The ASC
Animals in Science Committee

**Animals in Science Committee**

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

## Summary of recommendations for
## Animal Welfare Ethical Review Bodies (AWERBS)

**December 2020**

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## Background

Harm Benefit Analysis (HBA) of the use of animals in research and testing involves predicting and assessing the harms experienced by experimental animals and the weighing of those harms against the likely benefits of the research. Those benefits must be deemed to be sufficiently important to justify the harms.

The Animals in Science Committee (ASC) carried out a review of HBA of the use of animals in research and testing, which was published in 2017[1]. The review specifies and explains twenty-seven recommendations, all of which aim to strengthen the HBA process and to encourage its further development in response to changes in societal concerns. The intention of this summary is to highlight the recommendations in the HBA review that Animal Welfare Ethical Review Bodies (AWERBs) are in a position to support and to offer some suggestions on how that can be achieved.

The formal HBA is the responsibility of the Home Office (Animals in Science Regulation Unit (ASRU)). However, AWERBs will have processes in place for assessing the benefits of research and the harms to animals, which will take local factors into account. This means that, when deciding how to advise the Establishment Licence holder on whether or not to endorse a project licence application, AWERBs will carry out their own provisional HBA assessment to some extent. This links to one of the AWERB tasks, which is to: '*Advise the establishment licence holder whether to support project proposals, primarily considering such proposals from a local perspective and bringing local knowledge and local expertise to bear'*. With that in mind, the key steps in the process are illustrated in Figure 1.

Many of the recommendations in the HBA review could be helpful when AWERBs are assessing the harms and benefits of a project, as well as in delivering the tasks of an AWERB laid out in the Guidance to the Operation of the Animals (Scientific Procedures) Act[2]. These are summarised in here, in the following five sections:

1. Assessing harms experienced by animals
2. Monitoring and minimising harms experienced by animals
3. Assessing benefits of the programme of research
4. Weighing harms versus benefits
5. Societal concerns

One aim of the HBA review (2017) was to connect the operation of an established ethical framework with both research on harms and the refinement of processes for evaluating research impact and accountability, as they evolve. This guidance is intended to encourage AWERBs to consider how they can achieve that objective through their reflections on the project application processes and also through regional discussions via AWERB hubs[3], the National Centre for the 3Rs (NC3Rs)[4,5] Laboratory Animal Science Association (LASA)[6], the Royal Society for the Prevention of Cruelty to Animals (RSPCA)[7] and the online AWERB knowledge hub[8]

1 https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/675002/Review_of_harm_benefit_analysis_in_use_of_animals_18Jan18.pdf

2 https://www.gov.uk/guidance/guidance-on-the-operation-of-the-animals-scientific-procedures-act-1986

3 https://www.gov.uk/government/publications/awerb-hub-support-note

4 National Centre for the 3Rs [https://www.nc3rs.org.uk/]

5 https://nc3rs.org.uk/sites/default/files/documents/Tech3Rs/NC3Rs%20Tech3Rs%20newsletter%20-%20Issue%208%20%28August%202020%29.pdf

6 http://www.lasa.co.uk/PDF/AWERB_Guiding_Principles_2015_final.pdf

7 https://science.rspca.org.uk/sciencegroup/researchanimals/ethicalreview

8 AWERB Knowledge Hub [https://www.khub.net/ ]

# 1. Assessing harms experienced by animals

It is unavoidable that all assessments of the severity of a programme of research will be mere estimates. This is especially the case when considering all the harms that are likely to accrue over the lifetime of the animal (overall 'cumulative severity'). These harms will include everyday welfare issues - not merely the experimental procedures. However, AWERBs bring a broad range of expertise and perspectives to the process. This diversity is invaluable when deciding whether or not the estimation of the severity of harms is realistic.

It is also inevitable that the range of opinions of AWERB members, as well as relevant local factors, will differ both within and between establishments. Nevertheless, a realistic estimate of the harms that are likely to be experienced by the animals is essential to ensure that AWERBs can justify their final decision on the HBA **[2]**[9].

To help AWERBs achieve that, some steps that could be incorporated into their appraisal of project licence (PPL) applications are:

- To offer a constructive challenge to the rationale for the proposed research project, including its scientific validity and rigour **[9].**
- To consider the HBA in terms of both actual and potential sources of harm. These would include not only direct ('project-related') harms, arising from the scientific procedures and the euthanasia, but also contingent harms such as handling, transport, husbandry and care issues. The assessment of cumulative harm is particularly challenging in this respect. However, an important factor to consider is whether or not the severity is likely to increase over time to the extent that the overall assessment could change to a higher severity band.

  Sources of information that can help with this process include: *the Expert Working Group report on Severity Classification of Scientific Procedures Performed on Animals*[10]; *The Assessment of Cumulative Severity and Lifetime Experience of Non-Human Primates used in Neuroscience Research*[11] and the *FELASA / ECLAM / ESLAV Working Group report on the Classification and Reporting of Severity Experienced by Animals used in Scientific Procedures*[12] **[5 & 12]**.
- Discussion of the impact of the scientific procedures in conjunction with any event, or series of events, that the animal is likely to experience, especially if the harms could approach the upper limit of any category of severity. This is because each category includes a range of adverse effects. The moderate category includes a particularly wide range of harms, which some people might regard as severe. Moreover, long-lasting moderate suffering can cross from moderate to severe and, similarly, long-lasting mild suffering can become moderate **[12]**.
- Appraisal of any claim that severe suffering is unavoidable and to be satisfied that this severity is justified by the objectives of the study and the likelihood of achieving them. This is not least because, when deciding that the severity of a specific procedure and/or overall programme of research is justified, the AWERB is also agreeing that the severity is ethically acceptable.

[9] numbers in square brackets […] refer to the recommendation in the HBA review
[10] https://ec.europa.eu/environment/chemicals/lab_animals/pdf/report_ewg.pdf
[11] https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/261687/cs_nhp_review_FINAL_2013_corrected.pdf
[12] Smith et al., (2018) Laboratory Animals 52[1S]: 5-57. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5987990/

- Consideration of any interventions that are intended to minimise any adverse effects. In this context, AWERBs should bear in mind that it is widely assumed that animals habituate to repeated experience of a procedure (i.e., the severity declines, progressively). However, there is rarely (if ever) any evidence to confirm that habituation actually develops. It is possible that the animals become sensitized instead (i.e., the severity increases, progressively). Unless there is convincing evidence for habituation, the animals should be given the benefit of any doubt when assessing potential cumulative harms [**6**].
- Consideration of the possibility that species-differences can affect animals' vulnerability to experience harm, which could affect the severity of the procedure. This is important because the Animals (Scientific Procedures) Act (A(SP)A) requires animals with the lowest capacity to be used, commensurate with achieving the objectives of the research. If possible, such assessments should be evidence-based, rather than merely assumed [but see Section 3.2.2 of the HBA report].

## 2. Monitoring and minimising harms experienced by animals

Much can be done to help minimise harms and to improve animals' welfare through the sharing of information across different establishments. Monitoring the development and outcome of projects carried out in the establishment, taking into account the effect on the animals used, helps to facilitate that process.

This can be achieved through the mid-term and retrospective review processes, as a matter of routine. The midterm review can also be used to re-evaluate the severity (and benefits) of the procedures during the course of the project, which can be reclassified, if necessary. Both reviews can be used to identify findings that turn out to be to the benefit (or detriment) of any of the 3Rs. All this information could help to inform the appraisal of future work, reduce harms and define the boundaries of different severity categories **[4, 8, 10 & 11]**.

These processes enable AWERBs to fulfil their role in helping to: '*Follow the development and outcome (retrospective review) of projects carried out in the establishment, taking into account the effect on the animals used; and to identify and advise on elements that could further contribute to the 3Rs'*

AWERBs' strategies for finding new ways of working towards the elimination of severe suffering are likely to evolve over time. To facilitate that process, information gleaned from Retrospective Assessments of Severity could be used by AWERBs to highlight areas for refinement that reduce suffering, whether it be mild, moderate, or severe. This information could also be used to inform AWERBs when appraising future applications that use the same or similar procedures **[1, 4 & 11]**

AWERBs might further decide to take advantage of opportunities to promulgate information on successful developments in any of the 3Rs and strategies for reducing harms. This effort could be targeted locally, through internal 3Rs seminars and poster presentations, within and between groups, but could be extended to the wider community, through AWERB Hubs or the AWERB Knowledge Hub, for instance. These bodies not only offer a forum for expert discussion of the 3Rs, welfare and ethical issues but can also help to share good practice **[1 & 11]**. This would help AWERBs to fulfil another role, which is to: '*Advise on the application of the 3Rs, and keep it informed of relevant technical and scientific developments'.*

In connection with this, new opportunities are offered by the Animal Scientific e-Licensing (ASPeL) system, which records comments on project licence applications, including those added by ASRU. AWERBs might decide to invite applicants to share

this feedback, which could help with the appraisal of similar applications in the future. A further aspiration could be for AWERBs to share this information via the AWERB Hubs, or the AWERB Knowledge Hub, for instance, which would help to inform HBA assessments at other establishments in the wider scientific community **[9, 10 & 13]**.

## 3. Assessing benefits of the programme of research

The benefits of a programme of research can include: direct, project-related benefits; indirect benefits to the research field; and benefits to the 3Rs. There is no formal system for assessing benefits, which could range from 'potential', 'likely' or 'probable' outcomes or even be merely aspirations.

As when assessing harms, the diverse expertise of AWERB members means that different AWERBs may reach different conclusions when assessing benefits. Nevertheless, the HBA review offers suggestions on how AWERBs can enhance the consistency of their assessment. This involves considering two main aspects of the process.

The first is to assess the nature and importance of the expected benefits. Examples of relevant questions would be:

- What difference would the findings from this research make if it is successful?
- Why is that difference important?
- What will be the benefit(s) of the work in terms of the type of output: e.g., the development of a new treatment for an illness, or answers to scientific questions that enable the research field to advance?

If it is proposed that the findings could lead to a new treatment for an illness, the description of the benefit needs to be considered in the context of the burden of that illness (which is not defined by the total number of cases, alone):

- Who or what will benefit from the work: humans and/or other animals?
- What proportion of the population affected by the illness is likely to benefit from the research?
- How will the benefits accrue: for example, by improved efficacy, reduced mortality, enhanced quality of life or reduced cost of treatment?
- Is the illness short-lived, recurrent, or life-long?
- How long will it take for the benefits to be achieved?
- Are there any impact case studies that can help to inform the assessment of benefits?

The second factor to consider is the likelihood of achieving these benefits. Examples of some relevant questions are:

- Has the applicant carried out a review of the background literature?
- Does the proposed research plan meet contemporary quality criteria for experimental design and analysis of the results? **[19]**
- Are the research objectives and the anticipated research benefits realistic, clear and accountable? **[14, 15]**
- Does any research intended for future translation include appropriate translational research objectives, including realistic milestones and timelines, and does it incorporate effective pathways to translation? **[20, 21, 22]**
- Are there plans to make the raw data accessible to others, even if the findings

do not support the original hypothesis? **[16, 18]**

- Are there clear plans for reporting and dissemination of the findings, even if they do not support the original hypothesis? **[16, 18]**

As projects progress, and at their conclusion, AWERBs might decide to share feedback on successful refinements within and even between establishments, especially if the benefits were unexpected. This could involve cross-project and AWERB Hub collaborations, for example, as well as the curation and archiving of Open Data. **[11& 16].**

Considering such factors can help AWERBs to ensure that that they will advise Establishment Licence holders to approve the submission of a given PPL application to ASRU only if the project offers realistic and worthy benefit(s) with a strong likelihood of success.

## 4. Weighing harms versus benefits

The process of deciding on a favourable HBA involves considering whether or not the overall harm that the animals will experience is justified by the benefits that are likely to be delivered. This not only involves taking into account the importance of the problem addressed by the research, but also consideration of whether and how the programme of work has addressed points such as those listed in Box 1.

Assessment of harms and benefits is a dynamic process and might change during the lifetime of the project, such as during mid-term and retrospective reviews. These assessments might reveal changes in the harms and/or ways to ameliorate them. The mid-term review also offers an opportunity to reassess the likelihood that the anticipated benefits will be achieved, whether they be short-, medium- or long-term. If either of these factors change, the AWERBs might decide to adjust its earlier decision on the HBA, accordingly [**20].**

A scheme for the overall PPL approval process is illustrated in Figure 1, which is based on the procedure already adopted by many AWERBs. Such schemes help to ensure that PPL applications are not submitted to ASRU without the AWERB's approval and also helps PPL applicants to have a clear understanding of the AWERB's process for appraisal of a project licence application.

Further to such a process, AWERBs might decide to:

- Devise a checklist of factors, which could be included in the HBA, especially if there are any that have particular local or institutional relevance **[19]**.
- Consider the opportunities offered by bodies such as AWERB Hubs or the AWERB Knowledge Hub, for sharing experiences of unforeseen harms and benefits and good practice, generally **[16]**.
- Consider whether it would be helpful to use any of a range of decision support-tools (several examples are cited in the HBA review) and to monitor developments in their functionality.

For AWERBs of establishments engaged in regulatory toxicology testing, the HBA recommends that their mechanisms for weighing harms and benefits consider **[23]:**

- the context of the types and the utility of substances / products being tested.
- the opportunities for sharing data.
- the contribution to ongoing HBA review in this area of work.

## 5. Societal concerns

The HBA review acknowledges that there are societal concerns about both the harms to the animals and the merits of benefits that accrue from the research. Moreover, those concerns can change with time.

An important role of an AWERB is to encourage critical self-appraisal by the establishment of its approach to ethical issues, with due regard to societal concerns, as well as the endorsement of the harms and benefits arising from the research it hosts.

The HBA review encourages regular engagement with a wide range of societal views on such matters. This is needed to ensure the consolidation and accountability of the legislation and to address public concerns about animal integrity, human dignity and institutional responsibility **[24 & 25].**

Lay members of AWERBs have a particularly important role in identifying research in PPL applications that could be regarded as ethically contentious and addressing foreseeable societal concerns **[14, 21 & 25].** This role could incorporate review and dissemination of material that identifies societal concerns, generally. More information about these concerns could be gleaned from data-bases[13] and resources, which include: AWERB Hubs, LASA, the NC3Rs, the Royal Society, the RSPCA and bodies such as the Nuffield Council on Bioethics[14] **[26]**.

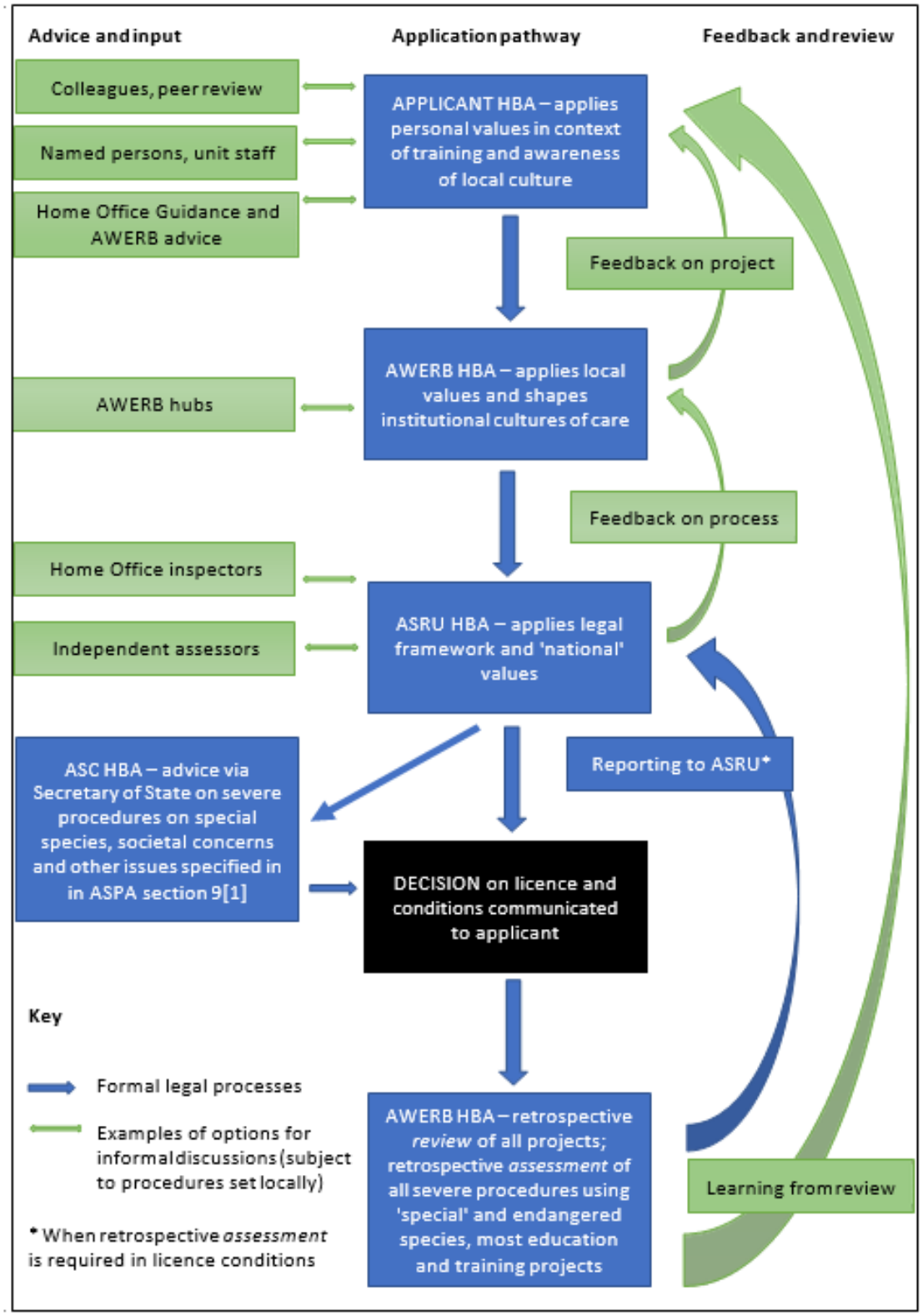
The HBA review proposed that it would be helpful for guidance to be developed that would help AWERBs identify and deal with PPL applications to carry out research that is novel and contentious, or that raise important ethical or societal concerns. Such guidance could be used to develop a shared understanding of what constitutes a societal concern, to identify resources to help understand these concerns and to support the HBA in better reflecting shifts in prevailing opinions and attitudes **[25 & 26]**

In the meantime, the review recommends that all procedures that currently attract societal concerns should be included, as a harm, in the HBA.

[13] https://www.ipsos.com/ipsos-mori/en-uk/public-attitudes-animal-research-2018

[14] https://www.nuffieldbioethics.org/

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



**Examples of points to consider as part of the Harm Benefit Assessment**

- 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(s) are known) adequate for removing bias?
- Are researchers aware of and compliant with *Animal Research: Reporting of In Vivo Experiments* (ARRIVE) guidelines in their past and planned publications?
- Is the research clear about how it is oriented on the basic/applied spectrum and amenable 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 others engaged in 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 are there flexible and alternative routes for development of the work?
- Do all researchers indicate how new opportunities to recognise and disseminate benefits can 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?