Home Office

Advice Note

Animals (Scientific Procedures) Act 1986

Project Licence Standard Condition 18 notification

April 2018

Contents

Summary

- The Animals in Science Regulation Unit (ASRU) is the authority responsible for regulating the operation of the Animals (Scientific Procedures) Act 1986 (ASPA).

- All project licences issued under ASPA by ASRU contain 25 standard conditions, which set specific parameters for the package of work for any person working with animals under the terms of the licence.

- Project licence Standard Condition 18 (PPL SC18) requires project licence holders to notify the Secretary of State if constraints on severity or observance of other controls described in the project licence have been or are likely to be breached.

- Breaches may have various causes; they might arise from human error, such as an unanticipated failure to observe the welfare controls specified in the project licence, or from unexpected or unforeseeable events.

- Notification of the Secretary of State under PPL SC18 relates to breaches or likely breaches of either severity limits or any other controls set in the licence. Notification provides an important opportunity for the licence holder, the establishment and ASRU to review whether any changes need to be made. Notification under PPL SC18 is not the same as reporting a non-compliance.

- Notification under PPL SC18 should be made without delay. The completed PPL SC18 Notification Form at **Appendix 1** should be emailed to the assigned Inspector promptly. The person reporting should notify an ASRU Inspector by email or telephone within 72 hours of the events that are being reported.

1. Introduction

Project Licence Standard Condition 18 (PPL SC18) is one of 25 standard conditions applied to all project licences issued under the Animals (Scientific Procedures) Act 1986 (ASPA).

This Advice Note explains both the purpose of PPL SC18 and how project licence holders can comply with the requirements of the condition, that is the circumstances under which they should notify the Secretary of State of a breach, or likely breach, of a constraint on the licence.

Since ASPA was amended in 2013 to implement Directive 2010/63/EU, the Animals in Science Regulation Unit (ASRU) has noted a substantial increase in the volume of reports submitted in accordance with PPL SC18. This may be due, in part, to a new requirement to assess and record the actual severity that individual animals suffer. There may also be an element of reporting 'just in case'.

This Advice Note is aimed at those working under ASPA, to give them greater certainty about when to make a PPL SC18 notification, and when other methods of reporting should be considered instead.

It is aimed primarily at project licensees although it will be of interest to others with responsibilities under ASPA and those involved in training practitioners. This Advice Note will also inform non-practitioners wishing to know more about these issues.

This Advice Note does not provide specific advice on other types of reports or notifications that may be required or advisable.

Good communication is one of the indicators of a good culture of care and helps to build trust between those with responsibilities under ASPA and ASRU.

1.1 How will the Advice Note be reviewed and updated?

The Secretary of State intends to review the advice contained in this and other Advice Notes approximately two years after publication. The intention is that information in Advice Notes will eventually be incorporated into the *Guidance on the Operation of Animals (Scientific Procedures) Act 1986*.

Please submit any queries or comments on this Advice Note to:
ASRUBusiness@homeoffice.gsi.gov.uk

2. What is ‘Standard Condition 18’?

The Animals in Science Regulation Unit (ASRU) grants project licences subject to 25 standard conditions. The wording of these conditions is fixed and does not vary between licences. Sometimes additional conditions may be set, but the 25 standard conditions are a consistent feature of all project licences. The wording of all the standard conditions can be found in the *Guidance on the Operation of Animals (Scientific Procedures) Act 1986* (ASPA), available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/662364/Guidance_on_the_Operation_of_ASPA.pdf.

(PPL SC18) is applied to all project licences, in order to ensure adherence to the specific severity limits (the scientific and humane endpoints that set limits on pain) in each licence. A similar condition applied to all project licences prior to 2013, which was referred to as ‘PPL SC8’.

PPL SC18 states:
“The licence holder shall ensure adherence to the severity limits as specified in the project licence and observance of any other controls described in the licence. If these constraints appear to have been, or are likely to be, breached, the holder shall ensure that the Secretary of State is notified as soon as possible.”

In order to understand whether a PPL SC18 breach has occurred, it is necessary to understand what is meant by the ‘severity limits’ and ‘other controls’ described in the licence.

2.1 Severity classifications and severity limits

Each project licensed under ASPA will have a unique series of protocols. The protocols will describe a procedure or series of procedures carried out for a particular purpose within the authorised project.

Any persons working under ASPA must have a good clear understanding of the severity categories **and** the limits of the expected adverse effects set out in each protocol for any licence they work to.

Severity classification

Since ASPA was amended in 2013 project licence protocols have been categorised in accordance with Annex 8 of Directive 2010/63/EU: Severity Classification of Procedures.

The text of Annex 8 is reproduced as Appendix G of the *Guidance on the Operation of the Animals (Scientific Procedures) Act 1986.*[1]

The severity categories of project protocols are:

- non-recovery;
- mild;
- moderate; and
- severe.

The prospective severity category of a protocol is determined by the degree of pain, suffering, distress or lasting harm expected to be experienced by an individual animal during the course of its use in that protocol. ASRU's decision in assigning the category will be based on the most severe effects that the animal is likely to suffer after applying the relevant refinement techniques. More detail on the factors taken into account in assigning the severity category can be found in Appendix G of the operational guidance (*ibid.*).

Severity limits

PPL SC18 requires the licence holder to adhere to the severity limits (and any other controls) specified in the licence.

The severity limits relate to the expected adverse effects and associated humane endpoints, which are usually specified in project licence protocols. Additional limitations are sometimes specified in the project plan of the licence schedule.

The term 'severity limit' should be thought of as a specific limit or limitation on suffering forming part of the controls of the project licence. The severity limits are the ***scientific and humane endpoints*** set out in the project licence. **Severity limits are not the same as the severity classification of a protocol**.

Examples of severity limits: **given in Appendix G of the operational guidance**

Quantitative limits (engineering standards)	*"Tumours will be measured at appropriate intervals. If the product of maximum length and maximum breadth exceeds 1.44 cm^2 the animal will be killed."* *"The percentage proportion of animals anticipated to experience [a particular adverse effect] is x %."*

[1] https://www.gov.uk/government/publications/operation-of-aspa

Qualitative limits (performance standards)	*"Animals will be killed earlier if the tumour ulcerates or impedes any vital function (for example, locomotion, vision, mastication, excretion)."* *"If a large number of small tumours or cysts accumulate in an area that impedes vital function, the mice will be killed."*
A humane endpoint applied to the protocol as a whole	*"Mice will be killed if they show signs of ill health, such as piloerection and hunched posture, inactivity or inappetence for a period of 48 hours. In addition, any animal that loses 20% of its body weight when compared to age-matched control or develops more serious clinical signs such as diarrhoea or dyspnoea will also be killed."*
An endpoint defined for a particular adverse effect	*"If anaphylaxis occurs and animals are seen to do x, y and z, they will be humanely killed."*
A single clinical sign or combination of signs not specified in the licence but judged as consistent with the appropriate severity classification for the protocol according to Annex 8 criteria	*"If adverse effects exceed those consistent with the moderate severity classification of the protocol, animals will be humanely killed;"*

2.2 Other controls

PPL SC18 also requires the licence holder to ensure observance of *"any other controls described in the licence"*. Project licences may specify specific or unique controls, which are intended to provide additional safeguards to limit suffering, for example:

- monitoring regimes (without proper monitoring, breaches of severity limits and other controls may go undetected);
- use of score sheets; and
- supportive measures, such as defined housing conditions, provision of foodstuffs for convalescents, use of medicines or analgesics.

3. The purpose of Project licence Standard Condition 18 notification

Project licence Standard Condition 18 (PPL SC18) requires that ***"If these constraints appear to have been, or are likely to be, breached, the holder shall ensure that the Secretary of State is notified as soon as possible."***

Notification under PPL SC18 is therefore how licence holders are expected to comply with the legal requirements.

A person making a report under PPL SC18 is not reporting a non-compliance. On further discussion with the relevant Inspector, a range of possible outcomes will follow notification. It might be that no action is required, or the project licence is amended, or a minor infringement is acknowledged. However, a failure to notify when there is a requirement to do so may itself be considered non-compliance, which could result action being taken.

3.1 **Unexpected or unforeseeable events**

The Animals in Regulation Unit (ASRU) recognises that during the course of research unexpected adverse effects may occur. The PPL SC18 notification requirement provides a mechanism for compliance when the unexpected happens and animals may suffer more than is authorised.

Reviewing the cause of the unexpected adverse effects provides an opportunity for the project licence holder, the Animal Welfare and Ethical Review Body (AWERB) and others at the establishment to review study protocols, systems, processes and staff training to identify whether there are any changes that might prevent a recurrence of the problem. In some cases a procedure will simply not be repeated where either an alternative that is expected to be more refined can be found or where the harms now expected are greater than can be justified.

In some situations the project licence holder will recognise that in order to continue with their research and achieve the satisfactory scientific results from that research, then these unforeseen or unexpected adverse effects are likely to reoccur. Often this will require an amendment to the project licence to specify:

- the now 'likely adverse effects';
- how they will be controlled and limited; and
- any relevant humane endpoints.

On submission to the Home Office, the Inspector will carry out another harm benefit analysis to determine whether the revised programme of work should be authorised.

3.2 **Events arising from failure to observe the project licence terms**

Alternatively, a requirement to make a PPL SC18 notification might be generated by a personnel failure to observe the specified terms or control measures set out in the project licence. An example of this might be a failure to note that the onset of defined endpoints was happening faster than anticipated, and had escaped detection despite normal monitoring. It could also happen as a result of an unanticipated independent factor, such as concurrent subclinical infection. Again, as long as the PPL SC18 notification is made, it may in due course be determined that there are alternative ways to resolve the matter, and it will not necessarily become a non-compliance matter.

3.3 **3Rs benefits of notification under project licence Standard Condition 18**

PPL SC18 notifications provide a key opportunity for the Inspectorate to work with licence holders to assess whether there is evidence that to comply with the principles of replacement, reduction and refinement (the 3Rs) an adjustment should be made to the project licence conditions or protocols. Adjustments are likely to be in relation to refinement or reduction, rather than replacement – but should be treated on a case by case basis, as illustrated by the following examples.

Refinement:

- by facilitating a review of the procedures to be undertaken and the likely adverse effects; and
- providing an opportunity for licensees, in conjunction with the Named Persons (the Named Animal Care and Welfare Officer, Named Information Officer [NIO] and the Named Veterinary Surgeon) to provide specific advice to minimise adverse effects in the future and to gather and disseminate 3Rs information.

Reduction:

- by ensuring that regulated procedures are not applied to animals that need to be humanely killed according to specified humane endpoints, which may need to be done before the desired data can be gathered; and
- by ensuring that unsuccessful approaches are not repeated.

PPL SC18 notifications may also alert licence holders to common themes of problems or emerging risks, and prompt them to address these issues with an establishment-wide approach. It might help to generate action to address reduction and refinement issues, for example, through discussion at the local AWERB or by improved information sharing by the NIO. Regular reviews of when and why PPL SC18 notifications are being made by an establishment should help to underpin the culture of care, improve 3Rs work and communication, and drive up collaborative working.

4. When are Project licence Standard Condition 18 notifications necessary?

A Project licence Standard Condition 18 (PPL SC18) notification needs to be made if the severity limits specified in the licence **or** any other control indicated in the licence has been, or is likely to be breached (the severity limit and the other controls may together be referred to as the 'limitations' specified in the licence). This can relate to any aspect of the project licence, and will depend on the information written into the licence. It should not be automatically considered as a notification of non-compliance.

What if there is breach or likely breach of a control, but the severity limit has not been exceeded?
It is important to note that the wording of PPL SC18 requires notification where there has been a breach, or likely breach of a control even where a severity limit has not been exceeded.

What if an animal experienced an unexpected adverse effect?
An unexpected adverse effect, by its very definition, is an unanticipated source of pain, suffering, distress or lasting harm. It has not formed any part of the consideration put into drawing up of the project licence. It has not been included in the harm benefit analysis that underpins the project licence and therefore has to be notified.

What if it was a simple personnel infringement, rather than a compliance failing?
A PPL SC18 notification is not necessarily a report of a non-compliance. A personnel failure to observe the specified terms or control measures set out in the project licence is likely to require a PPL SC18 notification if a severity limit or any other control has either been breached, or is likely to be breached as a result.

As long as the PPL SC18 notification is made, it may in due course be determined that some particular course of action is appropriate, rather than treating it as a non-compliance matter.

What if the breach has not actually happened, because the licensee realised and went back to following the protocol, should the licensee still report it?
Yes. The licensee is asked to make a report where a breach has occurred or is likely to occur. Of course, it is helpful to have prevented a potential breach. However, it may be that others in the establishment need to be aware:

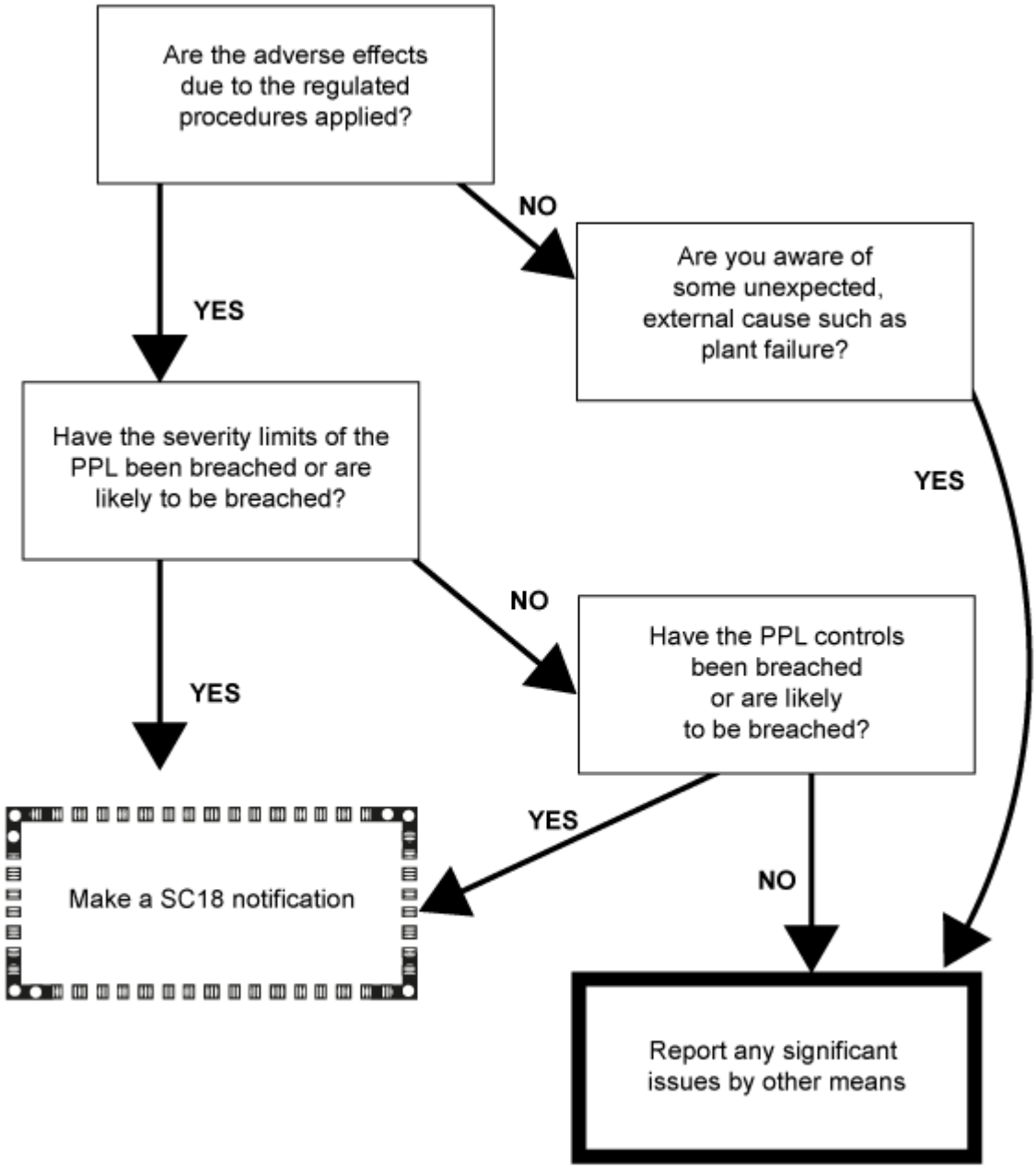
- of a change in practice; or
- that an amendment to the project licence is required to stop others from making the same mistake in the future.

The following questions may help the licence holder to decide whether or not to make a PPL SC18 notification.

- Is an animal experiencing adverse effects due to the regulated procedures applied?
- If so, are the effects specified in the project licence or are they unexpected adverse effects?
- If an animal is experiencing adverse effects have they exceeded, or are they likely to exceed, the authorised severity limitations specified in the project licence?
- Is the licence holder aware of either a failure to observe a project licence control or that such a control is likely to breached?
- Is the licence holder aware of some unexpected external cause not related to the regulated procedure, such as plant failure, leaking water supply, or incidental disease reports?

The decision tree at Figure 1 summarises these considerations.

Figure 1



4.1 Are the adverse effects due to the regulated procedures?

Events that are unrelated to the regulated procedures should not be notified through PPL SC18. In some circumstances it may be necessary to consider whether any adverse effects that occurred, but not as a result of a regulated procedure, will affect the overall suffering of an animal such that a severity limit might be reached earlier than expected.

Examples of adverse effects not related to the regulated procedures are:

- adverse effects associated with plant failure;
- adverse effects associated with leaking water bottles;
- fight wounds in animals on study; and
- incidental disease/injury not related to the study.

In the event that animals undergoing procedures are found dead as a consequence of those procedures, and mortality at this rate is not an authorised adverse effect in the relevant protocol, this is an unexpected adverse effect. This should be reported to the relevant Inspector using the PPL SC18 notification process. In addition, in these circumstances licence holders should also review the guidance in *Advisory notes on recording and reporting the actual severity of regulated procedures*.[2]

4.2 Have the adverse effects exceeded the authorised limitations specified in the project licence?

Where the adverse effects are due to the regulated procedures, the next stage is to consider whether the effects are unexpected, that is they were not specified in the protocol for the work or considered in the preparation of the project licence. Unexpected adverse effects should be the subject of a PPL SC18 notification.

Where the adverse effects are within the range of what was expected or specified in the terms of the project licence, the next stage is to consider whether they are within the authorised severity limits of the project licence. (See section 2.1 of this document for examples of how limits may be written in the project licence.)

Some examples of possible expected adverse effects that might need to be considered for PPL SC18 notification are:

- a humane endpoint is exceeded despite required monitoring or other measures;
- an unexpected harmful phenotype in a genetically altered animal being maintained on a 'mild' protocol causing pain, suffering or distress that is greater than mild and transient, for example, a genetically altered mouse exhibiting tremor that affects its ability to eat and drink; or
- adverse effects that are more severe or frequent than the descriptions on the project licence, for example, paralysis in all four limbs, when only partial paresis of one limb is authorised.

Note that there will be scenarios where the adverse effects noted are within the authorised limits, **and a PPL SC18 notification is not required**, as shown in the following examples.

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2 https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/276014/NotesActualSeverityReporting.pdf

- The mortality rate is authorised by the project licence.
- The frequency and degree of adverse effects is authorised by the project licence;
- The rate of unusual events is authorised by the project licence and appropriate action has been taken to minimise suffering.
- Appropriate and timely action is taken when a humane endpoint is recognised. For example, the project licence specifies that animals will be killed if they lose more than a certain proportion of their original body weight. In the case where an animal is found to have lost slightly more weight but has been promptly and humanely killed, then the animal has reached its endpoint and the correct welfare intervention has been applied, in a timely fashion.

An informed decision needs to be taken by the project licence holder as to whether a notification is necessary. An 'informed decision' is a decision based on:

- knowledge of what an animal is known to have experienced, or is reasonably likely to have experienced, or is likely to be about to experience; and
- the actions taken by those responsible for the animal.

This requires a suitable level of competence in the person making that decision. If in any doubt, advice should be sought from named animal care staff and the Named Veterinary Surgeon. If there is uncertainty over other scenarios, advice can be taken from the assigned Inspector

4.3 Has there been a failure to observe the controls described in the project licence?

In some circumstances, a report may be required even where the severity limits have not been exceeded. Where there has been a failure to observe the project licence controls for whatever reason, PPL SC18 requires a notification to be made, including an explanation as to how or why the specified controls were not observed.

4.4. What if an actual breach of either the severity limit or the control was likely to occur, but was prevented?

Under PPL SC18 a licence holder is required to make a report where a breach has occurred or is likely to occur. Of course it is helpful to prevent a potential breach. However, it may be that some permanent change needs to be made in order to prevent others making the same mistake. For example, a change in establishment operating practice, or an amendment to the project licence is required. By making a notification report, the licence holder can facilitate a conversation with colleagues and their Inspector about the right preventative actions.

4.5 Other reporting/notification

There may be other incidents, or significant events that do not require PPL SC18 reports but that Inspectors should be made aware of promptly. These include events where specially protected species or particularly unusual or unexpected scenarios are involved. Licence holders are encouraged to maintain good communication with their assigned Inspector, through telephone calls or secure emails.

Note that a PPL SC18 notification is not for reporting an actual non-compliance with project licence authorities. These should be notified to the assigned Inspector as soon as practicable so that the necessary enquiries can take place without delay. Examples of adverse effects that are potential non-compliance are:

- a failure to make the specified intervention in a timely fashion – for example, the adverse effects section of the project licence protocol states that animals will be killed if their tumours become ulcerated and such an animal is not killed in a timely fashion;
- continuing to breed genetically altered animals with an adverse phenotype not described in the project licence;
- failing to take all measures to minimise suffering – for example, failing to provide adequate analgesia to post-surgical animals; and
- a failure to monitor animals at a frequency specified in the project licence, resulting in avoidable harm.

5. Notifying the Secretary of State

The project licence holder is legally responsible for notifying the Secretary of State if constraints on severity or observance of other controls described in the project licence have been or are likely to be, breached. The project licence holder is responsible, amongst other things, for ensuring that:

- the degree and duration of adverse effects are minimised;
- the fewest animals die;
- long-lasting pain is ameliorated; and
- at the end of the procedures animals are killed promptly if they are suffering or likely to suffer due to the regulated procedures.

The project licence holder should therefore be aware of the adverse effects being suffered by animals being used under their project licences, and they should ensure that adequate monitoring regimes are in place.

Personal licensees have a responsibility under Personal licence Standard Condition 13 to *"notify the project licence holder as soon as possible when it appears either that the severity limit of any procedure listed in the project licence or the constraints upon adverse effects described in the project licence have been or are likely to be exceeded."* Project licence holders need to ensure good systems of communication with personal licence holders working under their project licence.

5.1 Notification process

The project licence holder should notify the Animals in Science Regulation Unit (ASRU) Inspector assigned to the establishment. The report may be submitted using secure email or in hard copy. An initial report can be made by telephone, but it should be followed up in writing.

The PPL SC18reporting template is at Appendix 1. The information provided should be clear and concise but sufficient to give the Inspector an understanding of what has happened and why, and what steps are being taken to prevent or minimise the likelihood of recurrence.

The Inspector will consider the contents of the notification and assess what action should be recommended to the Secretary of State. This may be straightforward, for example, to note the details and agree that the appropriate remedial measures have been put in place so no further action is necessary. Sometimes further discussion is required with the project licence holder to seek information and reassurances regarding the conduct of future studies. It may be that an amendment to the project licence is required before the procedures giving rise to the unauthorised adverse effects may be repeated.

Repetition of ‘unexpected’ adverse effects

Where an unexpected adverse effect is considered likely to arise again because it is now an expected adverse effect, an amendment to the project licence may be required to incorporate this adverse effect.

Typically the same unexpected adverse effects due to the same cause would become ‘expected’ after being observed twice or more in close succession.

The PPL SC18 notification may be the first step in recognising that a review of the circumstances by the Animal Welfare and Ethical Review Body, Named Persons and the assigned Inspector is required, and perhaps an application needs to be made to amend the project licence before the same type of study is undertaken again.

5.2 Timeliness of notification

PPL SC18 requires notification ‘as soon as possible’. ASRU’s expectation is that the Notification template at Appendix 1 should be emailed to the assigned Inspector without delay. This email, or at a minimum a telephone call, should be received by the assigned Inspector within 72 hours of the events having occurred, or being identified as a potential risk.

Notification should not be delayed pending completion of internal investigations. In such instances a PPL SC18 notification should be made as soon as possible. The project licence holder should then update the assigned Inspector by telephone or email to let them know whether an internal investigation is going to be pursued.

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
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 endpoint	Clear, predictable and irreversible criteria that allow the early termination of a procedure before an animal experiences harm that is not authorised or scientifically justified
PPL	Project licence
PPL SC	Project Licence Standard Condition. There are 25 standard conditions appended to every project licence issued under **ASPA**
Project Licence	A licence issued under **ASPA** authorising a scientific programme of work
Protocol	A procedure or series of procedures carried out for a particular purpose as part of an authorised project
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 that minimise the number of animals used for each experiment

Refinement	Methods that minimise suffering and improve animal welfare
Severity classification	The classification of severity as ‘non-recovery’, ‘mild’, ‘moderate’ or ‘severe’
Severity limit	The limit of the severity authorised for that **protocol** in the **PPL** according to the **3Rs** measures written into the PPL and approved by the **harm–benefit analysis**. Note that the severity limit, unlike the **severity classification** will vary between every PPL.

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Appendix 1

PPL Standard Condition 18 Notification Form

Please use this form to notify the Animals in Science Regulation Unit (ASRU) of procedural-related adverse effects that have exceeded or are likely to exceed the severity limitations or controls described in the project licence. ASRU will use this information to determine whether any further action is required.

Do not use to report:

- adverse effects that are due to non-procedural issues;
- potential non-compliance (report by other means);
- issues without adverse welfare consequences.

If you are in doubt whether or not you need to fill in this form, please contact your assigned Inspector.

Please clearly title your document: **'ASRU_establishment name_PPL number_PPLh surname_date_sc18'** and send to your Inspector (e.g. using cjsm) with the subject heading 'PPL SC 18 Notification PPL [Number]

Establishment Licence name	
Establishment Licence number	
Name of PPL holder	
PPL number	
Protocol no	
Protocol title	
Severity classification	

1. Date of incident	
2. Species	
3. Brief details of study and how the limits or constraints have been breached	
4. Have you taken advice from the Named Animal Care and Welfare Officer/Named Veterinary Surgeon/others?	
5. Cause of Problem, if known	
6. Action that has been or will be taken *(For example, formulation of drug changed, supportive treatment given, study design modified). If no action needed, indicate why (for example, none required as study has been terminated and will not be repeated)*	
7. Reported by (name)	
8. Date	

********************************For official use***

Inspector’s comments and recommendations:

Comments and recommendations	
Inspector name	
Date	