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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.

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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	University of Cambridge, Phenomics
Establishment Licence number	X81BD37B1
Name of PPL holder	Jill Reckless
PPL number	PAF4E3C19
Protocol no	18
Protocol title	Breeding and maintenance of GA animals with a moderate phenotype

Severity classification	Severe
1. Date of incident	19/03/2020
2. Species	Rat
3. Brief details of study and how the limits or constraints have been breached	This protocol facilitates the breeding and maintenance of Factor VIII KO rats, a model of Haemophilia A. As part of the phenotype these rats sometimes experience spontaneous bleeds, such as of the joints, intracranial or intraabdominal. These bleeds can sometimes self-resolve, but we have implemented a care regimen whereby the rat receives up to four daily treatments of factor VIII treatment while under close observation, when a bleed has been noted. The rat within this report was found dead due to an untreated bleed under the skin around its head, exceeding the moderate severity classification of the protocol.
4. Have you taken advice from the Named Animal Care and Welfare Officer/Named Veterinary Surgeon/others?	Animal was found dead with reason known. The NVS and NACWO are fully aware of these animals and their potential to experience spontaneous bleeds, along with the care regiment we have implemented. This is more of an issue of communication between care staff and researchers.

5. Cause of Problem, if known	Spontaneous bleeds are expected and can usually be resolved with up to four treatments (or cull if not), but unfortunately this rat was not given treatment quickly enough due to a miscommunication in the cage the rat was contained in. On the afternoon of 17/03/2020 a UBS staff member contacted RxCelerate to report a rat displaying lethargy, and that the affected cage would have its cage card flipped to notify which cage the animal was in. Approximately an hour later, and after UBS staff had left for the day, RxCelerate staff came to check and make a decision on treatment. A cage was identified due to the presence of a flipped cage card and saw no lethargy, or signs of a bleeding episode. Unfortunately, the cage checked was the wrong cage due to several cages having flipped cage cards at the time. The same incorrect cage was checked again the following morning by a different RxCelerate staff member, to check if any signs of lethargy or bleed were apparent. As the rat went unchecked and untreated and the bleed did not self-resolve the rat was found dead late morning on 18/03/2020. On post-mortem the bleed was unilaterally from the subcutaneous region of the head with no obvious origin, and no bleed within the skull.
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)*	All rats are ear marked for identification purposes, and we have introduced marks on the tail of rats identified as haemophilic by genotyping. When receiving notification of a spontaneous bleed from the UBS staff we will make sure to specifically ask for the rat ID number and/or cage number and ear mark, or if prior to biopsy, the cage number. We will also request for a tail mark to be added to animals in which a bleed is spotted prior to biopsy to allow for easy identification within the cage.
7. Reported by (name)	Amy Warner
8. Date	20/03/2020

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Inspector’s comments and recommendations:

Comments and recommendations	
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Date	

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Establishment Licence name	ASRU Mira
Establishment Licence number	X81BD37B1
Name of PPL holder	Jill Reckless
PPL number	PAF4E3C19
Protocol no	5
Protocol title	Breeding and maintenance
Severity classification	Mild

<table>
<tr><td>1. Date of incident</td><td>13/07/20-10/12/20</td></tr>
<tr><td>2. Species</td><td>Mouse</td></tr>
<tr><td>3. Brief details of study and how the limits or constraints have been breached</td><td>Haem B (FIX KO) mice were in a breeding colony from March 2020 to Jan 2021 in Mira, a total of 305 mice. During this time 15 mice were found dead. All underwent post-mortem, apart from 2 that were cannibalised and difficult to assess. 6 of these were found with bleeds and therefore their deaths may have been phenotype-related. There was no strong link for age or litter, although the mice did tend to be older.

<table>
<tr><td>ID</td><td>Type of bleed</td><td>Death date</td><td>Age at death</td></tr>
<tr><td>JRAL6.1f</td><td>GI</td><td>13/07/20</td><td>19 weeks</td></tr>
<tr><td>JRAL3.2d</td><td>GI</td><td>04/08/20</td><td>16 weeks</td></tr>
<tr><td>JRAL3.6e</td><td>GI</td><td>01/09/20</td><td>5 weeks</td></tr>
<tr><td>JRAL3.6i</td><td>GI</td><td>29/11/20</td><td>17 weeks</td></tr>
<tr><td>JRAL4.3c</td><td>GI</td><td>08/12/20</td><td>17 weeks</td></tr>
<tr><td>JRAL11.1b</td><td>Chest cavity</td><td>10/12/20</td><td>8 weeks</td></tr>
</table>

At the time it was thought that these would fall under the percentage allowed for colony deaths as expected in the background strain, and were therefore not reported as unexpected deaths. It is now clear that these mice were unexpected deaths and should have been SC18 reported individually at the time of death, with a view to increasing the severity limit/protocol they were on.</td></tr>
<tr><td>4. Have you taken advice from the Named Animal Care and Welfare Officer/Named Veterinary Surgeon/others?</td><td>We no longer have the colony so no immediate action is needed or welfare advice sought.</td></tr>
<tr><td>5. Cause of Problem, if known</td><td>The bleeds were found on post-mortem and therefore could have been the cause of death. However, as we no longer have access to these animals it is difficult to ascertain whether these bleeds were the cause of death, or whether they (especially of gastrointestinal origin) would have been present in a certain percentage of healthy (especially older) animals, discoverable at post-mortem but causing no harm.</td></tr>
</table>

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)*	The colony came to an end in January, due to end of study program. The distinction between expected and unexpected colony deaths is now very clear; any similar animals that exceed severity in a colony setting (i.e. suspected to be due to phenotype) will be reported individually and within 72 hours, even if the overall colony percentage is low. As a Team we will conduct training on the distinction between reporting expected vs. unexpected colony deaths. If a study program were to resume in the future with this strain we would seek to discuss about including them on our existing severe protocols on the same PPL.
7. Reported by (name)	Amy Warner (on behalf of Jill Reckless)
8. Date	24.02.2021

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Comments and recommendations	
Inspector name	
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Establishment Licence name	University of Cambridge, Mira
Establishment Licence number	X81BD37B1
Name of PPL holder	Jill Reckless
PPL number	PAF4E3C19
Protocol no	18
Protocol title	Breeding and maintenance of GA animals with a moderate phenotype

Severity classification	Moderate
1. Date of incident	14/04/2021
2. Species	Rat
3. Brief details of study and how the limits or constraints have been breached	JRAJ37.2f, a FVIII KO (Haemophilia A) rat was found dead mid-morning on 14/04/21 by RxCelerate staff. Health record information: 29/03/21 the rat had a hind limb ankle bleed and was treated with a single dose of haemostatic (Advate; 300 IU/kg) and pain relief (buprenorphine; 5 ml/kg in food). The ankle swelling receded over the following 5 days (from diameter 8.32 mm to 7.40 mm). On 04/04/21 the bleed reoccurred (ankle diameter 10.55 mm), and the rat was given the single Advate/bup regimen again. As a consequence the bleed had been receding ever since, with a slight hint of swelling remaining on 13/04/21 but no other clinical signs, and good weight-bearing on the limb. When found dead the ankle was only 1 mm diameter difference from the healthy ankle (7.36 mm vs. 6.35 mm); this is not unusual as we can see up to 5 mm difference when an ankle bleed is present, so we made the assumption that the ankle bleed was not deemed active. The weight chart on his health record shows increased/stable weight since the bleed started (last weighed 13/04/21). The rat did not have any regulated procedures; the only intervention being treatments on health grounds (as above). The current proportion of found dead animals (over 5 days old) in the colony is 0.34% (4 in 1,155), this rat is the only one past weaning age.

4. Have you taken advice from the Named Animal Care and Welfare Officer/Named Veterinary Surgeon/others?	We contacted the NVS to perform a post-mortem to determine cause of death.
5. Cause of Problem, if known	Cause of death, investigated by NVS Jo Keeley, appeared to be internal bleeding in the thorax.
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)*	During post-mortem examination lungs, heart and thymus were taken for histological analysis; this will ascertain any abnormalities that could explain the haemothorax. Any new information will be passed on. In addition to facility health checks by UBS staff, all homozygous rats are handled/open-cage checked on weekdays by RxCelerate staff to look for external signs of spontaneous bleeds. Although we have very rarely discovered homozygous rats exhibiting pallor and subdued behaviour, we have not found a rat dead through a bleeding event before (in 18 months of housing the colony and 288 homozygous animals). Therefore, we plan to continue closely monitoring to determine whether this was a true consequence of phenotype, or whether it was an unfortunate coincidental event or a bleed brought on by extraordinary circumstances.
7. Reported by (name)	Amy Warner (on behalf of Jill Reckless)
8. Date	16.04.2021

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Inspector’s comments and recommendations:

Comments and recommendations	

Inspector name	
Date	

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Establishment Licence name	University of Cambridge
Establishment Licence number	X81BD37B1
Name of PPL holder	Jill Reckless
PPL number	PAF4E3C19
Protocol no	6
Protocol title	Breeding and maintenance of GA animals with a severe phenotype
Severity classification	Severe
1. Date of incident	On-going
2. Species	Mouse

3. Brief details of study and how the limits or constraints have been breached	**No limits or constraints have been breached at this point; this is a request to keep animals alive in the future that may exceed adverse effect limits currently described in the PPL.** We have recently (14th June 2022) re-established a Haem A mouse colony using stock from Jackson Labs. These mice are the same genotype as we previously housed. The protocol, and in particular the adverse effects, on the current PPL were written based on our experience and observations of the previous colony. However, in the current colony, the phenotype and nature of the spontaneous bleeds are presenting differently from what we have observed before. Previously, bleeding from the ear showing more than a few blood spots was usually indicative of a major bleed, which if left would likely kill the animal. Upon post-mortem the bleed origin was usually from within the neck area. The expected adverse effects, as written currently in protocol 6, state: "Blood spots may be noted from the ears and digits that could indicate a minor, resolving bleeding episode. When this is seen then additional monitoring will be put in place and mice killed if the bleeding does not resolve with intervention. Mice that have major bleeds from the ears; or have piloerection and are subdued; or are reluctant to move will be killed." In this new cohort of animals (both imported and subsequently bred in-house) we have so far sch1 killed any animals showing substantial bleeding from the ear, as in previous colonies. However, two differences appear to be present in this new cohort: Typically these animals do not show any clinical signs alongside the bleed (other than in some cases scratching), and all have been classified as mild or (rarer) moderate actual severity when killed.

	These bleeds show signs of being self-limiting; animals have been found on checks with what looked to have been a significant active bleed from the ear which had since dried up, or blood found in the cage but no obvious origin from animals in the cage. We therefore believe that these bleeds are different in pathology and/or severity to previous cohorts. The number of animals experiencing bleeds overall has also increased. Due to killing any animals with significant ear bleeds as dictated by the adverse effects, and with these bleeds being more frequent, we are approaching the percentage expected to be killed due to bleeds (written as “up to 13%”, as of 30/09/2022 it is 11.2%). These ear bleeds of shoulder/neck origin make up 55% of all bleeds. For context the number found dead due to bleeds is roughly what we have seen with other colonies (currently 1.5%, with “up to 4%” expected on protocol). Therefore we seek authority to: • allow animals experiencing what are described currently as “major bleeds from the ear” to remain alive under observation so that we can fully characterise the new phenotype, and prevent animals being unnecessarily killed. This is strictly only animals without other significant clinical signs (such as anything other than mild irritation/scratching). Preventative measures such as nail clipping and styptic powder will still be used where appropriate. • be allowed to temporarily exceed the percentage of animals killed early due to bleeds, as this does not accurately reflect the new phenotype. When we have sufficient information on the nature of these bleeds, we will submit an amendment to cover them on the PPL.

4. Have you taken advice from the Named Animal Care and Welfare Officer/Named Veterinary Surgeon/others?	The unit NACWO and NVS are fully aware of the phenotype change. We continue to work closely with the unit staff to provide care and observation as before.
5. Cause of Problem, if known	We believe that some drift has occurred in the strain; previously we have maintained in-house, or obtained animals from a closed JAX colony for a client.
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)*	We are currently creating a score sheet to address these new ear bleeds specifically. For example, detailing presence of fresh blood, amount of blood, and any clinical signs. This will be used to help make decisions on when it would be appropriate to closely monitor a mouse rather than immediately schedule 1 kill the animal, where it is not currently an option as stated by the adverse effects, if we get authority to do so.
7. Reported by (name)	Amy Warner (on behalf of Jill Reckless)
8. Date	03/10/2022

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Establishment Licence name	University of Cambridge
Establishment Licence number	X81BD37B1
Name of PPL holder	Jill Reckless
PPL number	PAF4E3C19
Protocol no	20
Protocol title	A model of haemarthrosis in GA mice with a severe phenotype
Severity classification	Severe
1. Date of incident	24 Nov 2022

2. Species	Mouse
3. Brief details of study and how the limits or constraints have been breached	This mouse was in the second pilot study for investigating the development of haemarthrosis in FVIII deficient mice (Haemophilia A). The study consists of inserting a 30G hypodermic needle through the infrapatellar ligament of the knee to induce a bleed, to model the joint bleeds seen in haemophilia A patients. The mouse is typically monitored for 6 hrs on the day of insult while acute bleeding should occur, then daily for 3 days, then weekly. In the first pilot study, 2 mice were killed at the humane endpoint at 6 hrs as although responsive, they were subdued and not socialising with cage mates. Another mouse was killed at 24 hrs and a further mouse at 48 hrs (hunched, piloerection). In total 4 mice out of 24 were taken off study early. In this second pilot study, 3 mice out of 31 had been killed at the humane endpoint at 24 hrs post-insult for welfare concerns (subdued, reluctant to move, piloerection, one showing grimace). At 48 hours post-insult mouse 11 (JRBM16.2f; cage C00330954, 2R) was found dead. No concerns had been raised for this mouse, it had gained weight on study (7%) and appeared well the day before. Some swelling/bruising was observed around the insulted knee but this is to be expected.
4. Have you taken advice from the Named Animal Care and Welfare Officer/Named Veterinary Surgeon/others?	NACWO and NVS have been informed, and the unit staff continue to aid in monitoring the condition of the mice.

5. Cause of Problem, if known	Post-mortem examination revealed a substantial haematoma around the insulted knee, but no greater than seen in many of the mice that showed no clinical signs in the first pilot study. Literature reviews of this methodology, prior to these pilot studies, do not indicate that deaths or severe clinical signs would be expected in this strain. (e.g. K. Olvisen et al. Journal of Thrombosis and Haemostasis 2008, 6: 969:975). It is likely that loss of blood outside of the joint contributed to the death in this case (and to the other animals reaching humane endpoint where large haematomas were observed around but external to the joint). On the protocol (like other experimental protocols for this strain) we would expect to have sudden deaths, especially due to additional measures such as handling or dosing on study (up to 15%). However, we do not explicitly state that this will be due to induction of haemarthrosis. Indeed, we did not expect to have deaths through the technique specifically, but it appears this is either due to phenotypic differences in strain or has not been reported in the literature.
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)*	We will continue to monitor animals closely to capture any that reach the humane endpoints stated. The pilot studies have so far shown excellent potential for use in creating a therapeutic window to test efficacy. The researcher who did the procedure is already well-experienced in the technique, so we don't believe there are refinements to be made at this stage. We will submit an amendment to include a link between sudden deaths and the induction of haemarthrosis.
7. Reported by (name)	Amy Warner (on behalf of Jill Reckless)
8. Date	25/11/2022

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Establishment Licence name	University of Cambridge
Establishment Licence number	X81BD37B1
Name of PPL holder	Jill Reckless
PPL number	PAF4E3C19
Protocol no	20
Protocol title	A model of haemarthrosis in GA mice with a severe phenotype
Severity classification	Severe
1. Date of incident	21st Feb 2023

2. Species	Mouse
3. Brief details of study and how the limits or constraints have been breached	This mouse was in a study for investigating the development of haemarthrosis in FVIII deficient mice (Haemophilia A). The study consists of inserting a 30G hypodermic needle through the infrapatellar ligament of the knee to induce a bleed, to model the joint bleeds seen in haemophilia A patients. The mouse is typically monitored for 6 hrs on the day of insult while acute bleeding should occur (2, 4, and 6 hours), daily for 3 days, then weekly. All animals in cohort 1 were given the test agent (siRNA) by subcutaneous injection 8 days before insult. No problems were observed with the exception of a few mice in the cohort experiencing bleeds around the scruff area due to the restraint required for dosing. However, no bleeds were observed in the mouse in question. At 4 hours post-insult mouse 40 (JRBM26.2f; cage C00344915, 1L) was found dead. No concerns had been raised for this mouse, either at insult or acute recovery. Some swelling/bruising was observed around the insulted knee but this is to be expected.
4. Have you taken advice from the Named Animal Care and Welfare Officer/Named Veterinary Surgeon/others?	NACWO and NVS have been informed.

5. Cause of Problem, if known	Post-mortem examination revealed a substantial haematoma around the insulted knee, but no greater than seen in many of the mice that showed no clinical signs in the pilot studies. In the second pilot study, one mouse was found dead at the 48-hour check (SC18 sent - SC18_UniversityofCambridge_PAF4E3C19_Reckless_25112022). As with the previous mouse, it is likely that loss of blood outside of the joint contributed to the death in this case On the protocol (like other experimental protocols for this strain) we would expect to have sudden deaths, especially due to additional measures such as handling or dosing on study (up to 15%), and this is stated. However, we do not explicitly state that this will be due to induction of haemarthrosis. Indeed, we did not expect to have deaths through the technique specifically; it appears this is either due to phenotypic differences in strain or has not been reported in the literature.
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)*	We will continue to monitor animals closely to capture any that reach the humane endpoints stated. The pilot studies showed excellent potential for use in creating a therapeutic window to test efficacy. The researcher who did the procedure is already well-experienced in the technique, so we don't believe there are refinements to be made at this stage. We didn't receive feedback on the last SC18 filed, so have sent this one also on the basis that we are unsure whether the general humane endpoints cover this. We will submit an amendment to include a link between sudden deaths and the induction of haemarthrosis at the earliest opportunity; this PPL expires in September so the distinction is also included on the drafted replacement.
7. Reported by (name)	Amy Warner (on behalf of Jill Reckless)

8. Date	22/02/2023

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Comments and recommendations	
Inspector name	
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Establishment Licence name	University of Cambridge
Establishment Licence number	X81BD37B1
Name of PPL holder	Jill Reckless
PPL number	PAF4E3C19
Protocol no	6
Protocol title	Breeding and maintenance of GA animals with a severe phenotype
Severity classification	Severe
1. Date of incident	21/08/23
2. Species	Mouse

3. Brief details of study and how the limits or constraints have been breached	This report concerns our colony of Factor VIII KO (Haem A) mice. Weekly or fortnightly data is gathered on the proportion of mice being Sch1 killed or found dead due to bleeding events. The adverse effects section for the breeding protocol (6) states that we expect to see up to 13% of the colony humanely killed due to bleeding events. The percentage for the colony gathered for last week has reached 13.1%. This seems to be due in part to mice being transferred to the new PPL (PP0760009) in the last month as this current PPL expires on 30th Sept. New litters are not being included in the total colony number on PAF4E3C19, but adult animals remain and continue to have the possibility of a bleed, therefore skewing the percentage upwards. This will continue to rise as the PPL comes to an end as adult mice left on PAF might have bleeds without the overall colony number increasing. Before transferring litters, the percentage was around 11-12%.
4. Have you taken advice from the Named Animal Care and Welfare Officer/Named Veterinary Surgeon/others?	As there are no material change to the welfare of the animals they have been copied into the submission of this report.
5. Cause of Problem, if known	We don't believe we are experiencing a true increase in bleeds, but a consequence of shifting some of the colony to a new licence.
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)*	We currently have the following animals left on PAF4E3C19: 11 12-week-olds 3 13-week-olds 5 19-weeks-olds 1 22-week-old These mice will either be used for a short study or culled (i.e. ex-breeders), but there is a chance some may experience a bleed beforehand. **We ask that this percentage is allowed to exceed the 13% limit stated in the adverse effects for the ~5 weeks left of the PPL.**

7. Reported by (name)	Amy Warner (on behalf of Jill Reckless)
8. Date	23/08/2022

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Inspector's comments and recommendations:

Comments and recommendations	
Inspector name	
Date	