

Advice Note 02/2015: Animals (Scientific Procedures) Act 1986

Use, Keeping Alive and Re-use

Date: October 2015

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Summary

The document explains the interpretations of the terms 'use', 're-use' and 'continued use' under the Animals (Scientific Procedures) Act 1986 (ASPA). It also provides advice on the criteria that must be satisfied to keep animals alive at the end of a series of regulated procedures. See also the Guidance of the Operation of the Animals (Scientific Procedures) Act, March 2014¹.

The use of an animal involves one or more regulated procedures applied for a particular purpose. This 'use' lasts from the time the first regulated procedure is applied to that animal until completion of observations or collection of data or products for that particular purpose.

At the end of each use, a decision must be taken as to whether the animal can be kept alive. Any animal that, in the opinion of the personal licensee or the veterinary surgeon (VS), is suffering or is likely to suffer as a result of the regulated procedures at the end of its use must be killed **[ASPA section 15, PPL condition 11]**. Killing is often necessary to achieve the scientific objective or may be necessary as a control measure to limit suffering. Normally it will be clear in the project licence if some animals might be kept alive.

Animals that are kept alive must be maintained at the establishment under the supervision of a veterinary surgeon (VS) or the Named veterinary Surgeon (NVS)² until they are humanely killed, re-used, re-homed, set free or moved to another establishment **[PEL condition 23]**.

Animals that have been kept alive might be re-used subject to legal controls intended to limit suffering, including consideration of the animal's lifetime experience **[ASPA section 14]**. Re-use is one of the ways to strike an appropriate balance between refinement and reduction – balancing the degree and nature of suffering due to the re-use against a reduction in numbers of animals used and avoidance of using naive animals. All re-use must be authorised by the Secretary of State.

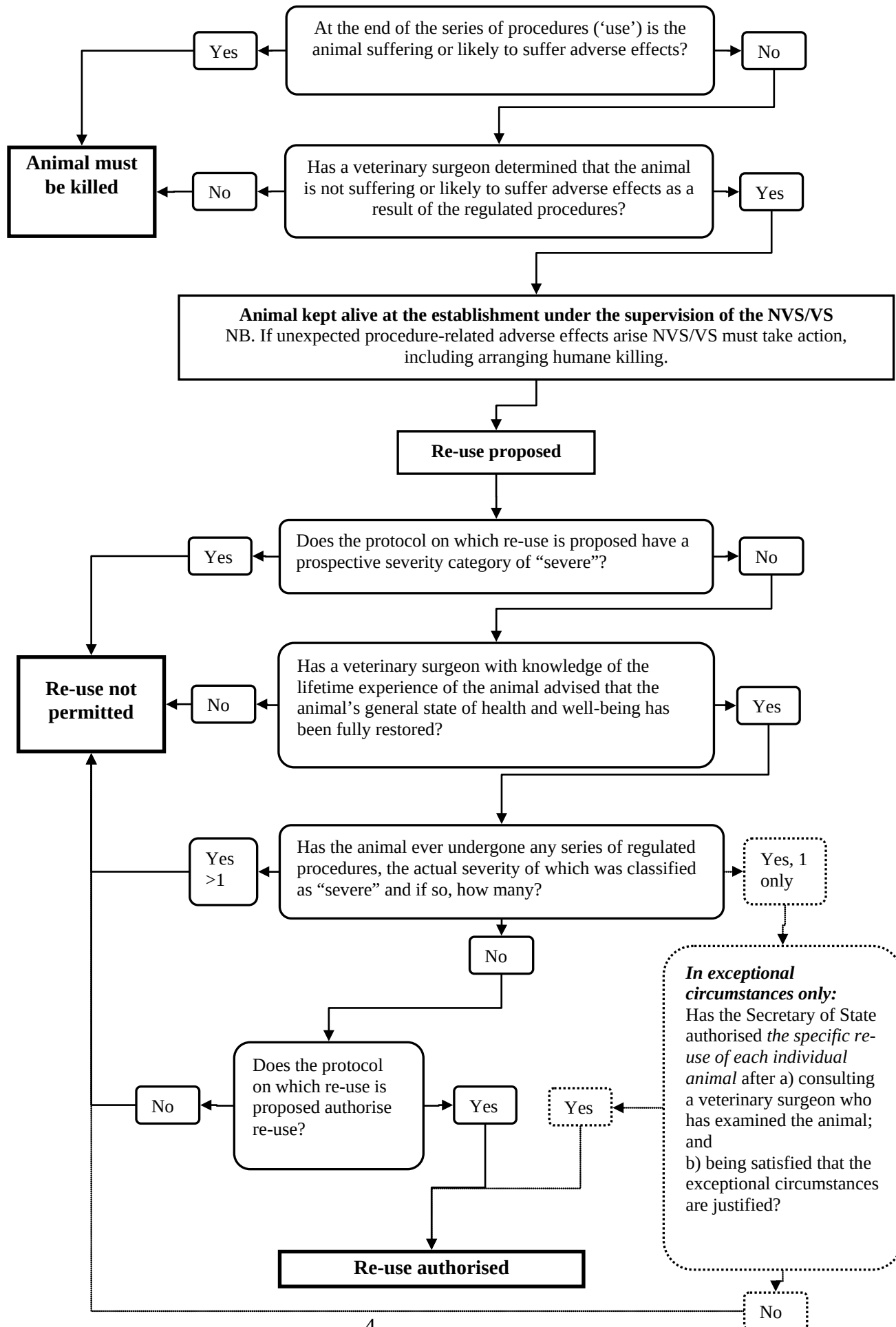
When a (series of) regulated procedure(s) is proposed the thought process should be:

- o Is this 'use' or 're-use'?
- o Is it permissible under ASPA?
- o Is it provided for in the project licence authorities?
- o Is the use/re-use likely to provide scientifically valid outcomes?
- o Will it strike an appropriate balance between reduction and refinement?

Decision making is summarised in Figure 1 and explained further in the rest of the document.

¹ Available from the GOV.UK website: <https://www.gov.uk/government/publications/operation-of-aspa>

² Where this Advice Note uses the term 'NVS', this can be taken to include an 'other suitably qualified person (SQP)' named on the establishment licence instead of an NVS. Where 'veterinary surgeon' is specified this should be a Member of the Royal College of Veterinary Surgeons (MRCVS). Note: where the project licence holder is a veterinary surgeon or SQP, then another veterinary surgeon should undertake these duties to prevent a conflict of interest.

Figure 1: Decisions for keeping animals alive and for prospective re-use

1. Introduction

This document is primarily intended to provide operational guidelines to inspectors and those working under ASPA to aid consistent interpretation of terms relating to use and re-use of protected animals across the UK. This current interpretation aims to strike a rational balance between reduction and refinement considerations, taking account of the legal constraints on keeping alive and re-use. The UK has a tradition of high-quality science coupled to high standards of animal welfare. This document aims to support both these considerations.

This document:

- is based on the current Guidance on the Operation of the Animals (Scientific Procedures) Act 1986, March 2014, and supersedes all previous sources of information published by the Home Office explaining the concepts of 'use', 'continued use' and 're-use';
- provides an explanation of how these terms should be interpreted; and
- provides examples of the project licence authorities needed.

It is aimed principally at the Home Office Inspectorate, existing licensees and applicants for project licence authorities under ASPA, Animal Welfare and Ethical Review Body (AWERB) members as well as veterinary surgeons and others who are involved in the decision-making process relating to keeping animals alive and re-use. It is important that those involved in training practitioners are aware of the content.

This document will also inform non-practitioners wishing to know more about these issues.

This document does not provide advice on re-homing issues or setting free. Please refer to other advice notes issued by the Home Office and the Guidance on the Operation of the Act for such information.

1.1 How will this Advice Note be reviewed and updated?

The Secretary of State intends to review the information contained in this and other advice notes approximately two years after publication. The intention is that these advice notes will eventually be incorporated into the Guidance on the Operation of the Act.

If you would like to provide comments on this Advice Note or otherwise contribute to the next version, please send your comments to ASRUBusinessSupport@homeoffice.gsi.gov.uk.

2. Definition of terms

2.1 Use of protected animals

The terms 'protected animal' and 'regulated procedure' are defined in ASPA sections 1 and 2.

The **use** of a protected animal under project licence authority extends from the time the first regulated procedure is carried out up to the time when it is clear that the observations or the collection of data (or other products) for a particular scientific purpose (usually a single experiment or test), are completed.

2.2 Re-use

Re-use is a term defined in Article 16 of Directive 2010/63/EU as the subsequent use of a protected animal that has already completed a series of regulated procedures for a particular purpose when a different animal on which no regulated procedure has previously been carried out (also referred to in this note as a *naïve animal*) could also be used.

It follows that the sole criterion for determining if an animal is being **re-used** is whether you could use a naïve animal for the second or subsequent use and still achieve your scientific objective.

Animals may, with appropriate legal authority, be re-used within the same programme of work or on different programmes of work.

2.3 Differentiating use and re-use

It is important to distinguish **use** of an animal from **re-use**. A logical approach helps to make this distinction, particularly when animals might be undergoing the same or a very similar series of regulated procedures.

The consideration is:

- *could* a different animal on which no procedure has previously been carried out (naïve animal) be used for the subsequent study, even if that means the naïve animal undergoing model preparation such as surgery?
 - o if yes, then any further regulated procedures would be **re-use**;
 - o if no, then any further regulated procedures are conducted as one **use** of the animal.

Examples of why a naïve animal could not be used are:

- there is data linkage between studies e.g. a crossover or longitudinal study requires data from the same individual animal – this would be written as use on one project licence protocol with a number of dosing and sampling steps;
- the use requires an animal that has undergone some type of model preparation or screening procedures on another protocol – this is one use written as continued use from one protocol to another.

Example 1. Sheep blood is needed for scientific use. It is proposed to take blood samples from an individual sheep every two months. Is taking the second and subsequent blood samples one use or re-use?

- Scenario A: The purpose is to monitor the levels of a hormone in the blood at different time points in the reproductive cycle. There is a scientific need to take multiple samples from the same animal. This is one, single use involving taking multiple samples, as set out in the protocol.
- Scenario B: The purpose is to use the blood to prepare plates for bacteriology. A different sheep could be used to supply blood on each occasion. There is no scientific need to take multiple samples from the same animal. The second and subsequent sampling from the same individual sheep is re-use. The project licence protocol will specify that a single sample is taken, the animal is kept alive and can be re-used.

Example 2. A series of compounds is administered to a rat and after each administration a series of blood samples is taken to evaluate the pharmacokinetics of the compounds. Are the repeated dosing/sampling cycles use or re-use?

- Scenario A: Serial data from the same individual animal is needed to interpret subsequent data (within animal design). Data from a different animal would not be suitable for the scientific purpose. This is one, single use.
- Scenario B: Data on metabolism of each compound will be interpreted independently, without reference to other findings and therefore a different animal could have been dosed. Each dosing/sampling cycle will need to be authorised as re-use.

Example 3. Fish gametes are obtained by gentle manual extrusion under general anaesthesia.

- Scenario A: There is a scientific need to take gametes on multiple occasions from the same individual fish for one particular study. This is one use and the protocol will specify multiple extrusion occasions.
- Scenario B: A different fish (albeit of the same genotype) could be used to supply gametes on each occasion. There is no scientific need to take multiple gametes from the same fish. The second and subsequent extrusion from the same individual fish is re-use. The project licence protocol will specify that extrusion is undertaken once, healthy fish are kept alive and are re-used.

2.4 Continued use

Continued use is an administrative way of specifying use over more than one project licence protocol within the same or different project licence(s). The regulated procedures authorised sequentially by the two (or, rarely, more) protocols must be essential to achieve the intended particular purpose.

Continued use is typically described to cover preparation and then experimental use on other protocols in the same or another project licence, for example:

- genetic alteration such as breeding/creation of genetically altered animals;
- surgical preparation such as cannulation of blood vessels;
- chemical preparation such as tumour induction;
- physical preparation such as irradiation.

‘Continued use’ is merely a convenient mechanism to simplify project licence authorisation and to avoid undue repetition in the project licence. It is the same as ‘use’ in all respects other than how the series of procedures is laid out in the project licence. Note that there cannot be ‘continued use’ within or back onto the same protocol.

Continued use between protocols should generally be avoided in cases other than model preparation and subsequent experimental use as the series of authorised procedures making up that use and associated harms can become difficult to follow. In all cases it is essential that the series of regulated procedures that any one animal will undergo, and hence the harms it is likely to experience, is clear and appropriately provided for within the project licence(s).

Example 4. A female genetically altered frog is bred and a regulated procedure is used to confirm the genotype. This is specified in one project licence protocol. In order to obtain a large number of eggs, injections are given to induce superovulation on another project licence protocol. It is essential for the subsequent use of the eggs for the genotype to be known, therefore this is one use. Frogs are moved from the breeding protocol to the superovulation protocol as continued use.

Example 5. A dog is implanted with telemetry devices on a 'surgical preparation' project licence protocol. It is then used for a first experiment testing the effect of compound X on the cardiovascular system using outputs from the telemetry devices on a different 'test' protocol. This is continued use. The combined regulated procedures on the 'surgical preparation' protocol and on the 'test' protocol describe one use.

The dog is then kept alive and used in a second experiment to test the effects on the cardiovascular system of an unrelated compound, compound Y, again using outputs from the telemetry devices. Investigation of compound Y is not related to the previous use investigating compound X. A naïve dog could have undergone surgery and been used to test compound Y but it might strike an appropriate reduction:refinement balance to re-use a dog that has already been surgically prepared and is habituated to the laboratory environment, procedures and staff. The second experiment (series of procedures) to test compound Y is re-use.

3. Keeping an animal alive at the end of a procedure

The use of an animal ends when it is clear that no further observations/collection of data or products is needed for that particular purpose or when a humane end-point has been reached.

At the end of the use, the personal licensee must arrange for the animal to be killed if the animal is suffering or likely to suffer adverse effects as a result of being subjected to the series of regulated procedures [**ASPA section 15**].

If the personal licensee considers that the animal is not suffering or likely to suffer at the end of a series of regulated procedures, it may be kept alive only if a veterinary surgeon (or other person competent to make that decision and following direction from a veterinary surgeon) has also determined that the animal is not suffering and is not likely to suffer adverse effects as a result of the regulated procedures [**PPL Standard Condition 11**].

These decisions as to whether or not an animal needs to be killed must be taken without undue or unreasonable delay, i.e. the assessment must be made at the earliest opportunity in order to avoid unnecessary suffering. Procedures should be carefully planned so that if there is a need to keep animals alive during data analysis (in case further data is required), the duration is minimised to prevent avoidable suffering.

This decision-making process applies whether the animal is intended to be re-used at some point in the future, re-used almost immediately, re-homed or set free, transferred to another establishment or maintained at the establishment.

What is 'suffering'?

In considering the degree of suffering in the context of ASPA section 15 and PPL Standard Condition 11, 'suffering or likely to suffer' means 'suffering or likely to suffer a degree of pain, suffering, distress or lasting harm as a result of the previously applied regulated procedures equivalent to suffering above the lower threshold for regulation'. Any interventions or measures that are necessary to maintain an animal's state of health or well-being as a consequence of the regulated procedures must be included when considering the degree of suffering.

What is 'likely to suffer'?

In this context, 'likely' means on the balance of probabilities i.e. more likely than not.

Animals kept alive become the responsibility of the establishment licence holder and must be held at the establishment under the supervision of the NVS or a veterinary surgeon [**PEL Standard Condition 23**]. The NVS/VS is tasked with ensuring the animal's well-being until such time as it is killed, re-used, re-homed, set free or transferred to another licensed establishment.

If, during this time, the animal unexpectedly experiences adverse effects as a result of the previous regulated procedures, the NVS/VS is responsible for ensuring that immediate and appropriate action is taken. For minor effects (not causing suffering as defined above) which are expected to resolve quickly, veterinary treatment could be provided but in other cases the veterinary surgeon should arrange for the animal to be humanely killed without delay. ASPA cannot authorise the conduct of any remedial procedures equivalent to regulated procedures, including surgery to remove implants or restore defects, unless this is necessary for the scientific programme of work. If incidental, non-procedural adverse effects arise, the NVS should, as is normal practice, exercise their professional judgement as to providing appropriate

veterinary treatment or other course of action under the Veterinary Surgeons Act.

If an animal is suffering at the end of its use then it cannot be kept alive. For example, if it has a painful condition or its physiology is altered detrimentally it must be killed. The tests for keeping it alive are not met.

Where there is a permanent genetic alteration that is regulated under the Act, the same decision-making principles can be applied at the end of the animal's experimental use. If the animal is deemed not to be suffering or likely to suffer as a result of the procedures (including the genetic alteration), then that individual genetically altered animal might be kept alive under the supervision of the NVS/VS.

Where killing is not necessary for the scientific use of that animal and is not required as a control measure by the adverse effects section of the protocol, the possibility of keeping alive a protected animal will normally have been considered in the 'fate' section of the project licence protocol so that the criteria for keeping alive are well known to all those involved in the use and care of the animals. Animals can be kept alive even if 'keeping alive' is not explicitly specified in the project licence protocol *provided that* the requirements outlined above are met in full, agreed locally and adequately documented.

3.1 Keeping alive for a limited period

There are some scenarios where suffering is not likely immediately but becomes more likely as the animal develops or ages. For example, it may be known that rats with intra-abdominal telemetry devices are not likely to develop intra-abdominal complications for six months after implantation, but after six months complications become progressively more likely.

In determining the likelihood of future suffering, the NVS/VS may take account of the planned length of time the animal will be held under their supervision before the animal is killed or re-used. If adverse effects are not *likely* within a pre-defined timeframe and there is a realistic expectation that the animal will be re-used within that time, then the animal could be kept alive for prospective re-use for that time period only. The NVS/VS should pre-define the length of time the animal is to be kept alive under their supervision and make this known to care staff.

There are some scenarios where an animal is not suffering at the time its use ends, but is likely to do so within a short period of time or else interventions that are above the equivalent of the lower threshold are necessary in due course to maintain the animal in good health. The project licence holder, NACWO, NVS and inspector might consider that re-use of some of these animals strikes a good reduction:refinement balance. Can this be provided for within the controls of the Act?

In such cases the animal must meet the criteria for keeping alive, albeit for a short period of time. The animal must also meet the criteria for re-use (section 4). Provided the personal licensee and veterinary surgeon can make their determinations within the short time period during which the animal is not likely to suffer (with good organisation this could be minutes), then in appropriate cases the animal could be placed back under the authority of a project licence that authorises its maintenance pending further study use. This is explained further in section 4.3.

3.2 Examples of decisions relating to keeping alive

Example 6. An animal has been rendered diabetic by administration of streptozotocin as part of an authorised project. Regular injections of insulin are needed to maintain the animal in good health. Maintaining the animal's state of health and well-being as a consequence of the regulated procedures requires interventions equivalent to above the lower threshold for regulation and the animal's health has been permanently and detrimentally affected (it is significantly physiologically abnormal); therefore the animal cannot be kept alive after use.

Example 7. A pig has been dosed and blood sampled to determine pharmacokinetic properties of a non-toxic substance. At the end of its use it is not suffering adverse effects and could therefore be kept alive at the establishment under the supervision of the NVS/VS.

Example 8. A rat has been dosed and blood sampled in order to determine pharmacokinetic properties of a toxic substance. At the end of its use it is suffering persisting adverse effects and must be killed promptly.

Example 9. A dog has been implanted with a telemetry device that allows it to carry out all normal physiological and ethological functions and to be housed under Code of Practice³ conditions. It is not likely to suffer adverse effects due to the previous regulated procedures, including implantation of the telemetry device, and does not require invasive interventions to maintain its normal state of health and well-being. It could be kept alive at the establishment under the supervision of the NVS/VS.

Example 10. An immunodeficient mouse is bred (a regulated procedure) on a breeding and maintenance protocol and transferred to another protocol for further regulated procedures for a particular purpose. At the end of the use, it is judged not to be suffering nor is it likely to suffer when housed under appropriate conditions. It can be maintained under the direct supervision of the NVS/VS and could be re-used if the tests of Section 14 of the Act can be met.

³ Code of Practice for the Housing and Care of Animals Bred, Supplied or Used for Scientific Purposes. Available from the GOV.UK website: <https://www.gov.uk/government/publications/code-of-practice-for-the-housing-and-care-of-animals-bred-supplied-or-used-for-scientific-purposes>

4. Eligibility for re-use

All re-use of protected animals requires the consent of the Secretary of State. Consent is given in the project licence. **ASPA section 14** establishes the qualifying criteria for re-use.

An animal should not be re-used if its previous use in regulated procedures has compromised its suitability, either in welfare or scientific terms, for re-use. Effects of previous treatments may not always be clear and any additional variability due to previous use should be carefully considered when re-use is proposed if this may impact on numbers of animals required or the quality of the scientific outcome. In any event, an animal should not be considered as suitable for re-use if it is suffering as a result of any health or welfare issues, including those not related to the previous use.

There are three initial tests under ASPA section 14 to determine whether an animal can be re-used.

1. The prospective severity category of the protocol in which the animal is to be re-used must be 'non-recovery', 'mild' or 'moderate'. Re-use on a protocol prospectively categorised as 'severe' is not permitted under any circumstances.
2. A *veterinary surgeon with knowledge of the lifetime experience* of the animal(s) must have advised that their *general state of health and well-being* is likely to have been *fully restored* following the series of regulated procedures.

o ***What is 'knowledge of the lifetime experience of the animal(s)'?***

In respect of lifetime experience, a user (e.g. personal/project licence holder) would normally be expected to know the conditions under which animals have been bred and any previous use under ASPA and to exercise due diligence in providing information to the veterinary surgeon. The veterinary surgeon must take account of the degree of suffering experienced by the animal from protected animal stage to the time of proposed re-use, as far as they can reasonably know, and make a judgement as to the acceptability of further use in regulated procedures. The veterinary surgeon therefore plays a key role in ensuring that animals are not exposed to unreasonable re-use under ASPA, taking account of cumulative suffering and the duration of being held at the establishment. The veterinary surgeon is responsible for making a professional judgement (in accordance with Royal College of Veterinary Surgeons (RCVS) guidance for NVSs) about the current and likely future quality of life of the animal.

o ***What does 'general state of health and well-being has been fully restored' mean?***

'General health and well-being' should be judged broadly in terms of the ability of the animal to perform, unaided, an adequate repertoire of functions to maintain itself in good health. In some animals there may be a persisting physical impairment or chronic alteration (see examples 11, 12 and 13) but the animal must be:

- able to eat, drink, excrete, respire, move and interact with peers;
- free of disease;
- not suffering pain;
- free of fear, distress or anxiety.

In practical terms, restoration of general health and well-being means that the animal is not suffering a persisting condition by which it is unable to cope with the requirements of daily life to maintain its health and well-being. The benchmark for 'suffering' can again be taken to be equivalent to the degree of suffering that would cross the lower threshold for regulation.

3. The *actual severity* experienced by the animal in any previous regulated procedure/series of regulated procedures was not classified as 'severe' (but see severe pain and distress below).

4.1 Severe pain and distress

Where an animal has been subjected to a series of regulated procedures and the *actual severity* of those procedures has been classified as 'severe', consent may be given for re-use only in exceptional circumstances. The Secretary of State's consent must relate to the *specific, individual animal* concerned. Consent will only be given after the Secretary of State has consulted a veterinary surgeon who has examined the animal for advice whether consent should be given. Furthermore, the Secretary of State must be satisfied that there are exceptional circumstances (for example those described in Example 13) that justify that particular animal being used for the further series of regulated procedures.

Of course, any such animals will need to pass the **ASPA section 15** test (see section 3) to be kept alive before they can be re-used.

If you consider that re-use under such circumstances is justified, you will need to apply, on a case-by-case basis, to ASRU at Home Office, Mailpoint A11/12, 1st Floor Peel NE, 2 Marsham Street, London SW1P 4DF or by email to your Single Point of Contact, providing the information and reassurances described above. You must not proceed without written consent for re-use of that specific animal.

4.2 Important considerations

Previous use must not compromise any subsequent use, for example:

- an animal that has been used in such a way that liver function has been or may have been compromised (even though the animal appears clinically normal) should not subsequently be used in work that requires or depends upon normal physiology;
- previously implanted telemetry devices should be shown to be adequately functional for subsequent studies that require that functionality.

Animals should not be held for indefinite periods of time where there is no realistic prospect of re-use. Even good laboratory conditions of housing and husbandry will compromise the animal's well-being to some degree and ageing animals may develop non-procedural-related clinical conditions. There should be regular, planned reviews by the NVS/VS at appropriate intervals to confirm that the animal continues to be suitable to be kept alive. General health checks might be undertaken by a veterinary surgeon under the Veterinary Surgeons Act but any testing involving regulated procedures would require project licence authority.

4.3 Maintenance pending re-use

If maintaining the animal for a short period of time does not cause suffering or require measures equivalent to the lower threshold for regulation (see section 3) and the animal meets the tests for re-use under section 14 of ASPA, it may be possible to re-use the animal in some cases.

The possibilities might then be (with appropriate project licence authority):

- immediate non-schedule 1 killing;
- immediate application of general anaesthesia and use of the animal in a study without it ever regaining consciousness;
- transfer to a project licence as re-use, either:
 - o onto an optional maintenance step within the project licence protocol on which it is to be used further; or
 - o onto a maintenance project licence protocol which specifies continued use onto more than one experimental project licence protocol for which the animal would be a suitable subject.

The receiving project licence holder must arrange for a personal licensee to take responsibility for the animal and this should be shown clearly on the cage label. Primary responsibility for the animal's health and welfare then lies with the project and personal licensees, although the named persons will continue to have oversight.

Where animals are transferred onto a maintenance step or protocol, the adverse effects section of that receiving protocol must consider expected harms, controls and humane end-points for all animals during the maintenance period awaiting further experimental use. If unexpectedly adverse effects arise that exceed the controls in the licence, the animal must be humanely killed. There is no mechanism to transfer the animal to another protocol or to another project licence before the animal has completed the re-use as described in the programme of work and been considered suitable to be kept alive and to be re-used further.

Example 11. A rat has been surgically prepared with an indwelling vascular cannula in order to take a series of blood samples following oral dosing with a compound. The animal has been fitted with a jacket and tether system. Following recovery from surgery, a series of related non-toxic test materials was administered to the animal to assess pharmacokinetics. This was one, single use. On completion of the dosing/sampling procedures the animal remains tethered, jacketed and in single housing. If held in these conditions for a prolonged period of time these restrictions would cause suffering or distress equivalent to suffering above the lower threshold for regulation **[ASPA section 15]**.

Surgical restoration, e.g. removal of the cannula, to restore the animal's state of health and well-being in order to keep it alive, would not be permissible under ASPA.

If maintaining the animal for a short period of time does not cause suffering or require measures equivalent to the lower threshold for regulation (see section 3) and the animal would be eligible for re-use under section 14 of ASPA, it may be possible to transfer the animal to a maintenance step/protocol on which re-use is authorised. This will need to be done swiftly before any adverse effects develop. The animal will be maintained pending further experimental use under project licence authority and will be subject to the controls over the adverse effects specified in the protocol.

5. 3Rs considerations

As recognised by Recital 25 to Directive 2010/63/EU, 'The number of animals used in procedures could be reduced by performing procedures on animals more than once where this does not detract from the scientific objective or result in poor animal welfare. However, the benefit of re-using animals should be balanced against any adverse effects on their welfare, taking into account the lifetime experience of the individual animal. As a result of this potential conflict, the re-use of animals should be considered on a case-by-case basis.'

Re-use of surgically prepared animals for more than one study, especially where the suffering associated with the preparation stage is high and the suffering associated with the study stage is low, can reduce both the total number of animals used and require fewer animals being subjected to the preparation steps. Examples 11 - 13 illustrate this.

This means that the reduction in numbers of animals that might be achieved by re-use must be weighed against the greater harms that will be suffered by individual animals. Project licence applications must contain sufficient information to allow the inspector to consider re-use as part of their harm–benefit analysis and to allow the Secretary of State to make a judgement on a case-by-case basis (see section 6 for the information needed).

Where an animal is transferred promptly to a maintenance step on a protocol (re-use) pending continuation of the re-use, any harms arising from maintaining these animals must be justified by the benefits of the subsequent re-use and reduction in numbers of animals used in the programme of work.

In considering re-use, there are a number of points at which the animal's welfare will be safeguarded:

- section 15/PPL Standard Condition 11 determination of suitability to keep alive;
- period of time maintained under the direct supervision of the NVS/VS as non-naïve 'stock';
- veterinary surgeon's consideration of the lifetime experience;
- veterinary surgeon's determination of general health and well-being;
- project licence limitations on re-use;
- project licence controls over maintaining animals awaiting the further use.

The Animal Welfare and Ethical Review Body (AWERB) will play a role in these issues by:

- considering applications for project licences and project licence amendments;
- providing a forum for discussion and the development of ethical advice relating to use and re-use;
- supporting named persons and other staff dealing with animals on animal welfare and ethical issues.

5.1 Examples of weighing reduction against refinement

Example 12. A dog has been surgically implanted with a vascular access port which requires periodic transcutaneous flushing. Periodic interventions above the threshold are required to maintain the patency of the access port but the dog is not immediately suffering adverse effects. The veterinary surgeon has advised that the general state of health and well-being has been fully restored and in all respects the tests of sections 15 and 14 of ASPA are met. If a further study is planned that requires the use of a dog with a vascular access port then either another dog could undergo surgery or it might strike a better reduction:refinement balance to re-use this dog by transferring to a maintenance step/protocol that authorises transcutaneous flushing pending the next study. The animal is subject to PPL controls.

Example 13. A marmoset is treated with a chemical to create a brain lesion as a model for Parkinsonism in humans. The animal suffers severely during the post-treatment phase but with nursing recovers and is able to eat, drink, perch, groom, interact with its peers and move around the enclosure. It is not suffering ongoing pain or distress. The animal is used to test the effectiveness of a set of related candidate drugs for the treatment of Parkinson's disease. If, at the end of the testing, the animal is in a condition which meets the criteria for being kept alive at section 4, it can be kept alive at the establishment under the direct supervision of the NVS/VS. The animal is not normal but continues to be able to eat, drink, perch, groom, interact with its peers and move around the enclosure. The condition is expected to remain stable for many years. Rather than put more marmosets through the severe brain lesioning phase, re-using the animal to screen more drugs strikes an appropriate reduction:refinement balance. Re-use would require specific authority from the Secretary State *on each and every occasion* it is re-used as the actual severity suffered by the animal during its first use was severe.

6. Applying for project licence authorities

It is important that the project licence application provides sufficient information so that:

- a correct harm–benefit analysis can be undertaken;
- the correct legal provisions are made in the project licence authority;
- it is clear to personal and project licence holders, named persons and Home Office inspectors what the current ‘use’ status of any particular animal is;
- it is clear at all times who is responsible for the animal; and
- a correct statistical return can be made to the Secretary of State at the end of each year.

6.1 Keeping alive

For project licences where animals will be kept alive, the project licence applicant should explain in Part D of the application form:

- the types of animals that might be kept alive; and
- the criteria that will be used by the veterinary surgeon to determine that animals can be kept alive, including any limitations on the period of time that the animal will be held under the supervision of the NVS/VS.

The ‘fate’ section of the protocol in the project licence application should be appropriately completed, for example:

Fate of animals not killed at the end of the protocol

Indicate the proposed fate of animals which are not killed at the end of the protocol.

☐

Continued use in another protocol under this or another project licence - give details below and ensure that you give an appropriate cross reference in the protocol sheet under which the continued use will occur.

☒

Kept alive at the designated establishment. Note that any subsequent re-use must be authorised in the relevant project licence.

☐

Discharge from the controls of the Act by setting free to the wild or by re-homing. Specify below the particular circumstances when animals may be set free to the wild or re-homed and detail how the qualifying criteria set out in section 17A(3) & (4) will be met.

[Example text] Kept alive:

Animals that have suffered no more than mildly during the course of procedures and which are not suffering or likely to suffer as a result may be kept alive in accordance with Standard Condition 11.]

6.2 Re-use

The criteria that have to be met before an animal is re-used must be made explicit in the project licence and should be known to all appropriate staff dealing with the animals. The NVS should be actively involved, together with the relevant personal and project licence holders and the NACWO, in determining these criteria.

For project licences where animals will be re-used, the applicant should explain in Part D:

- the reason for the proposed re-use, taking account of the balance between refinement and reduction;
- the welfare and scientific considerations that will be used to determine suitability for re-use; and
- the criteria that will be used by the veterinary surgeon to determine that animals can be re-used, including any limitations on the period of time that the animal will be held under the supervision of the NVS/VS.

Where animals are to be re-used on a protocol, this must be made clear at the start of the protocol. So for a protocol receiving animals for re-use:

Continued use:
Re-use: [Example text Animals that have been kept alive and maintained under the supervision of the NVS may be re-used in this protocol.]

Where animals are kept for a limited period under the supervision of the NVS/VS, then animals that will be re-used should be transferred to the project licence on which they are to re-used.

The possibilities are:

- immediate non-schedule 1 killing – re-use on a non-recovery category protocol;
- immediate application of general anaesthesia and use of the animal in a study without it ever regaining consciousness - re-use on a non-recovery category protocol;
- transferring to a project licence as re-use either:
 - o onto an optional distinct and separate maintenance step within the protocol on which it is to be further used in regulated procedures; or
 - o onto a maintenance protocol which specifies continued use onto more than one experimental project licence protocol for which the animal would be a suitable subject.

When animals are transferred for maintenance pending further use, the applicant must specify: in the adverse effects section:

- likely adverse effects, controls and humane end-points for any 'maintenance pending further use' step of the protocol or the maintenance protocol as a whole. It is expected that the animals will remain in a suitable state of health and well-being, taking account of any model preparation the animal has previously undergone;
- controls on re-use, for example:
 - o maximum number of times; and/or
 - o performance standards e.g. patency of a cannula; and/or
 - o humane end-points in the form of behavioural and/or physiological indicators that animals are suffering as a result of long-term laboratory housing or as a result of being re-used.

It is likely that most project licences will specify a combination of these factors.

6.3 Continued use

Where animals are being transferred *to* a protocol for continued use, this should be specified by completing the box at the top of the protocol, for example:

Continued use:

[Example text Genetically altered animals (and related wild-type animals) for use in this protocol may be obtained from:
 protocol 4 of this project (Breeding and maintenance of genetically altered animals);
 or
 other projects with authority to breed and maintain genetically altered animals of that type and to provide them for use on other projects.]

Re-use:

Where an animal is transferred *from* a protocol for continuation of the single series of regulated procedures in another protocol, this is authorised by completing the 'fate' box, for example:

Fate of animals not killed at the end of the protocol

Indicate the proposed fate of animals which are not killed at the end of the protocol.

☒ **Continued use in another protocol under this or another project licence** - give details below and ensure that you give an appropriate cross reference in the protocol sheet under which the continued use will occur.

☐ **Kept alive at the designated establishment.** Note that any subsequent re-use must be authorised in the relevant project licence.

☐ **Discharge from the controls of the Act by setting free to the wild or by re-homing.** Specify below the particular circumstances when animals may be set free to the wild or re-homed and detail how the qualifying criteria set out in section 17A(3) & (4) will be met.

[Example text **Continued use:** Following any identification of genetic status, animals produced under the authority of this protocol and not used in any other regulated procedures may be supplied to other protocols in this project or to other projects with authority to use genetically altered animals of this type.]

Glossary

3Rs	The Three 'Rs' – replacement, reduction, refinement
Actual severity	The actual intensity of pain, suffering, distress or lasting harm experienced by an animal in a procedure or series of procedures. It should be the highest level experienced at any point during the course of the procedure and should take into account any cumulative effects
ASPA/The Act	Animals (Scientific Procedures) Act 1986
ASRU	Animals in Science Regulation Unit
AWERB	Animal Welfare and Ethical Review Body
Code of Practice	Code of Practice for the care and accommodation of animals issued under section 21 of ASPA
Harm–benefit analysis	An analysis in which the likely adverse effects in a procedure within a project are weighed against the potential benefits of the project for people, animals or the environment
Humane end-point	Clear, predictable and irreversible criteria that allow early termination of a procedure before an animal experiences harm that is not authorised or scientifically justified
Lower threshold	A level of pain, suffering, distress or lasting harm equivalent to, or higher than, that caused by the introduction of a needle in accordance with good veterinary practice
NACWO	Named Animal Care and Welfare Officer
Named Persons	People with specific responsibilities at an establishment, including the NACWO and NVS
NVS	Named Veterinary Surgeon
Pain, suffering, distress and lasting harm	Includes anything that affects the animal's physical, mental and social well-being including disease, injury and physiological or psychological discomfort, whether occurring immediately (such as at the time of an injection) or in the longer term (such as the consequences of applying a carcinogen)
PEL	Establishment licensed under ASPA
Personal licence	A licence issued under ASPA which qualifies an individual to apply a regulated procedure to specified animals in accordance with project licence authorisation
PPL	Project licence
Project licence	A licence issued under ASPA authorising a scientific programme of work
Protected animal	All living vertebrates, other than a human, including certain immature forms, and any living cephalopod
Protocol	For the purposes of this Advice Note, a 'protocol' means the procedure or series of regulated procedures specified as a numbered Procedure in the schedule of a project licence (a 'project licence protocol')
RCVS	Royal College of Veterinary Surgeons
Regulated procedure	Any procedure applied to a protected animal for a qualifying purpose which may have the effect of causing the animal a level of pain, suffering, distress or lasting harm equivalent to, or higher than, that caused by the introduction of a needle in accordance with good veterinary practice
Reduction	Methods which minimise the number of animals used per experiment
Refinement	Methods which minimise suffering and improve animal welfare
Schedule 1 killing	Schedule 1 to ASPA lists killing methods appropriate for different types of animal which are considered to be reasonably straightforward and

SQP
Terminal general
anaesthesia
VS

can be performed consistently in a humane manner by someone with appropriate training and supervision

Suitably Qualified Person (named on an establishment licence)

General anaesthesia during the course of which the animal is killed

Veterinary surgeon