an evidence base for the FDA ban of fluoroquinolone antibiotic use in animals<br><br>Changing European Commission policy in relation to biocides as agents driving antibiotic resistance. | Dolly the sheep – the first cloned mammal and a public icon for regenerative medicine<br><br>Promoting public and policy-maker understanding of the benefits of genetic modification (GM) technology in chickens transgenic birds that do not transmit avian influenza<br><br>Public Understanding of Multiple Sclerosis Research<br><br>Informing Global Improvements on the Welfare of Fish. |
| Pathway to impact | Research groups or networks working in a field identify a critical need within a specific medical context, which supports innovative and at times radical experimental methods involving both humans and animals. This work is often highly integrated so routes to translation may be rapid. | These studies often identify a specific knowledge gap within standardised systems of animal production or healthcare management regimes. This is the focus of research project, designed to provide evidence to inform practices, supported by a programme of wider training and guidance. | Public engagement was a legitimate research impact under the Research Excellence Framework (REF). The case studies indicate the considerable role played by individuals in public engagement and outreach, but evidence of impact is more limited and many studies appear to have been assessed as having only a modest impact. |
| Issues for the harm-benefit analysis | Often involves large animals, but there is the clear possibility for breakthrough in these studies, with the close integration of medical research and clinical settings. Studies returned to REF2014 involving the discredited surgeon, Macchiarini, also demonstrate the risks. The subsequent enquiry around his work indicated that small collaborator groups, working in experimental situations with blurred boundaries between scientific research and clinical care and subject to institutional pressures to deliver translational benefit, may exaggerate claims and become normalised to the risks or uncritical about the research (Abbott, 2016). | Studies that focus on animal welfare outcomes can be divisive since research designed to optimise welfare often involves deliberately causing harm to animals. The optimisation of research benefit here follows from: research targeted to required evidence standards; new practices that can be scaled up rapidly through standardised systems; and a multifaceted dissemination strategy that includes workshops, training courses and changing legislation. Translation may be enhanced by working with the systems that will be implementing change from an early stage. | Public understanding or engagement is not an acceptable benefit from animal research under ASPA. However, there are considerations here on how to incentivise and support researcher openness and public engagement around animal research. Societal concern is a recognised 'harm' in HBA and outreach is increasingly recognised as a general benefit to researchers, regulators and public debate. Engaging researchers with the ethical, public and policy debate that accompany their work is likely to be most appropriately supported and evaluated at the institutional level. |

The case studies do have limitations in the context of HBA, but serve to illustrate how reported impacts are being linked to specific scientific studies in retrospective accounts. Characterising how the different routes that have delivered research impact in the past should provide insights to help to enhance the benefits of future research efforts.

The examples are not exclusive or exhaustive, but the case studies do indicate how different pathways to translation involve collaborations with distinctive groups of clinicians, policymakers, or spin-off companies and are organised around particular technologies, such as biomarkers, translational devices, or standardised platforms. Identifying these pathways can help to clarify what might make a 'persuasive argument' about benefits in different kinds of project licence applications, as well as being used to offer specific guidance on the realisation of research benefits once a licence has been granted.

The analysis also suggests that different pathways raise distinctive challenges for HBA, with Table 4 reflecting on how these challenges might be overcome and where additional scrutiny may be required.

**Recommendation 20**

Assessment of the benefits from translational research would be enhanced by researchers defining measurable translational research objectives . These should operate within the scope of the specific project and provide evidence of their ability to access appropriate pathways to translation in that area (for example, via clinical collaborations, data exchange, publishing plans, policy engagement and commercial partnerships).

The reporting and monitoring of research impacts has the potential to improve project-specific claims made by researchers about the benefits of animal research and the ASC encourages inspectors and AWERBs to explore these resources now.

**Recommendation 21**

Researchers, AWERBs and ASRU inspectors are encouraged to search the publicly accessible REF impact case studies for past examples in fields related to new applications in translational research. The current case studies have limitations, but do provide an overview of translational pathways in different fields. As data returned improve and new techniques for interrogating the case studies provide enhanced responses to queries, this database will increase its potential to inform the HBA process.

The ASC has responded to the 2017 REF consultation[15] with recommendations for enhancing the data collected on animal research in future research assessments to assist this review of benefits and help improve HBA in the future.

**Recommendation 22**

Future Higher Education Funding Council for England (HEFCE) evaluations of research impact should include a mandatory and consistent reporting framework for animal use, commensurate with its status as research that requires a special 'social' licence to operate. This would enable better analysis of the impacts of research using animals and help regulators to improve future HBAs for animal research.

### 4.3.5. COLLABORATIVELY EVALUATING BENEFITS IN REGULATORY TESTING

Regulatory procedures are performed to satisfy legal requirements for licensing potentially profitable substances and products, including medicinal products for human use, veterinary products, medical devices, industrial chemicals, biocides and in relation to food safety. Regulatory science usually requires standardised protocols, which aim to determine whether and how far such substances and products are sufficiently efficacious and safe for approval for use and marketing. A unique aspect of animal studies conducted for safety is that their primary purpose is to identify potential hazards for humans, or the environment, which means they focus on establishing the nature and scope of adverse effects in animals.

15 http://www.hefce.ac.uk/rsrch/refconsultation/ (last accessed 16/8/2017)

According to Home Office (2016) statistics regulatory procedures are primarily performed for the purposes of:

- toxicity and other safety testing including safety pharmacology
- the production of products, for example, blood-based products
- quality control, for example, batch safety and potency of vaccines
- pyrogenicity testing
- 'other efficacy and tolerance testing'

The Home Office statistics (ibid) report that 555,720 procedures were conducted for regulatory purposes in the UK in 2015. Of these:

- 51,022 (9%) were categorised as sub-threshold or non-recovery
- 322,669 (58%) were mild
- 93,991 (17%) were moderate
- 88,038 (16%) were severe

Four regulatory procedures are listed as triggering mandatory referral to the ASRU Regulatory Toxicology Group. These are:

- non-standard acute oral tests
- skin corrosivity or phototoxicity tests
- non-local lymph node assay skin sensitivity tests (using the guinea pig assay)
- non-standard eye irritancy tests

The percentage of procedures categorised as severe for regulatory purposes is higher than for other research purposes (see Table 3).

## Researchers, AWERBs and inspectors are required to minimise the harms of animal tests carried out for regulatory purposes

Researchers, AWERBs and inspectors are required to minimise the harms of animal tests carried out for regulatory purposes; yet, their focus on adverse effects means they remain a significant contributor to overall harms experienced by animals in research and testing.

The anticipated benefits from regulatory purposes thus require careful and continuous scrutiny. However, the benefits from regulatory science are specified through tests or data requirements set by regulatory authorities. Evaluating the validity and acceptability of these benefits involves considerations that are beyond the HBA of an individual project licence application. Changing mandated tests for generating safety and efficacy data requires collaboration across research, industry and the wider regulatory frameworks for product development in the UK and overseas.

The APC outlined the difficulties of evaluating the benefits from regulatory science in 2003. It argued that, "*there is an element of circularity in arguments about where responsibility for the scientific appropriateness of animal tests carried out for regulatory purposes actually lies, which is difficult to break. […] Although regulatory authorities should be open to negotiation so that only the most scientifically appropriate and necessary tests are carried out, it is not easy to challenge the requirements laid out in the regulations. Regulatory authorities do have a role in [harm-]benefit assessment of animal procedures and need to allow scientists flexibility of approach to ensure that only the most valid and vital animal tests are carried out. By the same token, toxicologists for their part have a duty to continue critically to evaluate the appropriateness of the animal tests they perform and to raise questions and concerns with the regulators.*" (APC, 2003, p31).

Since 2003, there have been significant investments in replacements for animals, where possible, alongside refining techniques and endpoints to reduce suffering. There are organisations focused on developing and validating alternatives (for example, Johns Hopkins University's Center for Alternatives to Animal Testing and the European Union Reference Laboratory for alternatives to animal testing), as well as bodies working through programmes and partnership to promote the 3Rs in regulatory safety and industry (for example, The National Centre for Replacement, Refinement, and Reduction of Animals in Research (NC3Rs) and the European Partnership for Alternative Approaches to Animal Testing).

There have also been collaborative developments in the evaluation of valid and acceptable benefits of regulatory testing since 2003. These demonstrate where change has been possible, including through the HBA.

- The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) has introduced more flexible approaches to safety assessment, openly promoting the application of the 3Rs and removing the requirement for acute toxicity testing from the guidelines in 2009.
- The European chemical testing legislation, known as REACH (Registration, Evaluation and Authorisation of Chemicals), which came into effect in June 2007, included amendments around mandatory data sharing and the promotion of non-animal test methods, including weight of evidence approaches.
- The Home Office has implemented a qualified ban on the testing of ingredients that are primarily intended for use in household products from 2015. This ban was not made by legislation but by amending the conditions on existing project licences through the HBA process (Home Office, 2015a).
- The European Directorate for the Quality of Medicines (EDQM) is active in developing alternative approaches to the use of animals, with new guidance on tests for vaccine development in 2016.[16]
- The regulatory framework in other sectors (for example, food) also allows for tiered approaches to testing or approaches such as weight of evidence that both minimise animal use.

The ASC suggests that there are four issues around the definition of benefits from regulatory procedures, which are the focus of ongoing research and debate and require further collaborative endeavour.

- Animal tests are used to assess the safety of substances that have **differing kinds of human benefit and levels of societal support** (for example, medicines, chemicals, pesticides and food additives). For example, the HBA advice note (ASRU, 2015) cites toxicological safety testing as an example of a benefit achieved within the lifespan of the project licence. However, this does not include consideration of the value to society of the substance being tested and whether the benefits of a new food colouring are given equal weighting to those of a more environmentally friendly pesticide, or a pharmaceutical to treat a debilitating condition. There are exceptions to this, with bans on cosmetic testing (since 1998) and the testing of household products (since 2015), which do appear to make distinctions for this purpose (Home Office, 2015a). There is scope to make the processes by which such distinctions may be made and bought into the HBA more transparent.
- There is still ongoing debate about the **scientific validity and recognition of the limitations** of animal tests (APC, 2002; APC, 2003; Nuffield Council on Bioethics, 2005). Considerable efforts are being made to replace animals in regulatory procedures (National Research Council, 2007; Spielmann, 2012; Bowes et al., 2013). Some specific animal tests have been and/or are being challenged with respect to necessity, for example, acute toxicity studies in the development of new medicines (Chapman and Robinson, 2007; Chapman et al., 2010). These issues around the scientific validity of animal research and testing are not unique to regulatory science, but given animal tests are mandated by regulators as part of safety protocols they do require continuing challenge and review.
- The medical sectors are required to use two species for safety assessment studies and the use of a **second non-rodent species**[17] raises additional ethical and societal concerns. The scientific value of a second, non-rodent species is also the subject of debate (APC, 2002; Smith et al., 2007; Bailey et al., 2013; Horner et al., 2013). The NC3Rs is working with

16 *https://www.edqm.eu/sites/default/files/press_release_pheur_commission_session_3rs_2016_11_22_24.pdf (last accessed 21/08/2017)*

17 *Many regulators, including the UK's Medicines and Healthcare Products Regulatory Agency (MHRA), require all medicines for humans and animals to be tested on two species of animals, one rodent and one non-rodent, in order to ensure patient safety. Commonly used non-rodent species include dogs, pigs and monkeys.*

the Association of the British Pharmaceutical Industry to review the use of 'non-rodent' as standard practice. This focuses on sharing data across industry to evaluate whether standard testing paradigms can be modified and asking whether data from one species could be sufficient for the progression of a potential new drug into human clinical trials[18]. Many regulatory toxicology tests were introduced 30 or 40 years ago. The pharmaceutical industry has changed considerably since with new drug targets, new types of compounds and new in vitro and in silico technologies available to evaluate safety. This challenge to requirements laid out in the regulations is an important part of ongoing HBAs.

- Some regulatory procedures are conducted in the UK solely to satisfy **non-EU regulations**. Most regulatory procedures on animals in the UK are carried out in accordance with UK/EU legislative requirements; according to the statistics 97% of regulatory procedures in the UK during 2015 were undertaken to satisfy this legislation (Home Office, 2016). Very few (less than 0.5%) were for UK requirements only. However, animals are still being used in regulatory toxicology procedures in the UK to fulfil non-EU legislative requirements. During 2015, 19,000 procedures (3%) were to satisfy non-EU requirements only (Home Office, 2016), in contravention of Article 13 of Directive 2010/63/EU. There are different views here that require wider debate. For some, carrying out procedures to enable substances or products to be marketed outside the EU calls into question the justification for causing these harms to animals. For others, there is a counter argument that these tests are best done in the UK where standards of animal care and science may be higher.

Given that the specific benefits from regulatory animal research are dependent on the requirements for tests and data set by regulators, answering these critical issues requires collaborative approaches between industry and regulators, as well as wider engagement with societal concerns around the acceptability of different types of benefits (see Chapter 5).

**Recommendation 23**

Local AWERBs of establishments engaged in regulatory toxicology testing should ensure that their mechanisms for weighing harms and benefits consider the context of the types and utility of substances/products being tested, the opportunities for data sharing and the contribution to ongoing HBA review in this area of work.

## 4.4. CONCLUSIONS

There is scope to broaden the resources used by researchers, AWERBs and in ASRU to assess benefits and to make judgements when weighing harms and benefits.

There is scope to broaden the resources used by researchers, AWERBs and in ASRU to assess benefits and to make judgements when weighing harms and benefits.

There is now more information available for evaluating and enhancing the value of animal research from work on systematic review, experimental design, research impact and changes to regulatory requirements. This review has sought to introduce, summarise and indicate how these resources might be used to inform HBA.

In concluding, the ASC supports further use of these resources to develop the criteria and checklists for assessing benefits that are available to those involved in HBA, including the HBA advice note (ASRU, 2015). Existing criteria for assessing benefits might be augmented by checking whether new resources have been consulted and asking additional questions that encourage the maximisation of benefits. The ASC suggest existing checklists could be supplemented by adding questions from the list of issues raised in this review.

18 *See: https://www.nc3rs.org.uk/news/launch-new-nc3rs-abpi-collaboration (last accessed 8/9/2017)*

- Has the review of prior work included a systematic review of past animal studies?
- Has the researcher employed the experimental design assistant, or other tools, to calculate and demonstrate appropriate statistical power?
- Are methods of randomisation and blinding (masking information about a test from participants until outcome are known) appropriate to remove bias?
- Are researchers aware of and compliant with Animal Research: Reporting of In Vivo Experiments (ARRIVE) guidelines in past and planned publications?
- Is the research clear about how it is oriented on the basic/applied spectrum and open to review if research changes? Are the intended benefits from oriented basic research appropriately explained?
- Do researchers demonstrate the potential to interact effectively and responsively with research users in instances of translational research (for example, clinical contexts, policy communities, learned societies and commercial outlets)?
- Is regulatory research clear and transparent about the specific direct benefits (for example, marketing and licensing)? Are licensing requirements mandatory or is there flexibility and alternative routes for development of the work?
- Do all researchers indicate how new opportunities to recognise and disseminate benefits may be identified and enhanced during and after the research?
- Do research programmes identify the potential to deliver wider benefits (for example, sharing good practices in the 3Rs, new data sharing opportunities)?
- Are proposals for gathering, archiving and providing access to research data adequate and appropriate?
- Do publication plans include the intention to publish all valid results from the study?
- Does animal research that involves known or likely societal concerns include the opportunity to engage broader social perspectives in and through this work? (see Chapter 5)

These questions have the capacity to enhance the review of benefits and ensure that benefits are more accurately and effectively weighed against harms. However, some uncertainty around benefits will always remain due to the temporal lag between the assessment and delivery of benefits and the fact that new areas of uncertainty also emerge as knowledge advances.

The ASC suggests that these enduring uncertainties should be acknowledged and used to enhance open and transparent debate about the practices and potential benefits of animal research. Opening up discussion around the anticipation of and evidence for benefits has the potential to contribute to ongoing reviews and improvements of HBA.

# CHAPTER 5

# UNDERSTANDING & INCORPORATING SOCIETAL CONCERNS

# 5. Understanding and Incorporating Societal Concerns

## 5.1. INTRODUCTION

In this final chapter, the Animals in Science Committee (ASC) considers how societal concerns, including around novel or contentious issues, should be factored into the HBA and given due weighting. This is important to ensure that the UK Animals (Scientific Procedures) Act 1986 (A(SP)A) is implemented as the public would expect. However, it is not known precisely which criteria are used to identify applications that warrant further scrutiny and how far expectations are being met. Greater openness is required with respect to these processes, with further consideration and initiatives as set out below.

ASRU does identify societal concerns through a range of mechanisms that are not specified in the HBA advice note (ASRU, 2015). All members of ASRU (including the inspectors) represent a cross-section of society. They may raise personal concerns, making judgements about current scientific research and emerging issues from science and welfare and decide whether to refer applications to the ASC (see Appendix C). It is down to ASRU inspectors to decide whether to undertake an internal or external referral in relation to individual project licence applications.

ASRU also meets stakeholders from animal protection groups and scientific societies on a regular, approximately quarterly, basis. This gives ASRU the opportunity to hear the wide range of views/concerns. Subgroups within ASRU also engage in horizon scanning procedures. In addition, independent members of Animal Welfare and Ethical Review Bodies (AWERBs) can provide a valuable perspective from outside the research facility, which can give expression to public concerns and attitudes, but this is not a formal representative role

There is thus scope for the different processes of HBA to learn from each other and from emerging research on understanding and incorporating societal concerns. That said, there are difficulties:

- social scientific work on animal research is methodologically diverse and distributed across disciplines; it is not always easily accessible and can be challenging to compare and evaluate
- societal concerns are often contextual, shifting over time and expressed differently in relation to different research contexts and forms of enquiries from learned societies, review bodies and the social sciences creating further problems in integrating data and drawing conclusions.

Despite these difficulties, as outlined earlier, this is a critical issue for both science and democracy and ongoing dialogue is essential. A range of approaches are required to facilitate exchange between the scientific community, the regulator, interest groups and concerned publics to understand the relationship of societal concerns to HBA.

## 5.2. SOCIETAL CONCERNS AROUND HARMS

The list of criteria that the Secretary of State uses to refer project licence applications to the ASC for advice under A(SP)A Section 9(1) (see Appendix C) focuses predominantly on harms. These criteria address a mix of concerns about:

- animal welfare
- conservation
- species with which humans have a 'special relationship' (either because they are viewed as companions or because of their cognitive capabilities and special requirements)
- novel, ethical, or societal concerns in general

Some of these are well defined and have been set out through legislative process (for example, the Directive 2010/63/EU 'safeguard clause' on the use great apes in scientific procedures) or public consultation (for example, animals containing human material (ACHM)).

Others are more general, open to definition and reflect concerns that go beyond suffering and severity.

It has been tacitly recognised by ASRU in the past that some procedures are of special concern because of the nature of harms they involve. This is borne out by a table, listing 'techniques of particular interest', that appeared in the annual Home Office Annual Statistics of Scientific Procedures on Living Animals until 2005. These were:

- interference with organs of special sense
- injection into brain
- interference with brain
- psychological stress
- aversive training
- radiation
- inhalation
- thermal injury
- physical trauma

Some of these categories relate to severity, although the severity will vary according to the way in which the procedures are conducted. The ASRU Internal Referral Policy Document (ASRU, 2015, Annex C) also lists some referral categories that relate to levels of severity, including:

- severe severity per se
- some toxicology tests
- the ascites method for producing monoclonal antibodies
- the use of strychnine in conscious animals

However, there is no mention of other sources of societal concerns that relate to the assessment of harms from proposed animal procedures.

There is a range of methods for engaging and understanding public views on animal research.

- There are regular large-scale surveys mapping broad trends in public opinion, via IPSOS/MORI in the UK (Clemence and Leaman, 2016) and the Eurobarometer in Europe (von Roten, 2013), enabling review of the different social and research characteristics that shape public concerns (Ormandy and Schuppli, 2014).
- There are detailed deliberative processes (for example, focus groups, citizen juries and consensus conferences) that can be used to explore the acceptability of certain harms and the desirability of certain benefits (for example, Einsiedel 2002; Macnaghten, 2004; see also Pound and Blaug, 2016).
- There are also hybrid analytic-deliberative approaches that take citizens through structured decision-making processes (for example, Deliberative Mapping, Burgess et al., 2007) or explore how the public make their own decisions about the HBA in animal research (Lund et al., 2014).

These differ in approach and outcomes, but there are common patterns across them that demonstrate:

- most social concerns about animal research are conditional upon the kinds of harms inflicted and the nature and delivery of benefits
- that people do have different views about the acceptability of different research species and procedures
- that there are a minority of people who maintain strong pro or anti animal research positions outside of these contexts

Moreover, qualitative research demonstrates that certain social processes recurrently shape societal concerns around animal research including:

- people's everyday experiences of nature and animals
- practices of personal and family caregiving (including pets)
- wider social relations of trust with science and medicine

Societal concerns can emerge from the value given to animal integrity and the fact that many people get profound enjoyment from animals and being in nature and enjoy seeing animals healthy and happy in return (Macnaghten, 2004). People may also have contradictory relationships to the animals used in research, as they care for both humans and animals in their personal lives, whilst having to rely on treatments developed through animal research to treat both. They may additionally have complex feelings about those carrying out and regulating animal research, whom they must trust to deliver safe and humanely produced medicine, often when they are most at need and lacking access to relevant information (Davies and Burgess, 2004) and even if they have strong personal views on animal research. There are thus tangible harms caused by high societal concerns around animal research, for individuals, for families and for the wider relationships around science, medicine and democracy.

What has been explored most extensively in the literature are challenges to the integrity of animals, especially in relation to suffering or genetic modification. The 1995 Banner Report of the Committee to Consider the Ethical Implications of Emerging Technologies in the Breeding of Farm Animals identify deep concerns about *"intrinsically objectionable"* harms that inflict very severe or lasting pain on the animals concerned, or involve an unacceptable violation of the integrity of a living being (Banner, 1995).

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For lay people, a perception that an animal's integrity has been violated may well influence their perception of what it is acceptable or justifiable to do for scientific purposes.

Examples of societal concerns that relate to violating the integrity of the animal include procedures that involve interfering with the brain or sense organs, or introducing human genetic material into brain or reproductive tissue. This issue was explored by the Academy of Medical Sciences (AMS) within its public dialogue on ACHM, which gathered people's views on 'naturalness', maintaining the integrity of human and animal species and their emotional responses to different types of experiment (AMS, 2011). The Nuffield Council on Bioethics has also run a project exploring what people mean by 'naturalness' (Nuffield Council on Bioethics, 2015).

Terms around naturalness and animal integrity are often translated into welfare concerns in the practical implementation of regulation. However, public consultations do reveal differences between expert expectations and lay views around the nature of these harms. The AMS reported that one concern people expressed related to human-like modification of an animal's external features. From purely scientific and animal welfare viewpoints, this need not be significant, but the public's view on this was respected when setting out the regulatory framework for ACHM. In research on xenotransplantation (Davies and Burgess, 2004), the public consulted were as concerned about the potential allocation of animal and human organs to those in need, in ways that reinforced existing lines of social inequality, as they were about the ethical issues in this proposed new use of animals. These processes illustrate how legislation and guidance can seek and respect majority public views, even when they overspill scientific understandings of the harms from animal research and blur the boundaries between concerns about animal integrity and human dignity.

There is a range of models for consulting the public about animal research, although conducting such engagement properly is resource-intensive. However, given that societal concerns about animal use have significant impacts on social experiences and wider social relations of trust, as well as being required under the A(SP)A, they do need to be researched, considered and respected.

## 5.3. SOCIETAL CONCERNS AROUND BENEFITS

Just as there are societal concerns relating to harms, some purposes and proposed benefits are also the subject of debate and controversy among the public. Research on societal concerns around benefits is more limited and tends to arise in relation to specific concerns around particular types of benefits.

Societal concerns around benefits include strong feelings about 'trivial' purposes, such as cosmetics and household products testing and 'socially harmful purposes', such as alcohol and tobacco development. These have led to the relevant bans on these specific uses of animals. These are widespread societal concerns and often still dominate public conversations and social imaginations around animal research, even with these bans in place.

The ASRU Internal Referral Policy Document (ASRU, 2015, Annex C) lists some referral categories that relate to controversial purposes, including exposing animals to tobacco smoke (as a pharmacological tool to induce diseases such as chronic obstructive pulmonary disease, not for product development) and the development or testing of weapons. These follow from prior policy bans, rather than explicit and ongoing consideration of societal concerns within the HBA.

In relation to animal research for health benefits, there are challenging questions emerging as changing societal views about personal health responsibility intersect with commercial incentives to increase markets for drugs. These concerns have often been shaped or channelled by campaigning groups, for example, the British Union for the Abolition of Vivisection (BUAV) argues against experiments to develop Viagra, whilst similarly, Animal Aid have campaigned about the growing numbers of mice used to test Botox, increasingly used for cosmetic purposes.

Some people have expressed views that animal use is not justified in research into other medical conditions such as addiction or obesity, because they see people affected as 'to blame' for their condition, although there are strong alternative views to this (Lund et al., 2013). Other concerns are expressed around the necessity for new pharmaceuticals, or other products, in areas where there are already many compounds that work in very similar ways and the 'need' for knowledge for its own sake, where this involves causing significant animal suffering.

Other more 'expert' public, patient and health practitioner debate concerns about animal experiments with proposed benefits for serious human mental health and welfare problems such as addiction, anxiety, depression and obsessive-compulsive disorder are based on validity and translatability (for example, Garner, 2014). These are controversial issues, with some feeling strongly that better animal 'models' are essential to help to address the relative lack of new pharmaceutical treatments in the pipeline, whereas others believe that there should be wider debate as to whether there should be more effort and investment made into ethically conducted social experiments, policy change, or non-pharmaceutical measures (Kuyken et al., 2015; Alderman et al., 2016).

Given the diversity of potential benefits, public perspectives and methods of engaging the public, there will never be a single societal view on the benefits of animal research. However, as new areas of research increasingly blur the boundaries between societal and medical problems and increase the level of engagement which patients and publics have with animal research, there is a pressing need for more regular engagement with a diversity of societal views around the appropriate benefits of animal research.

As new areas of research increasingly blur the boundaries between societal and medical problems and increase the level of engagement which patients and publics have with animal research, there is a pressing need for more regular engagement with a diversity of societal views around the appropriate benefits of animal research.

## 5.4. CONCLUSIONS

Attitudes to harm from the use of animals in scientific procedures change over time. This can and has, led to changes to legislation and regulatory requirements in the public interest, such as change to legislation in relation to the use of great apes.

There are benefits from engaging societal concerns in terms of the legitimacy and accountability of legislation; there are also clear harms in not engaging with genuine public concerns about animal integrity, human dignity and institutional responsibility.

There are benefits from engaging societal concerns in terms of the legitimacy and accountability of legislation; there are also clear harms in not engaging with genuine public concerns about animal integrity, human dignity and institutional responsibility.

At present, societal concerns relevant to harms and benefits (along with important ethical concerns and novel or contentious issues) are not well defined. In addition, there is no clear mechanism for ensuring that the diversity of relevant issues is identified and given due scrutiny within the project evaluation and HBA processes.

If and when societal concerns are identified, they should clearly be placed in the 'harm' side of the HBA and given due weighting. It should be the case that a project that was relatively mild, but raised significant societal concerns with respect to benefit, would not pass through the system without considerable scrutiny, with the potential for it not to be licenced.

One way to help to ensure that applications that include novel or contentious elements, or that raise important ethical or societal concerns, do not slip through the net would be to develop guidance for AWERBs. This guidance would enable them to:

- successfully identify such applications
- apply more stringent local review
- if they judge that the project can be justified, to flag up any concerns to their inspector

The inspector could then seek additional advice, up to and including consulting the ASC.

The ASC recognises the challenges here, in that processes are not clearly articulated and evidence is difficult to review systematically. The ASC thus suggests that a starting point for this work is the identification of existing mechanisms for identifying societal concerns and further discussion on their use and effectiveness by a range of bodies involved in HBA.

### Recommendation 24

ASRU currently identifies societal issues through personal concerns, knowledge of current debates in science and welfare, stakeholder engagement and horizon scanning. The specific focus of societal concerns will inevitably change over time. Reviewing and publishing the working criteria used to identify issues as 'societal concerns', 'ethical concerns' and 'novel or contentious issues' within and across these processes would enhance transparency and responsiveness.

### Recommendation 25

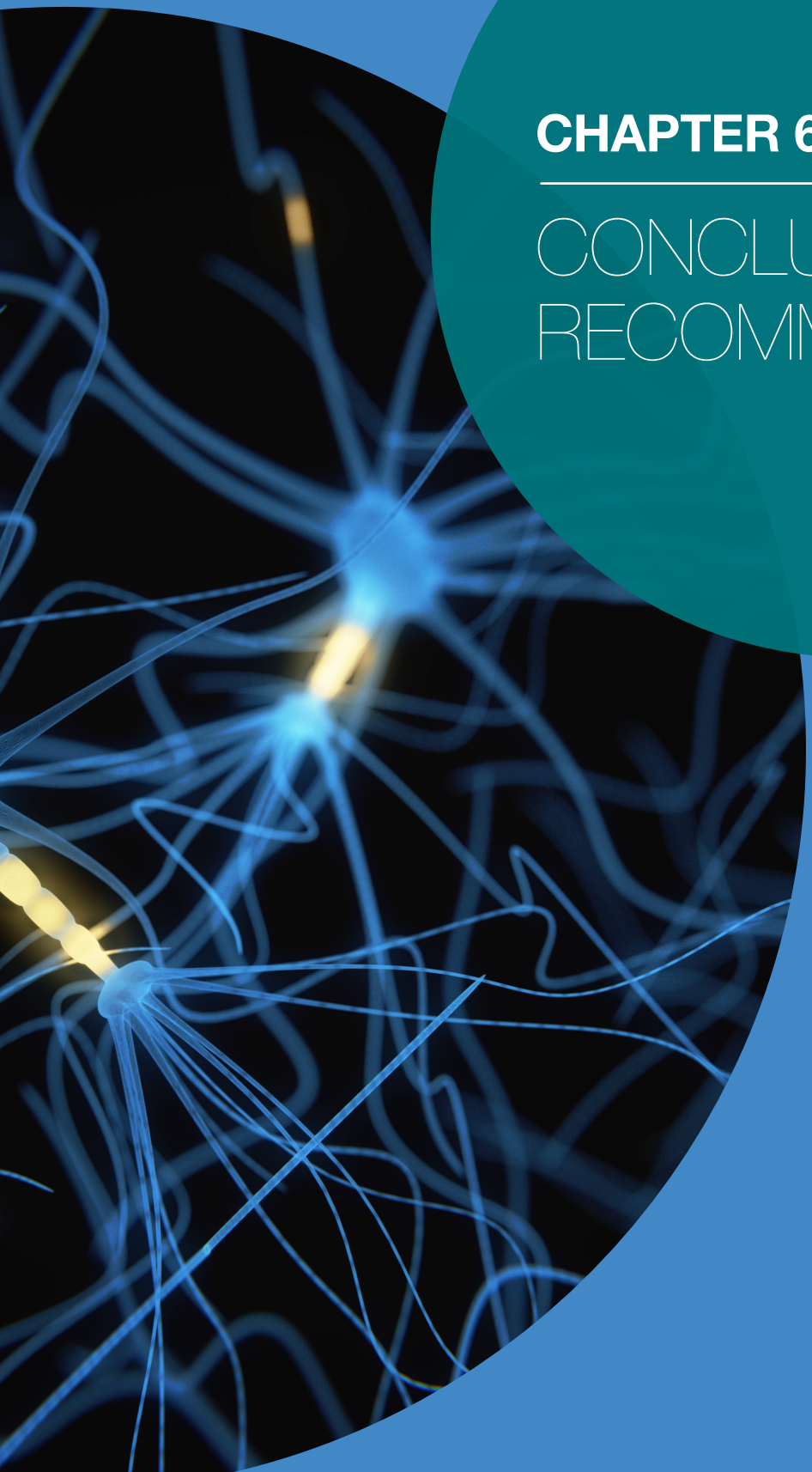
AWERBs and particularly lay members, also have responsibility for identifying and addressing societal concerns. Building on the ASRU experience, there is scope to review the guidance produced for AWERBs to help them to identify and deal with applications that include elements that are novel or contentious, or that raise important ethical or societal concerns.

### Recommendation 26

The ASC could usefully review the range of reports and mechanisms available to identify societal concerns, for example, via AWERB hubs, the NC3Rs, the Royal Society for the Prevention of Cruelty to Animals (RSPCA) and other ethical review bodies. This could be used to develop shared understandings of what constitutes a societal concern, identify existing public engagement and social scientific resources to understand these concerns and support HBA in better reflecting shifts in prevailing opinions and attitudes.

### Recommendation 27

There have been a range of public consultations on specific issues involving animal research (for example, ACHM, household testing) and there are regular public surveys through standardised questionnaires (for example, IPSOS/MORI). However, there is scope to supplement these with additional research or stakeholder dialogue on the mechanisms through which the public and interest groups would themselves identify and seek to have societal concerns heard in the HBA process (to be sponsored for example, via learned societies, science policy groups, or funded social science research).



# CHAPTER 6

# CONCLUSIONS & RECOMMENDATIONS

# 6. Conclusions and Recommendations

The report concludes by assembling the recommendations distributed throughout the text on how harm-benefit analysis (HBA) may be improved now and into the future. Some of these recommendations represent current (as at August 2017) good practice already in use by some involved in HBA; others present opportunities to reflect on and improve existing practice.

These recommendations comprise a mix of proposals including:

- those that may be easily achieved through changes of practice in the short term
- those that depend on exchange and learning across the different bodies involved in HBA and will deliver in the medium term and
- those that are longer term aspirations

The ASC has sought to identify potential targets for these recommendations below. Given that a central aim of this document is to encourage mutual learning across all the organisations and individuals involved in HBA, the ASC invites others to contribute and explore how these recommendations can be aligned with their ongoing aspirations and initiatives, for example, around improving experimental design, enhancing reporting in animal research and ending severe suffering.

## 6.1. ASSESSING HARMS EXPERIENCED BY ANIMALS

Recommendation 1: Data on animal welfare, including cumulative suffering, should be systematically collected in a format that allows comparison with other studies of a similar nature. Ideally, common reporting standards should be developed to facilitate such comparisons, for example, through publication, data repositories and the AWERB hubs.

Recommendation 2: Realistic estimation of the harms likely to be experienced by individual animals undergoing licenced procedures is critical throughout the different processes of HBA. Harms arising from all sources (not just procedures, as it is not significant to animals where the harms come from) should be taken into account by researchers, reflected on by AWERBs as part of their responsibilities for the application of the 3Rs and considered in the HBA.

Recommendation 3: Scientists should accept their responsibilities to research and obtain expert advice on factors affecting the welfare of their study species, recognising the impact on science as well as animal welfare. Wherever possible the HBA should be based on recent scientific evidence regarding harms. Where these data are not available, efforts should be made to obtain data through sharing across organisations, for example, via AWERB hubs and identifying priorities and funding for future research, for example, via the NC3Rs.

Recommendation 4: Retrospective severity assessments should be used by researchers, AWERBs and the Animals in Science Regulation Unit (ASRU) to inform HBAs for future applications that employ the same or similar procedures. Information gleaned from these assessments should offer opportunities for establishment AWERBs to reflect on their own retrospective severity data and to highlight areas for refinement to reduce suffering, whether it be mild, moderate, or severe.

## 6.2. ASSESSING CUMULATIVE SUFFERING

Recommendation 5: Consideration should be given by researchers, establishments and the regulator to the harms experienced over the whole lifetime experience of the animal, recognising the risks of considering the animal's experiences in isolation and being aware of all potential sources of harm.

Recommendation 6: Consideration of cumulative effects should be used by establishments to provide a focus for increasing the animal's positive experiences. Any assumptions about an animal's ability to habituate to procedures, or conversely to become sensitised, should be critically scrutinised, by researchers, AWERBs and regulator. Suggestions that an animal habituates should be verified with empirical, objective evidence.

Recommendation 7: Funders, including the NC3Rs, should consider further funding research into behavioural and physiological indicators of cumulative severity and into assessing the affective states of animals in research. Researchers should explore if this can be done by obtaining valid data from animals already undergoing regulated procedures, to avoid causing additional harms.

Recommendation 8: AWERBs should be encouraged to engage with new research tools for recognising and recording cumulative severity. These could be used to assist and develop the HBA by advising the establishment licence holder whether to support project proposals, following the development and outcome (retrospective review) of projects and providing a forum for discussion and development of ethical advice, including via AWERB hubs.

## 6.3. STRATEGIES TO MINIMISE SEVERE SUFFERING

Recommendation 9: Researchers and AWERBs involved in developing and/or reviewing project licence applications prior to submission should always provide a robust, constructive challenge to the scientific need and the ethical justification for using a severe model or procedure. Support for this might be provided through additional components in existing training for AWERB members and exchange via AWERB hubs.

Recommendation 10: Projects that may cause severe suffering should be given intensive scrutiny at every stage of their design, in the ethical review process and in subsequent reporting and publishing. This should not only include scrutiny by the researchers involved, the AWERB, the Home Office inspector and in some cases the ASC – but also, where relevant, funding bodies and journal editors who publish research involving animals.

Recommendation 11: Finding new ways of working to avoid and eliminate severe suffering is a challenge in which every establishment and its AWERB should participate. As projects progress and at their conclusion, feedback on successful refinements and ongoing concerns should be provided to all those within and across establishments (for example, via AWERBs and AWERB hubs) who have been involved in addressing severe suffering. The Royal Society for the Prevention of Cruelty to Animals (RSPCA) Road Map offers a systematic approach and opportunity to address questions in the broader research community, such as whether severe procedures currently in use are necessary and whether and by how much a 'ban' on severe suffering would impact on research and testing.

Recommendation 12: It is important that researchers, establishments, AWERBs and inspectors all understand that each category of severity includes a range of adverse effects and that the moderate category includes a particularly wide range of procedures, some of which other people might regard as severe. Severity categories alone are blunt instruments for HBA and at all times the likely and actual experiences of the animals should be used as the measure of harms in the ethical weighing process. There is a legal requirement for the project licence holder to notify the Secretary of State if the severity limits or other controls are, or are likely to be, breached. When approaching the upper limit of any severity classification, there should be particular scrutiny by researchers and establishments of the duration of suffering, as long-lasting moderate suffering can cross from moderate into severe and similarly, long-lasting mild suffering can become moderate.

Recommendation 13: Applicants and AWERBs play a key role in driving and implementing change and should seek opportunities to improve. ASRU already provides feedback to the licence applicant following decisions on project licences. There should additionally be feedback to and when necessary review by, AWERBs when an inspector, or the ASC, identifies ethical or welfare concerns that the AWERB and the applicant have not identified and sought to address.

## 6.4. ENHANCING THE EVALUATION AND REALISATION OF BENEFITS

Recommendation 14: Researchers and AWERBs should support the rigour, transparency and legitimacy of HBA by ensuring that research objectives and project milestones for realising research benefits are realistic, clear and accountable in advance. These should be reviewed over the lifetime of project licences and opportunities sought to enhance benefits. These processes may be facilitated by sharing checklists developed by local AWERBs and using other appropriate decision support tools.

Recommendation 15: Whilst targeted checklists and project-specific milestones may be valuable for evaluating the likelihood of success for the HBA, key information on animal research is often missing from highly ranked journals. This suggests that journal impact factors should not be used as a proxy for quality criteria around the likelihood of success when assessing individual project licence applications.

Recommendation 16: Not all benefits can be anticipated in advance, but the potential for realising unforeseen and additional benefits can be enhanced. Researchers and establishments should be encouraged to be responsive to opportunities to enhance emerging benefits (for example, through cross-project and AWERB hub collaborations) and should implement the most appropriate proposals for curating, archiving and providing access to their research data, to inform and enhance long-term benefits.

Recommendation 17: An explanation of the potential benefits of animal research in the project licence is justified through locating the research in the current relevant field and knowledge. As techniques become more refined and widely available, researchers are encouraged to supplement these with relevant reference to tools for systematic review and meta-analysis.

Recommendation 18: Researchers should strive to publish all the valid data that have resulted from animal research in an appropriate and accessible format, whether or not they support the original hypothesis.

Recommendation 19: Researchers, establishments, AWERBs, funders and regulators should work to support researchers in meeting current quality criteria for experimental design and reporting relevant to their disciplinary area. This should include facilitating informed discussions around methods for selecting appropriate sample size, mitigating bias, incorporating randomisation and the blinding of outcomes.

Recommendation 20: Assessment of the benefits from translational research would be enhanced by researchers defining measurable translational research objectives. These should operate within the scope of the specific project and provide evidence of their ability to access appropriate pathways to translation in that area (for example, via clinical collaborations, data exchange, publishing plans, policy engagement and commercial partnerships).

Recommendation 21: Researchers, AWERBs and ASRU inspectors are encouraged to search the publicly accessible REF impact case studies for past examples in fields related to new applications in translational research. The current case studies have limitations, but do provide an overview of translational pathways in different fields. As data returned improve and new techniques for interrogating the case studies provide enhanced responses to queries, this database will increase its potential to inform the HBA process.

Recommendation 22: Future Higher Education Funding Council for England evaluations of research impact should include a mandatory and consistent reporting framework for animal use, commensurate with its status as research that requires a special 'social' licence to operate. This would enable better analysis of the impacts of research using animals and help regulators to improve future HBAs for animal research

Recommendation 23: Local AWERBs of establishments engaged in regulatory toxicology testing should ensure that their mechanisms for weighing harms and benefits consider the context of the types and utility of substances/products being tested, the opportunities for data sharing and the contribution to ongoing HBA review in this area of work.

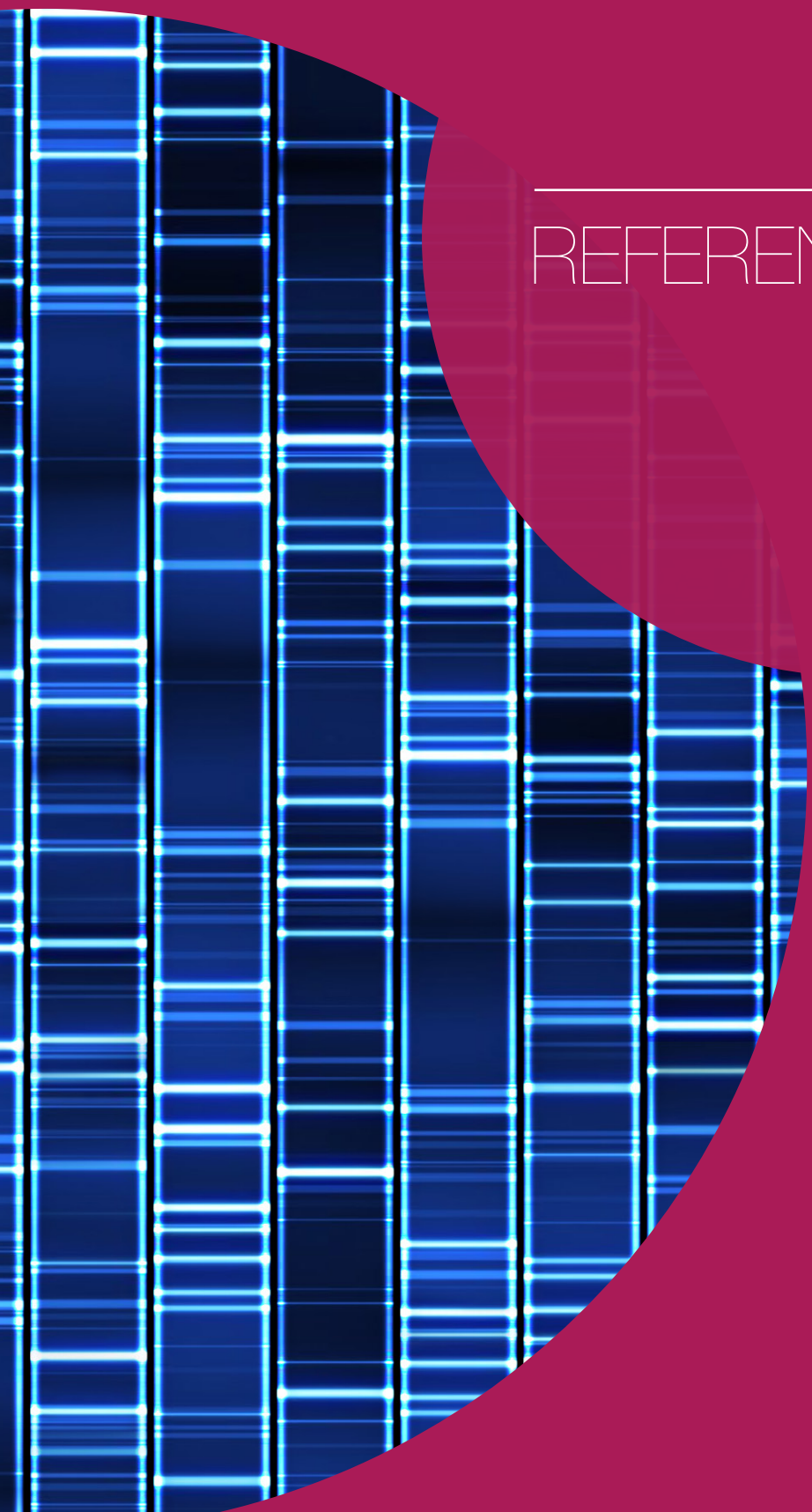
## 6.5. INCORPORATING SOCIETAL CONCERNS

Recommendation 24: ASRU currently identifies societal issues through personal concerns, knowledge of current debates in science and welfare, stakeholder engagement and horizon scanning. The specific focus of societal concerns will inevitably change over time. Reviewing and publishing the working criteria used to identify issues as 'societal concerns', 'ethical concerns' and 'novel or contentious issues' within and across these processes would enhance transparency and responsiveness.

Recommendation 25: AWERBs and particularly lay members, also have responsibility for identifying and addressing societal concerns. Building on the ASRU experience, there is scope to review the guidance produced for AWERBs to help them to identify and deal with applications that include elements that are novel or contentious, or that raise important ethical or societal concerns.

Recommendation 26: The ASC could usefully review the range of reports and mechanisms available to identify societal concerns, for example, via AWERB hubs, the NC3Rs, the RSPCA and other ethical review bodies. This could be used to develop shared understandings of what constitutes a societal concern, identify existing public engagement and social scientific resources to understand these concerns and support HBA in better reflecting shifts in prevailing opinions and attitudes.

Recommendation 27: There have been a range of public consultations on specific issues involving animal research and there are regular public surveys through standardised questionnaires. However, there is scope to supplement these with additional research or stakeholder dialogue on the mechanisms through which the public and interest groups would themselves identify and seek to have societal concerns heard in the HBA process (to be sponsored for example, via learned societies, science policy groups, or funded social science research).



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# Appendix A: Commissioning Letter

Home Office

Norman Baker MP
Minister for Crime Prevention
2 Marsham Street London SW1P 4DF

www.homeoffice.gov.uk

Dr John Landers
Animals in Science Committee Secretariat
2 Marsham Street
London
SW1P 4DF

11 August 2014

Dear Dr Landers

Animals in Science Committee – annual commission

I am writing to you to provide the Animals in Science Committee with a second annual commission of work. I would like to take this opportunity to thank you and your colleagues for your achievements to date.

An important piece of work to which the Committee contributed this year was the publication of the Working Protocol between the Home Secretary and the Committee. The document supports the provision and receipt of advice and places your independent scientific advice on a firm footing in the Home Office. In addition, the Committee recently provided its advice on lessons to be learnt from reviews and investigations into non-compliance. This was an important review and I was pleased to accept all of the recommendations the Committee made.

I understand that the Committee proposes to provide reports on its activities on an annual calendar basis. Therefore this commission is for the next 18 months to the end of 2015. My commissions for the period are as follows.

**Harm-benefit analysis**

The harm-benefit analysis is a cornerstone of our scrutiny process and guides our decision making. I am committed to reviewing the analysis that we conduct on all project licence applications. I believe it is essential the analysis continues to be robust so we can, with confidence, authorise only that work using animals that has a favourable balance of benefit. I therefore include four pieces of work under this theme:

I have asked the Animals in Science Regulation Unit to perform a review of the way in which the harm-benefit analysis is currently conducted and to prepare a report and guidance which makes this process much more transparent. I expect to publish this report in February 2015 and I therefore request the Committee to provide advice to ASRU by January 2015 to support this review.

I have recently received the Committee's consideration of the Animal Procedures Committee's report on cumulative severity. The report considered the potential lifetime experience of an animal and provided recommendations. I will provide a response to the advice shortly. There may, therefore, be further work in consideration of cumulative severity as part of a wider review of the harm-benefit test.

Building upon the ASRU report mentioned above and your further consideration of cumulative severity, I request that the Committee review the current arrangements for performing a harm-benefit analysis. The request is three-fold:

- Advice on current arrangements for performing a harm-benefit analysis and consideration of whether this might be improved,
- Advice that particularly considers the most severe procedures and, relevant to particular types or values of benefit, assists in determining where the level of harm lies above which we should not grant licences and
- Advice that reflects on the current process of licence referral (which enables the Committee to perform a harm-benefit analysis) and considers how the Committee can maximise the effectiveness of its expert scrutiny of such licence applications in a strategic way.

In the meantime, pending completion of the reviews above, a key element of the Committee's work should continue to be the scrutiny and consideration of project licence applications through the current referral process.

I also commission the Committee to provide advice on the following thematic areas.

### Section 24

The Home Office has recently completed a public consultation on the review of Section 24 of the Animals (Scientific Procedures) Act. Officials will provide the Committee with analysis of the responses arising from the public consultation for the Committee's comment. I would like the Committee to complete its review by 19 August so that I may make a public statement about our way forward on our commitment to openness and transparency.

### Household Products

The Coalition has made a commitment to ban the testing of household products on animals. I will be proposing a solution which would also effectively end the testing of ingredients primarily intended for use in such products unless a strongly justified case can be made for the need to test such an ingredient. I will seek the Committee's advice in the autumn on my preferred policy options with a view to implementing the ban by February 2015.

### Code of Practice

I intend to publish by Christmas this year a revised version of the Animals (Scientific Procedures) Act Code of Practice for the care and accommodation of protected animals. Officials will provide the Committee with a final draft version for consideration so that I can lay it before Parliament in December.

### Over-breeding

The Home Office will be reviewing the rationale for high numbers of genetically altered animals bred. With advice from the Committee, I would like to identify steps that can be taken to drive down figures for genetically altered breeding for publication in February 2015.

### Other functions

The Committee has a responsibility to engage with Animal Welfare and Ethical Review Bodies. I look forward to hearing how the Committee will be taking forward this agenda.

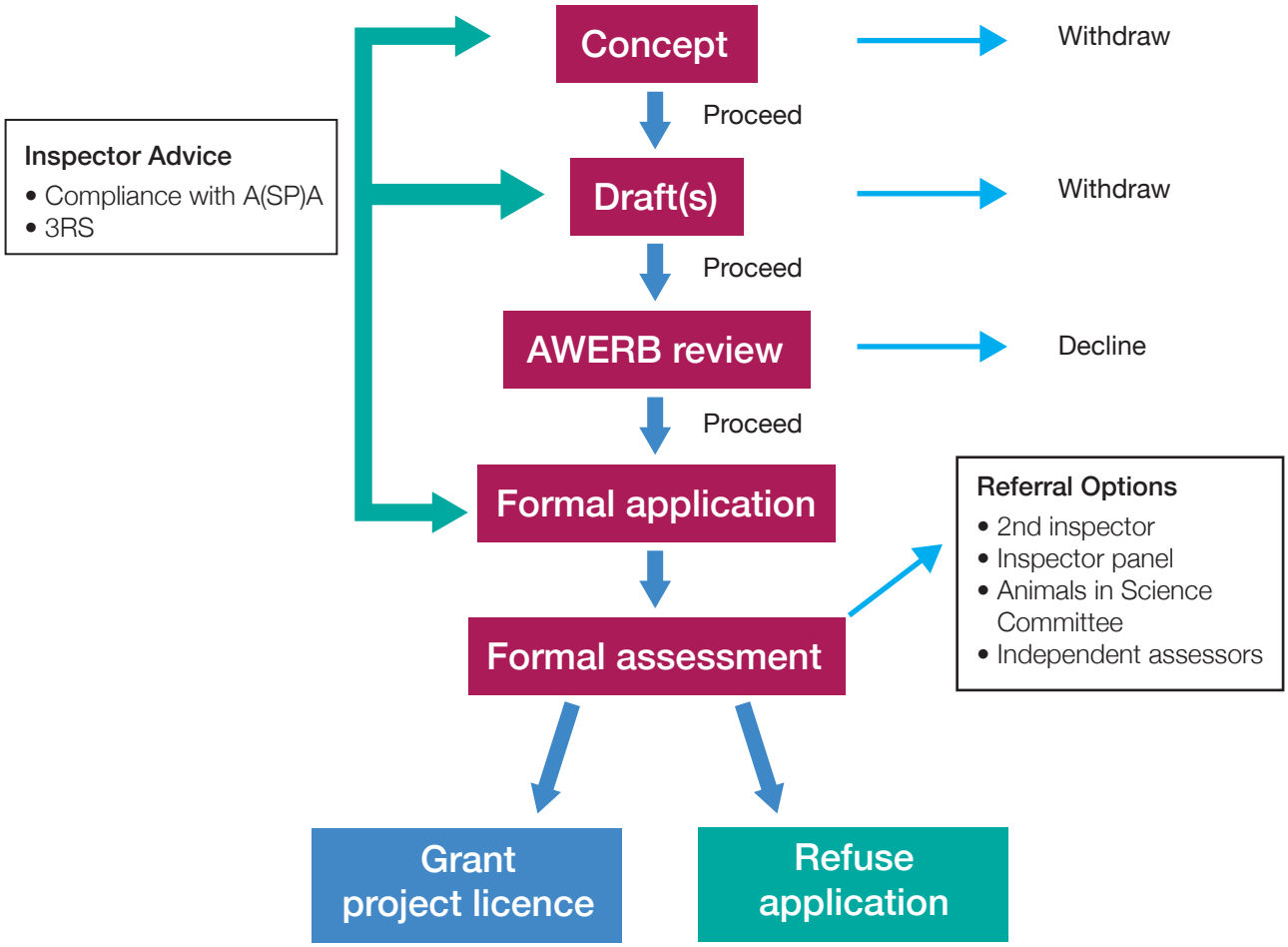
Yours sincerely

Norman Baker

**Norman Baker MP Minister of State**

# Appendix B: Animals in Science Regulation Unit Overview of the Application Process

## Overview of the Application Process



# Appendix C:Referral Processes in the Animals in Science Regulation Unit Advice Note

The following text is reproduced from pages 12-13 of the Advice note 05/2015: The Harm-Benefit Analysis [HBA] Process – New Project Licence Applications (ASRU, 2015)

Referral.

Where applications raise issues requiring more detailed consideration (e.g. high severity work or other matters of particular public concern), additional advice may be sought either by the Inspector or by the SoS [Secretary of State]. Applications may be referred within the Inspectorate, to officials or Ministers, to independent assessors, or to the ASC [Animals in Science Committee].

viii. Internal referral within the Inspectorate. An application may be referred to a second Inspector or panel of Inspectors if specific expertise is required on an aspect of the application, or if the application falls into certain categories. This process is covered by an internal policy document (see Annex C). Such referrals can be mandatory or recommended. They either focus on a particular aspect of the application (e.g. a protocol that has been classified as severe) or relate to the whole application

ix. Independent assessor. Advice from an independent assessor may be sought by the SoS when the issues raised require specific, expert knowledge not available within ASRU-I [Animals in Science Regulation Unit Inspectorate], or when there is debate within the scientific or welfare communities, or between the Inspectorate and the applicant about:

- the scientific validity of the proposed hypothesis(es) to be tested
- the scientific validity of the proposed methodology
- the scope for further application of the 3Rs [replacement, refinement and reduction of the use of animals in research]
- the likely benefits arising from the programme of work
- the likely harms to animals
- the choice of species (e.g. is the use of a specially protected species essential?).

Independent assessors are typically active researchers with relevant expertise. They can be drawn from the international research community, or may be UK-based. When the SoS intends to consult an independent assessor the applicant is notified, in accordance with Section 9(2) of A(SP)A [the Animals (Scientific Procedures) Act 1986] and the SoS will take account of the applicant's views regarding the choice of independent assessor. The applicant is usually told the identity of the independent assessor and the questions they have been asked to address. The applicant may also be given the opportunity to read the independent assessor's report. The report may also be made available to the ASC. The assessor's advice will be taken into account in the SoS's decision, but is not binding.

ASC. There are a number of criteria that require PPL applications to be referred to the ASC:

- the use of wild-caught non-human primates (NHPs)
- the use of cats, dogs, Equidae or NHPs in severe protocols
- use of endangered species
- projects with major animal welfare or ethical implications
- projects involving the use of admixed embryos falling into Category 3 of the Academy of Medical Sciences (AMS) report on animals containing human material (ACHM) and Category 2 where the predominance of the admixed embryo is unclear or uncertain
- projects which may invoke any of the 'safeguard clauses' in European Directive 2010/63/EU with respect to the purpose of NHP use, proposals for the use of a great ape or proposals to cause long-lasting pain, suffering, or distress that cannot be ameliorated
- projects of any kind raising novel or contentious issues, or giving rise to societal concerns.

The applicant is always invited to attend the ASC meeting at which the project is considered and is given the opportunity to make a presentation about the application. They are also questioned by the Committee. The assigned Inspector also attends in order to provide any technical advice that the Committee might require. Other Inspectors may also attend. The Committee may recommend to the SoS that a PPL be granted (with or without further changes or additional conditions) or that the application be refused. Where appropriate, the assigned Inspector discusses the points raised by the Committee with the applicant and, if necessary, a final version is produced.

# Appendix D: Analysing the Research Excellence Framework Impact Case Studies

For the 2014 Research Excellence Framework (REF), higher education institutions submitted a specified number of impact case studies. These followed a four-page template, recording the impact of research carried out by researchers at that institutions in the 20 years prior to the REF submission date.
The template included free text sections for:

- a summary of the impact
- an explanation of the underpinning research
- references
- the nature of the impact and supporting evidence

The impact case studies were submitted to expert review panels for assessment on a four-star scale, ranging from 4* research rated outstanding impacts in terms of their reach and significance to 1* research impact rated as having only modest impacts in terms of their reach and significance.

Full information on the REF assessment methodology is available at: *http://www.ref.ac.uk/pubs/2011-02/* (last accessed 22/08/2017). The searchable database of submitted impact case studies is available at: *http://impact.ref.ac.uk/CaseStudies/* (last accessed 22/08/2017).

The searchable database contains 6,637 studies. The template did not require any information to be returned around the use of animals under the Animals (Scientific Procedures) Act 1986 (A(SP)A). The first stage of research was to identify these studies. The database was interrogated for species covered under A(SP)A, using searches to identify case studies reporting on the use of birds, fish, amphibians, mammals, primates and farm animals and individual species including mice, rats, rabbits, guinea pigs, hamsters, dogs, cats, horse, mini-pigs, macaques, marmosets, tamarins and cephalopods.

Given certain species names also appeared in the text as personal or institutional names, or in other descriptions of research, the searches were limited to submissions to Main Panel A, which includes units of assessments for:

- clinical medicine
- public health, health services and primary care
- allied health professions, dentistry, nursing and pharmacy
- psychology, psychiatry and neuroscience
- biological sciences
- agriculture, veterinary and food science

Submissions to Panel A represented 24% of all case studies. This generated a dataset of 362 studies to consider. The selection was further reduced through manually checking to exclude research that was likely to have taken place outside of A(SP)A, removing many observational, veterinary, agricultural and overseas studies. Given the limited resources for this analysis, studies were excluded unless they were clearly covered by A(SP)A. The final set of 134 studies was summarised in a spreadsheet incorporating information on higher education institution, unit of assessment, named researchers, case study title, species used, type and routes to impact.

There are limitations in this use of retrospective REF data to inform the prospective evaluation of benefits. The assessment exercise only covers higher education institutions. Some studies were redacted from the searchable dataset: 296 were wholly redacted and a further 428 case studies were partially redacted. Studies involving research on animals may have been held back for national, institutional, or personal security reasons.

The REF2014 case studies were selected by institutions based on projects best able to fulfil the reporting requirements and assessment criteria for measuring research impact. The dataset is thus self-selected from the portfolio of ongoing research at any institution.

The grades awarded to individual impact case studies are not published, so assessments of quality are extrapolated from institutional evaluations. A proxy of quality for the case study was constructed by using the percentage of impact rated as over 3* for the submission of that institution to the relevant unit of assessment (see, for example, the impact profile for Unit of Assessment 1: *http://results.ref.ac.uk/Results/ByUoa/1/Impact, last accessed 22/08/2017).*

The most significant challenge for this review is that the impact case studies focus on explaining the nature of research impact, rather than detailing underpinning research. Many studies report limited details of the procedures on animals. Some case studies provide information on species, disease model, location of research, funding and timescale in development; but in a few studies, there was only reference to a prior 'animal model'. Further information is available via original research articles, but even here reporting is often partial, with a lack of published information on the animals, location and procedures used in research making it difficult to evaluate whether the original work was regulated under A(SP)A. Given these limitations this analysis focused on a qualitative, rather than quantitative, description of REF2014 impact case studies. More resources, including text mining techniques, would allow a fuller numerical description of these data in future. A recommendation for the future REF is that animal research data should be more fully recorded.

For this research, the REF case studies were then organised into six categories, identifying indicative pathways to impact. These are described in the main text (see Section 4.3.4). Case studies within the six categories were sampled to extract information about the processes involved in generating impact from animal studies, which may aid the prospective evaluation of benefits. Sampling was both:

- random – including a selection within each category
- purposeful – in sampling case studies with the most and least confident assessments of impact quality and studies involving animals in severe procedures, for which high benefits would be expected to achieve a positive harm-benefit analysis

The search of impact case studies includes the ability to 'view similar case studies', which was used to inform both the categorisation of case studies and the assessment of different the pathways to impact.