VETBIONET

Veterinary Biocontained facility Network for excellence in animal infectiology research and experimentation

Deliverable D4.5

Ethics Committee Best Practice Guidance

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1. Executive Summary

A key objective of the VetBioNet project is to harmonise best practices and promote the use of global standards in European BSL3 infrastructures as well as ensure high ethical standards. In this context ethical review is an integral process in achieving this objective. The aim of this document is to provide specific guidance on how to support effective ethical review through the functions of a robust Ethics Committee.

This guidance draws on existing literature and experience relating to the ethical review system used in the UK, the combined Animal Welfare and Ethical Review Body (AWERB), putting it into the context of the specific issues and challenges faced by high containment facilities.

To facilitate 'Best Practice' in ethical review and reflection, information on the optimal Committee structure, membership and remit are given as well as practical recommendation on how the functions of the Committee can be addressed by BSL3 facilities.

A number of useful resources and tools are highlighted as well as examples of current practice and documentation for Users of this Guidance to adopt and adapt to their specific needs.

This Guidance is intended to be a dynamic document that will evolve with feedback from Users and with further investigations in to how current facilities operate and how that experience can be shared and improved.

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2. Introduction

Ethical review is essential in any system that regulates the use of animals in research and testing. It is a process that enables continuous critical evaluation of the ethical, scientific and welfare issues associated with animal experimentation. The Royal Society for the Protection of Animals (RSPCA) website[1] provides a very useful explanation of what the ethical review process is and why it is important;

> '*This process of **ethical review** involves evaluating **whether** individual scientific projects justify the use of animals (usually through a **harm-benefit assessment**) and consideration of practical issues relating to **how** animals will be used. The latter encompasses **application of the 3Rs**, including good experimental design, animal **housing, husbandry and care** that takes account of the physical and behavioural needs of animals, and related issues such as provision of **staff training and assessing competencies**. All of these factors can have profound effects on both animal welfare and the quality of the science.*
>
> *Ethical review is not a single 'event' that takes place during authorisation of a project. It is a dynamic process that should encompass the **lifetime of the project** from application for funding, through the design stage, to completion of the work, its publication and the application of the results. Throughout this process, every opportunity should be taken to ensure the ethical, scientific and practical welfare aspects are carefully considered.*'

European Directive 2010/63/EU[2] stipulates that before a project to use animals for scientific purposes can be authorised there is an assessment of the compliance of the project with the requirements of replacement, reduction and refinement; and particularly important here, a harm-benefit analysis of the project, to assess whether the harm to the animals in terms of suffering, pain and distress is justified by the expected outcome taking into account ethical considerations, and may ultimately benefit human beings, animals or the environment.

While the Directive stipulates that establishments must form an Animal Welfare Body (AWB) it does not stipulate that it must undertake ethical review of proposed or authorised projects. Therefore, how and which bodies do the ethical review of animal experiments has been interpreted in different ways by different Member States. These different models of ethical review are noted here but this guidance will focus on the system adopted by the UK Home Office of integrating ethical review into the functions of the AWB (so creating the Animal Welfare and Ethical Review Body [AWERB]), as this is one of the few models which has been established for many years and has significant supporting resources, networks and infrastructure.

[1] https://science.rspca.org.uk/sciencegroup/researchanimals/ethicalreview (accessed 13/5/19)
[2] Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes *Official Journal L 276*, 20/10/2010 pp. 33-79.

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This guidance document will draw upon some of these resources, in particular the RSPCA and LASA (Laboratory Animal Science Association) (2015)[3] '*Guiding Principles on good practice for Animal Welfare and Ethical Review Bodies*' and will highlight the general principles of Best Practice for ethical review. It will address the specific issues and practical applications related to ethical review for VetBioNet partners who conduct experiments using animals in their high containment farmed animal facilities (HCFAFs). In addition, this document is intended to be a dynamic resource that will evolve with user experience and with further research into achieving effective and efficient ethical review, so further developments and methods of improving this guidance are outlined.

3. Aim and Scope

The aim of this guidance document is to define 'Best Practice' approaches for ethical assessment, reflection and engagement processes for BSL3 facilities to achieve a key objective of the VetBioNet project: to harmonise best practices and promote the use of global standards in European BSL3 infrastructures as well as ensure high ethical standards.

This Guidance is intended to be used by Ethical Committee members and Chairs as well as staff and management throughout BSL3 animal facilities. It provides information on optimal Committee structure and makes recommendations about practical delivery of its functions to enable effective and appropriate ethical review of animal experimentation.

It can be used to evaluate existing Ethical Committees, review current practices and make improvements if necessary or if there is no Committee it can be used as a blueprint for establishing a new one.

4. 1 Committee Structure

While the structure of welfare and ethics committees varies between institutions, regions and countries there is usually a mandatory minimum set of requirements. Here these are outlined, and additional recommendations made in order to achieve best practice in the context of high containment infectious research. This section outlines; the types of Committee and recommends the most relevant model structure for high containment facilities, the remit and main tasks of the Committee and the minimum and suggested membership.

4.1.1.1 Types of Committee

The implementation of the Directive was through national legislation and Member States have different structures in place to deliver the requirement. In the context of ethical review some

[3] RSPCA and LASA (2015) *Guiding Principles on Good Practice for Animal Welfare and Ethical Review Bodies, Third Edition*. UK: RSPCA and LASA, pp.62. Available at: http://www.lasa.co.uk/PDF/AWERB_Guiding_Principles_2015_final.pdf (accessed 13/5/19).

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Member States implement it at institutional level and others have Committees that are regional or national. Some of the key ethical review models are:

- Combined institutional/local animal welfare and ethical review bodies (e.g. the AWERB in the UK)
- Separate institutional/local AWB and Ethics Committee
- Regional Ethics Committees (e.g. Sweden)
- National Ethics Committee (separate from Competent Body)
- No Ethics Committee (Competent Body solely does ethical evaluation)

The RSPCA provide further information on different systems of ethical review globally on their website[4]. As noted above, this guidance focusses on the combined animal welfare end ethical review body model used in the UK. The reason for this choice is that whether the national legislation requires an institute level ethical review or not, VetBioNet considers it best practice that institutes establish an effective internal ethical review process, as it is fundamental for meeting the requirement for the moral use of animals and in the case of high containment there are very specific local issues to account for within the assessments. In addition, within the UK there has been a great deal of research and deliberation given to effective ethical review and the systems and infrastructure are well established. Therefore, the remainder of this document will draw on these important resources and experience.

4.2.1.2 Remit of Committee

In order to fulfil their function to ensure good ethical practice and add value to their host institutions Ethics Committees/AWERBs should at the very least:

- promote awareness of animal welfare and the 3Rs (Replacement, Reduction and Refinement)
- provide a forum for discussion and development of ethical advice to the establishment licence holder on all matters related to animal welfare, care and use at their establishment;
- support named persons under the legislation and other staff dealing with animals, on animal welfare, ethical issues and provision of appropriate training; and
- help to promote a *'culture of care'* (see appendix 1 for further details) within the establishment and, as appropriate, in the wider community.

4.3.1.3 Minimum Tasks of Committee

In order to address this remit, the minimum tasks of the Committee are to:

- advise staff dealing with animals in the licensed establishment on matters related to the welfare of the animals, in relation to their acquisition, accommodation, care and use;
- advise on the application of the 3Rs, and keep the Committee informed of relevant technical and scientific developments;

[4] https://science.rspca.org.uk/sciencegroup/researchanimals/ethicalreview/differentsystems (accessed 13/5/19).

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- establish and review management and operational processes for monitoring, reporting and follow-up in relation to the welfare of animals housed or used in the licensed establishment;
- 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; and
- advise on re-homing schemes, including the appropriate socialisation of the animals to be re-homed.

In addition, Committees have the following advisory and reviewing tasks to:

- advise the establishment licence holder whether to support project proposals, primarily considering such proposals from a local perspective and bringing to bear local knowledge and local expertise;
- assist with the retrospective assessment of relevant projects carried out at the establishment; and
- respond to enquiries, and consider advice received, from the National Committee for the Protection of Animals used for Scientific Purposes (the Animals in Science Committee [ASC] in the UK)

Section 2 provides guidance on how the Ethics Committee can function to deliver on these tasks.

4.4.1.4 Membership of Committee

Directive 2010/63/EU states that the *minimum* membership of an AWB shall include at least the person or persons responsible for the welfare and care of the animals and, in the case of a user, a scientific member. The Animal Welfare Body shall also receive input from the designated veterinarian.

The UK implementation of this is that the Committee (AWERB) must include *at least one* of the establishment's;

- *Named Animal Care and Welfare Officer(s) (NACWO)*
- *Named Veterinary Surgeon(s) (NVS)*

Plus, if it is a user establishment;

- *A scientific member (to be useful this should be with project and preferably personal licensee training and experience under the Directive)*

For best practice the UK Home Office also recommend that the Committee should include;

- *The Named Information Officer(s) (NIO)*
- *The Named Training and Competence Officer(s) (NTCO)*
- *Somebody with bio-statistical training*
- *Somebody who is independent of the establishment*

Further to these representatives this guide recommends that for institutes with HCFAFs it is best practice that this membership includes individual(s) with a practical knowledge of undertaking experiments in this grade of facility and if the main Committee has any sub-

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committees at a minimum the Chair of those sub-committees has the appropriate working experience.

For structure and effectiveness it is important that there is a Chair of the Committee and the Committee is supported by a secretariat to manage the administration, its meetings, including recording the advice/decisions of the committee, and administering any actions or policies that result from these.

5. 2 Committee Function

In order to fulfil its tasks and remit there are some general processes and procedures that can aid the smooth functioning of the Committee. This section outlines some of these broader functions but also details recommendations for the more specific actions of a Committee which ensure good practice. Generally, it is important that the Committee has an agreed Terms of Reference with the institute's management. This is often done through a Terms of Reference document which outlines the aims, method of working and expected outcome of the Ethics Committee. To be successful the Ethics Committee should be efficient and "*add value*" over and above the work of other external and internal bodies.

To achieve this the RSPCA[5] recommends that as well as thinking about specific roles that are relevant to the membership the Committee should also consider whether its members have certain key competencies among them, in particular that they have knowledge, understanding and expertise in:

- animal husbandry, care and welfare;
- each of the 3Rs;
- education and training;
- ethical issues;
- individual techniques;
- public opinion and perspectives;
- relevant scientific fields to running a HCFAF;
- statistics, experimental design; and
- welfare assessment and humane end-points.

It is the Chair's role to ensure all these elements are present through the selection of the membership. The members should have the right personal qualities not only to work effectively as a committee but also to engage with the departments they come from and the wider institute. To improve this engagement, if possible, it helps to have a rotation of membership particularly of the scientific representatives. Open Ethics Committees are also best practice, where there is opportunity for staff unrelated to animal work at the institute to observe. This can be done with one or two observers per meeting, by putting the meeting schedule on the institutional intranet and have the secretariat manage the requests to attend. It is also best practice that both members and visitors sign a confidentiality agreement (example in appendix 2).

[5] RSPCA and LASA (2015) *Guiding Principles on Good Practice for Animal Welfare and Ethical Review Bodies*, *Third Edition*. UK: RSPCA and LASA, pp.62. Available at: http://www.lasa.co.uk/PDF/AWERB_Guiding_Principles_2015_final.pdf (accessed 13/5/19).

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Physical meetings with the applicant present are considered best practice to give the appropriate level of interaction between committee members and the applicant. Documentation (see appendix 3 for an Ethical Review Form example) should be circulated to the Committee with sufficient time for them to familiarise themselves with it and an overview of the application should be given at the meeting, as a presentation to help the Committee understand the nature of the request.

At intervals it is best practice to re-evaluate the Ethics Committee's Terms of Reference and outcomes and whether its operation is efficient and appropriate.

With farm animal research on highly pathogenic infectious diseases, due to its potential to have severe adverse effects and the relatively limited number of experiments done in the high containment facility, it is best practice to review each experiment. If this is being done, it is also reasonable to give the Chair of the Committee, the ability to approve the following outside the meetings:

- changes that do not affect the harm benefit assessment (HBA) once experiments have been approved; and
- repeat experiments using the same design and HBA.

The Chair's actions should be reported back to the Committee at the next meeting. This system works well for experiments with mild to moderate adverse effects. However, with the focus on trying to eliminate severe suffering the Committee may not allow the Chair to approve projects or experiments with this level of adverse effects. These decisions are contextual and down to individual Committees and their Chairs.

It is best practice for the Committee to work by consensus, however there may be times when consensus cannot be reached across the whole Committee. If there is a substantial majority in favour of an option a lot of committees will pass the option and record that it was a majority vote and what the opinion/objection of the minority was. If there is a split across several options, it suggests that more work needs to be done by the Chair and applicant to work out a more acceptable way forward.

Depending on the size of the institute, the number of functions of the Ethics Committee means there may need to be one or more sub-committees to spread/manage the workload. This can be divided up in various ways but at a minimum the Chair of the sub-group should be a member of the main Committee. The use of sub-groups, as well as managing the workload of the main Committee gives more members of staff across the institute the opportunity to be involved hence improving the engagement of the institute as whole with ethics and animal welfare.

Taking into consideration these general principles the following sections now provide guidance on some of the more specific functions of an Ethics Committee, including examples of their application in the context of high containment research.

5.1.2.1 Ethics and the 3Rs

On a routine basis a lot of the Ethics Committee function is about applying the 3Rs (see Box 1 for definitions) to project licence applications and experiments on areas of work that the institute routinely carries out. However, there are times when more fundamental ethical questions have to be asked, examples of this are:

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1. New areas of research and new techniques. If an application for funding of new research work moves the institute into a new area of research or requires new techniques, the Ethics Committee should be consulted prior to application. A distinction should be made between what is legal under the Directive and the areas of research the institute wants to undertake. The decisions about the latter are based around whether the institute feels the work fits with its research strategy and its staff are competent to undertake it or can if necessary, develop this competence.

2. Work undertaken by other institutes particularly outside Europe. It is best practice that the Ethics Committee has a policy on this and reviews this work before it starts. The Committee will need to understand why the work is being undertaken outside the institute and by whom. It is important the Committee know what legislation the work is being authorised under and how the organisations delivering it maintain animal welfare and the 3Rs, and the competence of the staff undertaking the procedures.

3. Undertaking experiments where for some reason there is a higher risk of failure. For example, mechanical failure in a HCFAF that requires the animals to be terminated before the experiment is completed. For this reason, it is best practice that information about the operational state of the facilities in relation to compliance should be fed back to the Committee on regular basis.

Box 1: The Principle of the 3Rs; Replacement, Reduction and Refinement

Originally conceived by Russell and Burch in 1959*, the principle of the 3Rs is now an integral aspect of Directive 2010/63/EU and in much of the animal experimentation regulation around the world. Russell and Burch advocated that Replacement should be the ultimate goal but while working to achieve this Reduction and Refinement should be implemented. While Russell and Burch's original definitions of each of the Rs have been altered over the years they can simply be defined as:

Replacement – of experiments and studies on sentient animals with alternative means of enquiry.

Reduction – of the number of sentient animals used in each experiment or for a specific purpose.

Refinement – of experiments on sentient animals towards more humane practices.

* Russell, W.M.S. & Burch, R.L. (1959). *The Principles of Humane Experimental Technique*, 238pp. London, UK: Methuen.

It is important that the Committee clearly demonstrates the value it places on the 3Rs, by ensuring that they are integral to the work at the establishment. To achieve this the Committee should work closely with, and support, the Named Information Officer (NIO) to provide a 'hub' for 3Rs knowledge and advice, capturing innovations and proactively disseminating information such as institutional policy decisions concerning local good practice. In addition,

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the Committee can support the institution to provide a mechanism to encourage and facilitate wide staff involvement in the 3Rs, motivating people to:

- be proactive as well as reactive;
- think about and implement existing 3Rs opportunities;
- develop new 3Rs initiatives and activities; and
- disseminate 3Rs information as widely as possible,

Below are some practical examples of how the Committee can advise on the implementation of the 3Rs particularly in the context of high containment work.

1.1.1 Replacement

The replacement of animals in experiments with non-sentient substitutes should be the goal of all Ethics Committees. Although unlikely for a lot of HCFAF work it is important when undertaking ethical analysis to ensure that the applicant has checked thoroughly that there are no available alternatives to animal use for their experiment and that the information that will be generated by the experiment is not already available. Systematic literature searches are best practice in this area and what has been done should be evidenced in the application (see the Useful Links and Resources Section for relevant tools to help with this).

1.1.2 Reduction

One of the most effective and efficient ways to achieve reduction is to ensure the correct experimental design is used and that appropriate statistical analysis is undertaken. Therefore, to achieve significant reduction of animal numbers used but maintain the scientific validity of the work it is best practice that a biostatistician is member of the Committee and that the Committee has a policy on the use of statistics in experiments (for a policy example see the end of appendix 3).

1.1.3 Refinement

Researchers using high-risk infectious agents have a variety of ways to achieve refinement in experiments using animals; these include (but are not limited to):

- Using less virulent challenge agents, with reduced clinical effects;
- Developing species-specific welfare assessment protocols and score sheets for commonly used procedures/models and establish a mechanism for their regularly review; and
- Early humane endpoints, including predictive endpoints using markers for disease, such as white blood cell counts (WBC), body temperature and pathogen load in the blood and other body fluids. Early humane endpoints should be used when assessing the phenotype or pathotype of the disease is not required, *e.g.* in positive controls on vaccine challenge experiments.
- Using technology such as in vivo bioimaging and physiological and/or behavioural monitoring with realtime computer analysis to identify endpoints earlier. These techniques are being developed and analysed in tasks 9.3 and 9.2 in VetBioNet.

Some practical ways of achieving these refinements are given in appendix 4.

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More recently the concept of Refinement has been modified to encompass the approach of not just reducing the negative impacts of experiments but in providing a positive experience for the animals involved by improving their welfare, including changes in husbandry and care. This is now established practice in HCFAFs, which had historically been a barren environment. HCFAF best practice now is to use environmental enrichment and increasingly units are being designed or modified to provide bedding in them. It is best practice to

1) have a variety of different to environmental enrichment techniques which are swapped in and out to keep interest
2) that if the project cannot for some reason have environmental enrichment this is considered as an additional cost by the Ethics Committee when it reviews the experiment.

It is an important role of the Ethics Committee to ensure that any 3Rs advance in one area are communicated to other areas and adopted if possible. Overall, the Committee needs to facilitate communication of, and engagement with, the 3Rs. This requires the secretariat or tasked individuals to have mechanisms for disseminating information, bringing important issues (legislation, meetings, and reports) to the relevant people's notice and fostering interest more widely (see appendix 5 for examples of 3Rs communication activities).

5.2.2.2 Project Review

There is a large amount of information available to aid Competent Authorities and Ethics Committees to perform robust project review (for example see the European Commission (2013) *Working document on Project Evaluation and Retrospective Assessment*[6]) and the requirements of projects undertake in HCFAFs are no different to projects undertaken elsewhere in the principles of what the Committee should seek reassurance on, namely:

- there has been a **robust analysis of the methodology** including experimental design, ensuring that, where necessary, statistical advice has been sought;
- all the **potential harms have been identified** (encompassing the animals' cumulative lifetime experience), clearly described and understood, and that these will be either avoided or effectively recognised, assessed, and alleviated throughout the life of the project;
- there is evidence that **the 3Rs have been fully considered** and implemented as far as possible and that staff with relevant expertise (NIO, NACWO and NVS in particular) have had the opportunity to contribute in this respect;
- **local policies and good practice procedures will be implemented** (e.g. on humane endpoints, use of analgesics, injection volumes, score sheets);
- the **benefits and quality of science have been considered** (e.g. with respect to the appropriateness of the animal model) and that the scientific approach is fully justified;
- there is a **realistic appraisal of what can be achieved from the animal work**, within the timeframe for which the licence will be granted;
- the project licence **applicant is appropriately qualified and has the necessary skills** to manage the project within the establishment and any

[6] European Commission (2013) *Working document on Project Evaluation and Retrospective Assessment*. Brussels: European Commission, 42pp. Available at: http://ec.europa.eu/environment/chemicals/lab_animals/pdf/guidance/project_evaluation/en.pdf (accessed 14/5/19).

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training/supervision/competency needs of the staff who will work under the licence are being addressed;
- suitable **funding, facilities and equipment are available**, and there are enough staff with the necessary expertise to carry out all work associated with the project within the time frame outlined in the project licence application;
- ethical concerns have been identified and the balance of harms and benefits has been thoughtfully weighed, with **sufficient justification provided for the specified animal use;** and
- there is a **clear and transparent non-technical summary** which adequately covers possible animal welfare issues as well as the justification for and benefits likely to arise from the work.

As most projects are five years in duration, it is good practice to have a retrospective review of projects at least twice during their life-time**.** This is to determine whether the actual costs and benefits are in line with those anticipated, and ensure information and experience gained during the course of the review period is applied to future assessments.

During these interim reviews it is important that the licence holder contacts all key staff involved, as this defined review point provides a 'time-out reminder' for all relevant staff to raise any concerns they may have regarding the project and to determine how to resolve them. It also provides the opportunity to report things that are going well and that could influence future directions for this and other projects. Issues to consider include:

- whether the science is on-track and the results are as expected;
- how the actual adverse effects and severity compare with those predicted;
- whether any problems have been identified and addressed;
- whether there are any recent developments in science or technology which influence the direction or conduct of the study or affect its value; and
- whether anything has changed which might alter the original harm-benefit judgement.

5.3.2.3 Supporting Staff and Training

When Directive 2010/63/EU came into force it placed more emphasis on training and competency than its predecessor. Given the acknowledged importance to science, animal welfare and compliance of having sufficient, appropriately trained and competent staff, the Ethics Committee needs to be confident that the establishment has in place a good system of education and training and assessment of competence for all staff who need it - including Ethics Committee members. There are a various source of information and courses including:

- RSPCA and LASA (2017) *Developing Induction Materials for AWERB Members*[7]
- Jennings and Smith (2015) *A resource book for lay members of ethical review and similar bodies worldwide*[8]

[7] RSPCA and LASA (2017) *Developing Induction Materials for AWERB Members*. UK: RSPCA and LASA, 11pp. Available at: http://www.lasa.co.uk/wp-content/uploads/2017/04/AWERB-IP-Final.pdf (accessed 14/5/19).

[8] Jennings M and Smith J (2015) *A resource book for lay members of ethical review and similar bodies worldwide*. UK: RSPCA, 64pp. Available at; https://view.pagetiger.com/EthicalReviewJanuary2015 (accessed 14/5/19).

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- The RSCPA run a forum for lay members on an annual basis, see their website[9] for further information.
- The Fund for the Replacement of Animals in Medical Experiments (FRAME) run an annual Training School in Experimental Design and Statistics. The 2019 event was held at the University of Nottingham (VetBioNet partner) in collaboration with VetBioNet. For further information see the FRAME website[10].

It is best practice for the Ethics Committee to have a policy on training and competency for undertaking research projects involving animals and the associated techniques that have to be performed on them. For training in techniques, it is best practice that trainers have gone on a course on how to train and that candidates are assessed by another trainer. For competency there should be a requirement for observation by the NACWO, NVS, NTCO or another licensee that is competent if the licensee has not undertaken the technique for some time or there is an identified need to retrain.

There are particular challenges with HCFAF work involving zoonotic pathogens. Due to the hazardous nature it is regarded as bad practice to train staff using animals infected with category 3 zoonotic pathogens (e.g. transmissible H5N1/H7N9 avian influenza viruses). Therefore, opportunities have to be created to train staff on either uninfected animals or ones where the biosafety hazard is not so great (e.g. those infected with not transmissible low pathogenic avian influenza viruses). In addition, the actual environment of the HCFAF when doing high-risk work, particularly if this work requires wearing respirator masks, is not conducive to good communication, which is necessary for effective training.

There is no specific difference between supporting staff running an HCFAF and those running other sorts of units, so this topic is not dealt with in depth as the guidance available is already comprehensive (see for example RSPCA and LASA, 2015[11]). It is best practice to have a mechanism (and policy) where staff can raise causes for concern (see appendix 6 for an example).

5.4.2.4 Forum for Discussion

As is the case with Ethics Committees in other institutions the guidance for best practice for a HCFAF Committee is that it should provide '*Provide a forum for discussion and development of ethical advice to the establishment licence holder on all matters related to animal welfare, care and use at the establishment*' (RSPCA and LASA 2015, p.50)

Therefore, providing the opportunity to raise and discuss ethical issues is integral to the Committee's role in promoting a culture of care. The Committee should aim to be alert to the wider ethical and legal issues arising from the use of animals, both within the establishment and beyond. It should encourage staff to be aware of these issues and consider the implications for their own work. The wider resulting engagement should benefit staff

[9] RSPCA Lay Member's Forum Website: https://science.rspca.org.uk/sciencegroup/researchanimals/ethicalreview/differentsystems/uk/events (accessed 14/5/19).
[10] FRAME Training School Website: https://frame.org.uk/training-events/training-school/ (accessed 14/5/19).
[11] RSPCA and LASA (2015) *Guiding Principles on Good Practice for Animal Welfare and Ethical Review Bodies*, *Third Edition*. UK: RSPCA and LASA, pp.62. Available at: http://www.lasa.co.uk/PDF/AWERB_Guiding_Principles_2015_final.pdf (accessed 13/5/19).

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development and should help promote better understanding of the role and value of the Ethics Committee.

The RSPCA advise that the nature of the "*forum for discussion"* is not defined and this could take different forms depending on the establishment. A Committee by virtue of holding meetings, *in itself* provides a forum for dialogue and discussion, albeit largely between people directly involved in the process. However, it is beneficial to go beyond this and encourage other staff to contribute topics that, in their view, would be helpful for the Ethics Committee to be aware of and discuss and invite a wider group of people to engage (see RSPCA and LASA (2015) for more recommendations on this function).

More recently, Hawkins and Hobson West (2017)[12] provide guidance to help Ethics Committees (AWERBs) to fulfil the tasks of providing a forum for discussion. They provide practical recommendation for:

- Improving the quality of ethical discussion;
- Widening engagement across the institution; and
- Encouraging openness beyond the institution.

5.5. 2.5 Managerial Systems and Institutional Infrastructure

In terms of supporting managerial systems and institutional infrastructure, although the environment differs for HCFAFs, again the requirements for best practice are the same as for other institutions. The Committee should establish and review management and operational processes for monitoring, reporting and follow-up in relation to the welfare of animals housed or used in the licensed establishment.

This task can be seen as helping the institute's management responsibilities by providing an overview of how processes combine to ensure high quality animal care and use, perhaps also considering how processes interact and how resilient they are when staff change.

These issues are usually addressed through internal management systems and procedures that support animal welfare, quality science and regulatory compliance. The mechanisms adopted will vary depending on the size of the establishment and the nature, and complexity of the work being carried out and species used. The Committee should receive regular reports from those responsible for managing facilities and provide feedback to them.

The RSPCA and LASA (2015) recommend that mechanisms that will help in establishing and reviewing management and operational processes include:

- Formal or informal audits of projects or procedures. This may involve committee members or others observing procedures. It is important that any audit findings are recorded and remedial actions tracked;
- Use of external experts to review internal systems and/or animal facilities. This might be through formal processes such as AAALAC, or visits by clients, or through less formalised visits by colleagues from other institutions ;
- A standard process for dealing with non-compliance or welfare concerns, *e.g.*:

[12] Hawkins P and Hobson-West P (2017) *Delivering Effective Ethical Review: The AWERB as a 'Forum for Discussion'*. UK; RSPCA, 11pp. Available at: https://view.pagetiger.com/AWERB/AWERB (accessed 15/5/19).

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- procedures to track issues and ensure they have been followed up and resolved;
- monitoring of trends in/recurrence of issues;
- identification of a specific individual as responsible for tracking and monitoring issues;
- an internal mechanism to enable anyone to report animal welfare concerns confidentially and without fear (i.e. a 'whistle blowing' process – see appendix 5); and
- mechanisms to raise concerns with senior management;

- Periodic internal reviews of specific issues, e.g.:
  - minimising animal surplus;
  - ensuring that the correct authorities are in place for the ordering and issuing of animals and that these are maintained when staff change; and
  - reviewing anticipated versus actual severity and how often humane endpoints are reached;
- Systems in place to ensure overall compliance with legislation e.g.: to prevent unauthorised use or re-use of animals; and that all the associated legislation associated with the Codes of Practice and Advice Notes are implemented;
- Ethical Committee conduct animal housing facility reviews with input and feedback to scientific and care staff;
- Review of proposals for any new facilities or refurbishments or repairs, or acquisition of newer types of accommodation;
- Reviews to ensure that staffing levels are appropriate and that the systems in place to monitor animals are adequate to optimise welfare (e.g. the day-to-day cage-side, observations and recording of behaviour and clinical signs);
- A 'team approach' to setting out and implementing a welfare assessment protocol for each study. The EU Guidance Document on a Severity Assessment Framework[13] recognises that this is good practice. It also recommends that the Ethics Committee play a role in defining protocols for actual severity assessment, to help ensure consistency. A verification process, in which judgements made by different people are compared, is also cited as helping to promote consistent use of the system;
- System for internal follow-up of formal inspections by the regulator; and
- A check that the Committees own procedures are effective and not overly burdensome.

5.6.2.6 Culture of Care

The Ethics Committee is not solely responsible for an establishment's culture but it is in an ideal position to drive the culture of care, and should, along with senior management, demonstrate effective leadership in this area. The additional challenge for HCFAFs is that the culture of care should be implemented in a contained, 'biosafe' environment; however, a large amount of the culture of care is what is expected anyway in a good biosafe environment (appendix 1).

The culture of care should permeate throughout the institute, but it is essential that senior management understands the issues and visibly demonstrates commitment to, and support for, generating and maintaining such a culture. The Committee provides a good channel of communication to and from senior management since it advises the establishment licence

[13] European Commission (2012) *Working document on a severity assessment framework*. Brussels: European Commission, 71pp. Available at: http://ec.europa.eu/environment/chemicals/lab_animals/pdf/guidance/severity/en.pdf (accessed 14/5/19).

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holder, who is a senior manager. Many of the ideas for committee activities throughout the other sections of this document contribute to achieving a good culture of care and so these will not be discussed again here.

All institutes should ensure that they have a clear vision of what a culture of care means for them (an example is in appendix 1). The culture of an organisation relates to the beliefs, values and attitudes of its staff and the development of processes that determine how they behave and work together. Every institute that uses animals for a scientific purpose should have a culture that demonstrates caring and respectful attitudes and behaviour towards animals and encourages acceptance of responsibility and accountability in all aspects of animal care and use. This should go beyond simply having animal facilities and resources that meet the minimum requirements of the legislation. Every institute should strive for improved animal (and staff) welfare and enhance scientific outcomes.

A healthy culture of care requires a shift away from merely responding to externally imposed standards, to one in which leaders and frontline staff are actively committed to improving 3Rs, animal welfare, research and work together to do so.

6. 3 Feedback and Development of Guidance

This guidance is intended to be a dynamic document that evolves with User feedback and further research into what constitutes Best Practice in terms of ethical review in the context of high containment research. Therefore, the authors welcome any comments or suggestions regarding Users' experience of using this document or on its content. Please send any constructive feedback to Michelle Hudson-Shore and she will distribute to the full set of authors (contact details on page 3).

In addition to responding to User feedback two of the authors (Drs Michelle Hudson-Shore and Kate Millar) will be conducting a survey with VetBioNet members (2019) to identify different perspectives on good approaches and best practices.

A workshop will be convened to share institutional Animal Research Ethics Committees' (and welfare boards) approaches and discuss experiences. The findings from both of these investigations will be used to develop and improve this existing document.

A further deliverable will be published after the workshop by the end of 2020 (Deliverable 4.5 – Version 2).

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7. Appendix 1: Features of a "Culture of Care"

Structural Elements

- A corporate expectation of high standards in legal, ethical, animal welfare, 3Rs and scientific aspects of the use of animals that extends above and beyond the legal minimum, and which are endorsed and implemented at all levels throughout the establishment.
- An effective operational structure with clear roles, responsibilities and tasks in which animal technologists and care staff, named persons [NVS, NACWO, NIO, NTCO], trainers and assessors are listened to and their work supported throughout the establishment.
- Effective and well supported ethical review of scientific work undertaken with a thoughtful and rational approach.
- A robust framework for training and assessment of competence, together with recognition of the importance of continuing professional development (CPD) for all staff, and with adequate opportunities and resources provided.
- Good establishment-wide communication processes regarding animal welfare, care and use issues and the relation of these to good science, with good communication between researchers and animal technologists and care staff.
- Mechanisms to ensure that standards at animal suppliers, contracted organisations, and research partners overseas are consistent with the good practice that is implemented in-house.
  Commitment to provide sufficient resources to achieve all of the above.

Behavioural Elements

- Strong commitment, support and leadership from senior management which provides the resources to deliver the values of the institution.
- Demonstrable respect for animals and for differing ethical perspectives on animal use.
- A common set of values and standards which are communicated, understood and implemented across all parts of the establishment.
- A proactive attitude and approach to improving standards of animal care and use (including environmental enrichment) and related organisational and management practices, rather than merely reacting to problems as they arise.
- Staff having the appropriate attitude, demonstrating empathy for colleagues and animals and working within ethical and welfare frameworks, such as 3Rs and LASA good practice and guiding principles documents.
- Acceptance of individual responsibility and accountability for animal use, from staff who are willing to take the initiative to resolve problems should any arise, with collective responsibility where appropriate.
- Willingness to challenge the status quo, to speak out without fear and to support those that do; internally, an open culture where staff are confident to report problems and raise any concerns, and where these are listened to, discussed and resolved in a positive way.
- Commitment to openness and honesty about animal use both internally and in the public domain.
- Dedication to a cycle of review and improvement of policies and processes to strive towards higher standards of animal welfare.

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8. Appendix 2: Example Ethics Committee Confidentiality Agreement

As a member of the Ethics Committee, or a visitor attending it, it is important that the committee keep professional confidentiality when dealing with the information that is presented as part of discharging the committee's functions.

For the purposes of this agreement "Confidential Information" is any know-how, or information not in the public domain. It excludes information relating to the 3Rs (Replacement, Reduction and Refinement) but includes the intellectual property defined below.

The background intellectual property, which has arisen before the commencement of, or acquired in parallel with, the planned work discussed at the Committee. This belongs to the applicant and it may be necessary to disclose it to the committee for the purposes of obtaining ethical approval.

The intellectual property which is obtained, found, produced, devised, developed, or made in the course of the project undertaken at [Institution Name], and may be presented to the Committee as part of reviewing this work to show that objectives and benefits were achieved.

This information should not be discussed with anyone else apart from within the Committee review process or with colleagues who are directly involved in advising upon or delivering the study.

I have read, understood and agreed to the above.

Signature:

Name (print):

Date:

Please note reason for attending Committee meeting:

Member / Observer/ External presenter/ External observer

If not a member, please note date meeting attended:

Date:

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9. Appendix 3: Example of an Ethical Review Form for of an Animal Experiment

This ethical review form is an example used by one of the VetBioNet partners based in the UK. It can be used as a template and adapted to suit individual institutions' needs.

Reference Number:

Please complete the relevant sections using "lay" (plain English/non-scientific) terms as much as possible in order to enable all members of the committee to assess the application.

Title:	
Financial code:	
Applicant:	
Preferred Start Date:	

1) Home Office Compliance

Home Office Project Licence Number:	
Name of PPL Holder:	
Section E / 19b Protocol number:	
Severity Limit as stated on PPL:	
Expected severity (if different to above):	

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If different please give explanation; including evidence from previous work if applicable:			
Signature of PPL holder:		Date:	

2) Other Compliance

Is this experiment required to meet licensing requirements such as European Pharmacopoeia? (If yes, Please state compliance and add reference for identification)	

3) Quality

Please note which scheme your work is required to comply with (tick relevant box):

GLP	GMP	GCP	OTHER (specify)

Please quote study protocol/plan reference as agreed with the sponsor and attach/submit as an additional document:

4) Safety/Containment

Please note which agent your work will use and the category for compliance (tick relevant box):

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Infectious Agent to be used GM	SAPO	ACDP

Are there any safety issues that may affect the study commencing?	

5) Funding/Peer Review:

How is this work being funded?	
What scientific peer review has been undertaken?	

6) Objectives

Please add a brief summary, in plain English/non-scientific terms, of the work/study plan. Please ensure this is compliant with the Project Licence protocol and that it is easily understandable for lay members of the Committee.	

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Please state what you aim to achieve and how you intend to do so.	
Please illustrate how this work meets the objectives of the Home Office Project Licence. [Maximum 250 words please]	

7 Animals/Species

Give details of numbers, ages, sexes, strains/breeds and origin (*where animals are to be sourced from)*	Species Nu Age/Sex Groups/numbers Origin / Supplier:

8) 3Rs

8.1) Replacement

Replacement Please add a statement to confirm that there are no available alternatives to animal use.	

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Please confirm that you have undertaken steps to ensure that the information you aim to obtain is not already available – that there are no publications etc.	

8.2 Reduction

Please read the Appendix at the end of this document for advice/requirements.

Reduction Statistical review: explain animal numbers and the statistical analysis and calculations used to provide group sizes. Give details of statistician incl. name and date.	
Explain how the study is designed.	
Explain how the animals will be randomised or reasons if not randomised.	
Give details on blinding or reasons if study is not blinded.	

8.3) Refinement

Refinement Please advise why the specified animal model has been chosen - is it the lowest justifiable, in terms	

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of capacity for suffering, for the scientific output?	
What procedures will be carried out? List all procedures, frequency, use of anaesthesia, methods of restraint, volumes of substances administered and/or taken, details of inoculate. Please add how you intend to minimise any sampling or other techniques being undertaken.	
What are the expected adverse effects? What are the harms? List all potential adverse effects from procedures as well as disease progression.	
Give details of the humane endpoints - Please include clinical score sheets for humane end points for procedures – to advise signs and action required *(For protocols with a moderate or substantial severity limit)*	
Housing and Enrichment Does the study require that animals be housed in a way that may cause additional stress or	

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distress, such as single housed or in isolation? Is there a requirement to change feeding or husbandry regimes or to withhold enrichment?	

9) Input from Named Persons

For studies that will use new/unfamiliar species, new techniques that have not been tried before or pilot studies where the outcome is not known and may not yield any results, the NIO/NACWO/NVS must be consulted prior to submission to the Ethical Committee. Please note their name and any advice given below.

NACWO	
NVS	
NIO	
Others (if applicable, give details)	

10 Training and Competence

Please confirm that all staff to be involved with the study are sufficiently trained and competent. *(e.g. competence to undertake regulated techniques (PiLs), Schedule 1 etc.)*	Yes No If No - please specify and request assistance from the NTCO.

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Who is the principal licencee? Give name and brief details of their training and experience	

For Committee Use –

11) Recommendation by the Ethical Committee

APPROVED - *no further action required*	Date of meeting:
ACTION REQUIRED: Applicant to make amendments *(as detailed right)* and return for final approval to – the chairman or a representative group or the full committee by …….. (insert date)	
NOT APPROVED - *give details as to why:*	

Appendix to the Ethical Review Form: Ethics Committee - Standards for statistical approval

Part of the role of the [Institute] Ethics Committee is to ensure that all research involving animals at [Institute] has been subject to the 3Rs (Replacement, Refinement and Reduction).

For Reduction to be achieved it is important that experiments have both a robust experimental design and statistical validity.

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The Ethics Committee membership includes a statistician.

Animal work requiring statistical input:

The committee statistician will confirm that a proposed experimental design is acceptable if it meets one of the three standards below:

1. The study design for the experiment has been prepared with the professional support of a statistician or with input from a scientist who is suitably competent in statistical analysis. This person should also be known to have relevant competence by the statistician representative on the Ethics Committee.
2. The study design for the experiment has been reviewed by a person with statistical skills known to have relevant competence by the statistician representative on the Ethics Committee.
3. The statistician on the Ethics Committee can confirm that the study design for the experiment exactly matches a study design prepared or reviewed professionally by a statistician known to have relevant competence, within the life time of the current project licence that the work is being undertaken.

Animal work NOT requiring statistical input:

- For animal usage to meet mandatory standards, these standards should be precisely quoted/cited, *e.g.* the European Pharmacopeia (A copy of the mandatory standard should be included to allow immediate reference).
- Non-experimental work where the minimum number of animals required is self-evident, *e.g.* antisera stocks to meet a defined demand.
- Applications should clearly state which of these standards the design meets.

In these cases, sufficient information should be provided to allow a competent statistician to reconstruct the calculation used to decide the minimum number of animals required by the study.

In most cases, the design should be sufficiently specific to be publishable as evidence of the statistical analysis planned for the study.

It is a requirement that all research projects involving animal experiments undertaken by/involving [Institute] staff have professional statistician time included when funding is applied for.

It is a requirement of the Ethics Committee that all work submitted for approval using the form has had statistical standards applied prior to submission.

Failure to provide this information will result in a delay until such time this has been obtained.

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10. Appendix 4: Practical Actions to Facilitate Welfare in Farm Animal High Containment Experiments

- Effective meetings before work commences so that everyone (scientists, NVS, NACWO and animal care staff) is aware of the welfare decision points within the facilities;
- WhatsApp (or other electronic communication tool) groups for ease of communications;
- Conduct non-infectious work outside of high containment (BUT must allow time for acclimatisation when moving into high containment). Being out of high containment makes it easier to train animals and habituate them to procedures to reduce stress;
- Selection of animals/breeds by temperament e.g. some breeds such as Limousin cows are unsuited to being in containment;
- Start experiment on a certain day so that the critical part will be early/mid-week:
- Sample early in the morning so that results (e.g. white blood cell counts and pathogen loads) are available that day to facilitate decisions on end-points;
- Experienced staff for the critical groups, e.g. unvaccinated controls;
- Provide environmental enrichment
- Technologies such as microchips, non-invasive bioimaging and remote telemetry can be helpful as they reduce handling;
- Be aware that as white blood cell counts and platelets decrease clotting time post venepuncture increases, so make appropriate provisions when planning work;
- Observe animals after sampling or feeding –lying down will often be the first sign for the need to be euthanised;
- CCTV can be helpful to increase observations BUT not as a substitute for extra monitoring;
- Ensure there is a wash-up meeting (or meetings if analysis of material generated is going to take some time) to ensure that both successes are captured and areas that could be improved are recognised and strategies to improve are put in place in a timely manner.

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11. Appendix 5: Examples of 3Rs Communication Activities

- Provide access to on-line information sources: for example, a central local intranet, external websites and on-line discussion groups;
- Provide a 3Rs staff newsletter or email alerts with information on 3Rs publications, grant availability, meetings, courses or other activities;
- Ask the NACWO, NVS, or HOLC to assist the NIO in assimilating 3Rs information and sharing it with each other and those who need to consider it. Staff in the named person roles often have a good national communications network through which to gather and disseminate information both locally and externally;
- Encourage project licence holders to keep the NIO informed about any developments in the 3Rs so that this information can be shared widely across the institution;
- Ask project licence holders to summarise any 3Rs developments for the Ethics Committee either annually, or at retrospective review. At some establishments this has been linked successfully to an internal 3Rs prize or poster day;
- Convey information through animal user group (and other similar) meetings;
- Encourage all staff to disseminate information on 3Rs and environmental enrichment innovations internally and externally through publications, posters and conferences; and
- Encourage staff to visit other establishments to observe different working practices, environmental enrichment or 3Rs initiatives; bursaries are available for such exchanges from organisations such as LASA, Laboratory animals Limited (LAL) and Animals in Science Education Trust (ASET).

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12. Appendix 6: Example Policy for Raising Concerns under Culture of Care for Staff

When to act:

If you have concerns about general animal well-being, or regulated procedures undertaken.

What to do:

1) Licensed procedural issue: If possible, raise directly with personal licensee undertaking the procedure or responsible for the animal.

2) Animal well-being issue: Contact the Named Animal Care and Welfare Office (NACWO) or the Named Veterinary Surgeon (NVS).

Under culture of care it is hoped that that issues can be resolved by these actions. It is important that the project license holder responsible is informed of any concerns and what has been done to resolve them.

What to do if this fails:

If the concern is not resolved raise it with the Chair of the Ethics Committee or the institute senior manager responsible.

Note: Any concern raised will be investigated in confidence. If an individual raises a genuine concern in good faith it does not matter if it becomes apparent that they are mistaken.

Feedback:

The outcome of the investigation and course of actions will be fed back to staff raising the concern, the Ethics Committee and the parties involved.

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13. Useful Links and Resources

13.1. Committee Structure and Function

- RSPCA and LASA (2015) *Guiding Principles on Good Practice for Animal Welfare and Ethical Review Bodies*, *Third Edition*. UK: RSPCA and LASA, pp.62. Available at: http://www.lasa.co.uk/PDF/AWERB_Guiding_Principles_2015_final.pdf (accessed 13/5/19)
- Jennings M and Smith J (2015) *A resource book for lay members of ethical review and similar bodies worldwide*. UK: RSPCA, 64pp. Available at; https://view.pagetiger.com/EthicalReviewJanuary2015 (accessed 14/5/19).
- Hawkins P and Hobson-West P (2017) *Delivering Effective Ethical Review: The AWERB as a 'Forum for Discussion'*. UK; RSPCA, 11pp. Available at: https://view.pagetiger.com/AWERB/AWERB (accessed 15/5/19).
- European Commission (2014) *Working document on Animal Welfare Bodies and National Committees to fulfil the requirements under the Directive*. Brussels: European Commission, 28pp. Available at: http://ec.europa.eu/environment/chemicals/lab_animals/pdf/guidance/animal_welfare_bodies/en.pdf (accessed 15/5/19).

13.2. Ethical Review and Harm Benefit Analysis

- The RSPCA Ethical Review Website: https://science.rspca.org.uk/sciencegroup/researchanimals/ethicalreview (accessed 13/5/19)
- European Commission (2013) *Working document on Project Evaluation and Retrospective Assessment*. Brussels: European Commission, 42pp. Available at: http://ec.europa.eu/environment/chemicals/lab_animals/pdf/guidance/project_evaluation/en.pdf (accessed 14/5/19).
- European Commission (2012) *Working document on a severity assessment framework*. Brussels: European Commission, 71pp. Available at: http://ec.europa.eu/environment/chemicals/lab_animals/pdf/guidance/severity/en.pdf (accessed 14/5/19).
- Animals in Science Regulation Unit (2015) *The Harm–Benefit Analysis Process New Project Licence Applications Advice Note: 05/2015*. UK: Home Office, 36pp. Available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/660238/Harm_Benefit_Analysis__2_.pdf (accessed 15/5/19).

13.3. Systematic Review and Searching for Information on the 3Rs

- SYstematic Review Centre for Laboratory animal Experimentation (SYRCLE) https://www.radboudumc.nl/en/research/departments/health-evidence/systematic-review-center-for-laboratory-animal-experimentation
- Hudson-Shore M (2019) *Searching for information on 3Rs and 3Rs Resources Presentation*. Available at: https://norecopa.no/media/8214/mhs-searching-for-information-on-3rs-and-3rs-resources-jan-2019.pdf (accessed 15/5/19).

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13.4. Training and Competency

- RSPCA and LASA (2017) *Developing Induction Materials for AWERB Members*. UK: RSPCA and LASA, 11pp. Available at: http://www.lasa.co.uk/wp-content/uploads/2017/04/AWERB-IP-Final.pdf (accessed 14/5/19).
- RSPCA Lay Member's Forum Website: https://science.rspca.org.uk/sciencegroup/researchanimals/ethicalreview/differentsystems/uk/events (accessed 14/5/19).
- FRAME Training School in Experimental Design and Statistics Website: https://frame.org.uk/training-events/training-school/ (accessed 14/5/19).

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