

Efficient Breeding of Genetically Altered Animals

Assessment Framework

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Introduction

This assessment framework is intended to assist establishments to consider the efficiency with which they breed genetically altered (GA) animals. ASPA requires licensees to apply the 3Rs at all times, including in the context of the production and use of GA animals. This framework is intended to help with the assessment of establishments' success in this regard.

The framework was created in consultation with breeding experts and establishments, and provides background information, lines of enquiry and examples of acceptable findings, as well as the underlying performance standards and potential performance outcomes that establishments may wish to measure in order to track progress. This assessment framework is designed for the breeding of GA mice, although the principles will apply to many species.

There is no such thing as a single “breeding management blueprint” that will work in every establishment. Establishment factors, scientific factors, species and strain factors and the resources available will all influence what an optimum breeding programme looks like in each establishment. However, even if the way they are achieved is different, core underlying performance standards are common to every establishment.

This assessment framework is not in itself mandatory and does not define mandatory or additional requirements. Some elements within it are, however, required by licence standard conditions or the Code of Practice. It is anticipated that AWERBs may find this assessment framework useful to assist them with their statutory duty to advise on the application of the 3Rs within their establishments. Project Licence holders and Animal Unit Managers may also find it useful for self-assessment. Inspectors will use this assessment framework when considering how establishments apply the 3Rs to their GA breeding programmes.

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- Cancer Research UK Manchester Institute
- University of Aberdeen
- RSPCA
- MRC Harwell, Mary Lyons Centre

ASRU will aim to review this framework every two years and will update as necessary. If you have any further suggestions for improvements to this framework please get in touch with us at health.protection@health-ni.gov.uk.

Background

This background section provides supporting information for each focus area and explains the significance of the lines of enquiry.

Not all focus areas will be applicable to every establishment. They can be read in any order and accessed independently from the contents page.

Establishments of all sizes will find this framework contains information relevant to them. Small establishments should review their GA breeding practices as frequently and in as much depth as large establishments.

EXAMPLES OF LINES OF ENQUIRY

Examples of questions that may be used for assessment of the focus area.

Not all of the possible lines of enquiry will be listed here.

EXAMPLES OF SATISFACTORY FINDINGS

Examples of satisfactory findings.

There may be several contrasting findings that would all be satisfactory if they met the underlying performance standard.

Different establishments need and will have different practices and systems.

The findings should be:

- a) demonstrable
- b) context-and/or establishment-specific

Not all of the possible satisfactory findings will be listed here either.

Performance Outcomes

- These are measurements that establishments may wish to make in order to monitor performance within each focus area
- It is not mandatory that they are monitored or reported, although your inspector may make a special request for specific outcomes to be measured
- Target values may be set on an establishment-specific basis to assist with focused improvements where necessary

EXAMPLE FOLLOW-UP QUESTIONS Questions or lines of enquiry that may follow on from those above.

An efficient breeding establishment...

- The underlying performance standards for each focus area are listed in this box;
- The performance standards can also be found in a comprehensive list (see contents).

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Background

Archiving is the storage of cryopreserved sperm and/or embryos such that the particular strain can subsequently be recovered/rederived as required.

Archiving is a powerful safety device for ensuring valuable lines are not lost due to infection or another unforeseen event. Archiving can also present an opportunity for efficiency benefits, particularly where a strain will not be required for experiments for some time.

However, archiving in itself requires animals to produce the sperm/embryos to be preserved and potentially a larger number to recover the lines. There can also be strain-specific variation in the ease of obtaining embryos for cryopreservation. There is therefore a balance to be struck between archiving an unused line too early or too late.

Some archiving services require that lines are made publicly available after a certain period, and this can cause reluctance to archive due to protection of intellectual property.

EXAMPLES OF LINES OF ENQUIRY

Do you have an establishment-wide archiving policy?

Do you have arrangements in place so that scientists can archive lines if they wish to?

How do you decide whether or not it is appropriate to archive a line?

How do you decide *how* to archive a line?

How do you manage tick-over colonies?

Have you analysed whether or not there are any disincentives at work that inappropriately discourage scientists from archiving?

What information do you keep with your archived lines?

EXAMPLES OF SATISFACTORY FINDINGS

Yes, we have a policy that requires that each colony is reviewed regularly to ascertain whether or not archiving is appropriate.

Yes, we perform that in house.

Yes, scientists use a free archiving service as we do not have the facilities to do that ourselves here.

We discuss the likely “down time” before the colony will be needed again (in-house or by collaborators) and assess the relative cost of low-rate tick-over versus archiving/rederivation. We also consider any strain-specific technical factors that may influence the number of animals required to complete the archiving/recovery process.

We consider the relative merits of embryos vs sperm and the future recovery of the line in the context of the strain in question and select the technique(s) most closely aligned to the 3Rs.

We reduce the number of breeding pairs to the minimum we can, striking a balance between the numbers required to assure continued genetic integrity and reduction.

Yes, we have asked scientists about the barriers to archiving and have minimised these as far as possible.

We keep the mouse passports, as well as information about what has been cryopreserved, how it was done, and protocols for thawing and using the materials.

Performance Outcomes

- Proportion of lines that have been reviewed for archiving (i.e. whether or not archiving is appropriate, and whether the technique chosen is that most closely aligned to the 3Rs) within last 6 months.

EXAMPLE FOLLOW-UP QUESTIONS Are your scientists generally happy to archive lines when it is appropriate to do so? Do you have technical difficulties rederiving the lines? Are you aware of the *Sharing and archiving of genetically modified mice: opportunities for reduction and refinement* booklet produced by the RSPCA Resource Sharing Working Group and endorsed by the BBSRC, CRUK, MRC and NC3Rs? Are you aware that MRC Harwell offers a free mouse archiving service to the scientific community (Frozen Embryo and Sperm Archive (FESA))?

An efficient breeding establishment...

- Will have or make use of facilities to archive lines;
- Will have minimised as far as possible the barriers faced by scientists to archiving lines;
- Will have a policy and process in place to ensure that tick-over colonies are assessed to determine the point at which archiving would represent a reduction;
- Will have considered the optimum strategy for managing tick-over colonies to minimise the over-production of animals.

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Background

The AWERB should play a key role in advising the establishment licence holder on the application of the 3Rs at the establishment.

In addition, the AWERB should advise staff dealing with animals at the establishment on matters related to the welfare of animals, in relation to their acquisition, accommodation, care and use.

More generally, the AWERB should promote awareness of animal welfare and the 3Rs and help to promote a “culture of care” within the establishment.

Performance Outcomes

- Regular breeding programme report defined, requested and received by AWERB.
- Proportion of Project Licence applications involving GA breeding given specific scrutiny with respect to the need for and design of GA models.

EXAMPLE FOLLOW-UP QUESTIONS Does the AWERB include questions about breeding and maintenance of GA lines when they are considering new project licence applications? Do researchers have access to support and advice when they are first considering the use of GA animals, and designing their models?

An efficient breeding establishment...

- Will have active oversight of the GA breeding programme by the AWERB.
- Will ensure that researchers have access to expert advice when they are first considering the use of a GA model, and to advise on *de novo* model design.

EXAMPLES OF LINES OF ENQUIRY

Does your AWERB take an interest in the efficiency of your GA breeding?

Are projects scrutinised to ensure that GA mouse models cannot be replaced? Is there sufficient expertise available to ensure that *de novo* model design is optimised?

What proactive steps does your AWERB take to ensure the 3Rs are applied as effectively as possible to your GA breeding?

EXAMPLES OF SATISFACTORY FINDINGS

Yes, the AWERB requests a report on our breeding programme every year, and the GA breeding lead defends this report in person at one of the AWERB meetings.

We have experts upon whom the AWERB can call with an in-depth knowledge of alternatives, who can provide appropriate critique of the design of new GA models, and who can advise on the use of the different genetic engineering technologies available, for example targeted genome editing.

The AWERB requests specific reports from colony managers about particular aspects of the programme - they tend to examine a different area each time. The AWERB also sets performance outcomes for the establishment and these are included within the GA breeding lead's report.

Background

Specialist breeding-only establishments inevitably use a large number of GA animals. Small changes in efficiency can therefore have a large impact.

Efficient breeding aligns to both welfare and business goals, and there is therefore a strong incentive towards best practice.

These lines of enquiry are specifically tailored for specialist breeding establishments, however they may equally apply to other establishments supplying GA animals to other organisations.

EXAMPLES OF LINES OF ENQUIRY

Do you keep a stock of frequently ordered GA lines “on the shelf” so that customer orders can be fulfilled at short notice?

How do you encourage your customers to give you as much notice as possible?

How do you discourage your customers from changing their minds?

EXAMPLES OF SATISFACTORY FINDINGS

Not as such. Although we keep popular lines ticking over (this is more efficient than archiving/rederivation between orders) all GA lines require sufficient lead-in time with each order so that we can vary our breeding according to demand.

We have an early order discount and we charge for cancelled orders.

As well as the cancellation charge we never breed animals unless there’s a contract in place. Where the animals are going to be used in experiments, we require confirmation that necessary licence authorities are already granted and that funding is available.

Performance Outcomes

- Proportion of tick-over lines with no orders in the last six months
- Proportion of orders where rederivation of the line was required within six months of archiving
- Proportion of orders cancelled
- Number of animals bred but not used for a scientific purpose (not sold to user or used for breeding/research)

EXAMPLE FOLLOW-UP QUESTIONS How do you predict demand? Did you lose custom when you moved to a demand-led system (requiring the customer to give more notice)? Did this have any knock-on impact on animal welfare?

An efficient breeding establishment...

- Will have minimised the number of animals kept “on the shelf” and will, as far as possible, breed on demand;
- Will have considered incentives and disincentives to customers for appropriate timings of orders, and to minimise cancellations.

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Background

Matching the supply of animals with the scientific demand for them is an essential element of efficient breeding. Failure to do this may lead to under-powered studies (not enough animals available to produce statistically significant results) or overproduction of animals, contributing to avoidable surplus.

Active and informed colony management is essential for efficiency. The colony manager must be able to ascertain how many animals are in the programme, when they were paired, when the litters were born, the size of the litters and other basic information to facilitate good management.

EXAMPLES OF LINES OF ENQUIRY

How do you decide whether to set up and breed a new colony in-house versus buying in animals required for specific experiments?

How do you match the production of animals to the demand for them?

How do you keep track of how your colony is doing? For example, how many animals there are, how many matings, how many litters of what size, etc.

EXAMPLES OF SATISFACTORY FINDINGS

We evaluate the scientific need and whether the number of animals required and the anticipated timescales justify breeding in-house. We also consider whether the conditions animals have experienced prior to starting the experiment may influence the science and must be standardised. Sometimes it is more efficient to buy animals in than to generate them in-house.

We perform breeding calculations before we plan our experiments and only produce the numbers of animals that we need. (Demand led)

We know in advance what experiments we want to run, but we finesse the details of the experiments based on how the particular strains breed. The scientists have to make a case that their experiment is the best use of the animals that we have. (Supply led)

Animal production is consistent throughout the year. We plan our experiments based on this predictable "pipeline" of animals.

We have a database that tracks all this information and also gives me historical data. It is very easy to see how many animals there are in each colony, how frequently they are producing litters and the size of the litters. It is easy to see when the pairs need to be replaced.

In our small establishment the technicians complete spreadsheets which are held on the shared drive so I can access it whenever I want.

Background

See also [Section 10: Oversight, leadership and training](#)

EXAMPLES OF LINES OF ENQUIRY

Who does the colony management for each group?

How do you identify people who need extra support with their colony management and/or whether colonies are being efficiently managed?

How frequently and by whom are breeding programmes reviewed?

What indicators of good breeding performance do you use?

EXAMPLES OF SATISFACTORY FINDINGS

This depends on the skill and experience available in the group. About half of the PIs do their own colony management, but for new or inexperienced researchers the GA breeding lead gives someone in the group very close guidance (“on the job training”).

The GA breeding lead liaises closely with the colony managers and the technicians so he/she picks up on situations where extra support is required.

Every colony manager has a monthly meeting/ phone call with the GA breeding lead to discuss how the colony is doing and any issues that have cropped up.

The technicians have a list of requests or unusual situations that automatically flag the need for sign off from the GA breeding lead (e.g. requests for second genotype sample, unusual pairings).

The principles of management of breeding programmes are considered formally every year by the AWERB. Monthly check-ups are held with colony managers of all ongoing programmes. Colony managers are responsible for day-to-day monitoring of their programmes.

We determine appropriate indicators depending on the genetics. It is often (but not always) appropriate to compare litter frequency and size for each pair against the strain norm.

Background

The controls that are the most convenient to generate are not necessarily the most scientifically robust.

Environmental factors such as light, noise, temperature and the enrichment available may greatly influence breeding success. For example it can be important to reduce extraneous noise during late pregnancy and early lactation to reduce the risk of mismothering and cannibalism. There can be considerable variation in the sensitivity to environmental disturbance and conditions between strains.

Performance Outcomes

- Proportion of colony managers who have received formal training in colony management.
- Proportion of colony managers who complete annual CPD or training updates in colony management to keep key skills up to date.
- Proportion of colony managers who report that they have sufficient expert support in colony management available to them.
- Proportion of colony managers who feel their skills are up-to-date.

EXAMPLES OF LINES OF ENQUIRY

How do you track the characteristics of each strain?

How do you approach breeding strains that are known to be “difficult breeders”?

How do you provide control animals?

How do you ensure that environmental conditions are optimised for each GA strain?

EXAMPLES OF SATISFACTORY FINDINGS

We have a mouse passport system but also a cage-side label that contains a very brief summary of what harmful phenotypes to look out for.

We make very careful observations of the strain and analyse the core reason for the difficulty. This can then be directly addressed through husbandry interventions, or we adjust the expectations of the scientists with regards the productivity of the line. We also liaise with other groups/establishments where the same strain is being bred. If a strain is found to be difficult, the NVS, NACWO and/or AWERB review the scientific justification for its use.

We nearly always need controls specific to our experiment and have to generate them each time. Controls are often required to be line-, gene-, breed-, age- and dam-specific, therefore using previously-generated controls may not be scientifically valid and may represent a “false economy”.

We ensure any welfare or husbandry requirements of the strain have been identified. The cage-side phenotype card alerts people to any special welfare or husbandry requirements. If there are particularly sensitive strains we put a warning sign on the door of the room.

Performance Outcomes (continued)

- Proportion of colony managers who report that they have easy access to the information they need to efficiently manage their colonies.
- Proportion of technicians reporting they feel confident to challenge or report any instructions or requests that are unusual or that they don't understand.
- Proportion of colony managers who monitor strain-appropriate breeding performance indicators.
- Pre-weaning loss rate (by strain).
- Proportion of technicians/scientists who report that they can easily find phenotype information for familiar and unfamiliar strains.

EXAMPLE FOLLOW-UP QUESTIONS Who is involved in deciding whether to breed in-house or buy animals in? How do you assess whether a colony is being well managed? How quickly are any issues identified and dealt with? What training do you give new researchers in colony calculations? Is it convenient for colony managers to access the colony data? How often do you [colony manager] look at it? Is historical data easy to access? How do you determine if someone is sufficiently skilled at colony management? How does this change with multiple knock-out strains (complex genetics)? Where do you get information about the “strain norm”? Are you aware of the *GA passports: the key to consistent animal care* booklet by the RSPCA Passport Working Group and endorsed by the Wellcome Trust Sanger Institute? Where ticking over a colony is appropriate, how many pairs do you keep? Why have you settled on this number?

An efficient breeding establishment...

- Will have an individual identified as the primary colony manager for each colony;
- Will have regular reviews of colony performance and management at individual colony and establishment-wide levels;
- Will have colony managers who are skilled in matching supply and demand, so that sufficient animals are available to ensure high quality science, while minimising the avoidable production of surplus animals;
- Will provide training and support to colony managers to equip them with the skills they need, keep their skills up to date and assist them with challenging situations;
- Will have oversight of the relative strengths of their colony managers, and will understand situations where individuals may require extra support or training;
- Will have colony managers who are able to keep up to date with accurate information about their colonies;
- Will gather all the information required by colony managers to make sound breeding decisions;
- Will have technicians who are empowered to challenge colony managers directly or indirectly if unusual or unclear requests are made;
- Will have defined strain-appropriate breeding performance indicators for each colony, and be monitoring against them;
- Will have a methodology for assessing strain-specific tendencies, preferences and phenotypes and planning and providing optimum conditions for those strains;
- Will have considered the optimum strategy for maintenance of colonies, balancing genetic needs against practical constraints;
- Will have considered the optimum controls for conditional knock-outs and will have a system for making these available across research groups;
- Will have considered environmental requirements for each strain and will make strain-specific adaptations as necessary.

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Background

The nature of an establishment's user-charging structures can exert a major influence on user behaviour. Inappropriate charging structures may hinder good science and discourage good breeding practices.

Charging structures may also positively influence practices: For example, charging per cage rather than per animal may reduce the number of singly housed animals, which may be beneficial for animal welfare.

Other areas that may be influenced by charging structures include use of equipment/technology, staffing levels, provision of enrichment and/or environmental conditions.

Whatever charging structure is used, it should be carefully examined to ensure it is supporting good welfare and good science, and not inadvertently encouraging undesirable practices.

Performance Outcomes

- Annual review of user-charging structures and their influence on GA breeding practices reviewed by AWERB.

EXAMPLE FOLLOW-UP QUESTIONS What are the financial pressures that your colony managers face? Do they encourage desirable practices while enabling good science?

An efficient breeding establishment...

- Will have analysed the barriers to efficient breeding and ensured that any influenceable barriers are minimised or removed, including financial barriers;
- Will have considered the design and use of charging structures that encourage desirable practices as well as encouraging and supporting good science.

EXAMPLES OF LINES OF ENQUIRY

How have you ensured that charging structures encourage efficiency and discourage poor practices with respect to breeding GA lines, while supporting good science?

EXAMPLES OF SATISFACTORY FINDINGS

We have analysed the barriers to best practice experienced by [colony managers](#) and we are actively working to minimise as many of these barriers as possible. We are prioritising addressing the financial barriers because these are particularly strong drivers of behaviour. We are also investigating how financial incentives can be used to encourage desirable breeding practices at the same time as encouraging and supporting good science.

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Background

Practices around genotyping can have a major impact on the number of animals bred but not used, and also the number of animals kept alive and any one moment. Inefficient, inaccurate or delayed genotyping can lead to avoidable surplus animals.

Gene-editing approaches are reported to substantially reduce the numbers of mice needed in the generation of new strains in comparison with embryonic stem-cell micro injection. However, off target and multiple gene insertions and 'mosaicism' can occur and the detection of these animals using genotyping techniques is technically demanding when compared with genotyping of founders generated by embryonic stem-cell micro injection. The quality of the new strains must be carefully proven by the rigorous use of precise genotyping methods (e.g. qPCR etc) before the strains are bred on for use in research.

Wherever possible, genotyping should occur pre-weaning, to allow the identification of the animals prior to onset of any phenotype. This also allows more efficient use of space and more nimble decision-making, for example to re-breed for missing genotypes in a more timely manner.

EXAMPLES OF LINES OF ENQUIRY

How do you avoid genotyping mistakes?

Do you outsource your genotyping or perform it in-house? Why?

How long does it take for animals to be genotyped?

How/when do you set up the genotyping method for new lines?

EXAMPLES OF SATISFACTORY FINDINGS

We have a set procedure for genotyping that is the same across the unit. That way the technicians do not have to change the way they work between colonies.

We do our genotyping ourselves because it is the most efficient way of analysing the small number of lines that we hold.

We outsource the genotyping because the external provider is far more efficient, fast and cost-effective than employing someone in our lab to do it. In addition, they can easily set up new PCRs for complex genetics and there is no downtime due to technical problems that we would inevitably have in our own small lab.

We are a large facility and run a central genotyping service that caters for all the lines we hold.

It only takes a couple of days for the results to come back and we can do that prior to weaning.

Genotyping for new lines is always planned in advance of the line being produced, so that we don't find ourselves in a position where there's a new line and we don't immediately have a way of genotyping it. We don't allow new lines to be brought into the facility until a satisfactory genotyping programme is in place and ready to be used. The adaptability of methods and the complexity of the design of the construct are important factors to consider.

EXAMPLES OF LINES OF ENQUIRY

How do you ensure that the least invasive method for taking samples for genotyping is always used?

Do you bank your samples?

How do you minimise downtime of equipment critical for genotyping (e.g. PCR)?

Where gene-editing techniques such as CRISPR/Cas9 are used for the creation of new strains, what quality control and assurance processes will be followed to ensure animals produced contain the precise genetic alteration planned?

EXAMPLES OF SATISFACTORY FINDINGS

If a method other than ear notching is used (at the same time as identification) the colony manager has to report this to the NACWO. In this way we can monitor the use of other techniques and ensure they are justified.

Yes, we always bank samples in case we need to re-run an analysis.

We have a proactive maintenance regime and robust emergency response plan, including the use of a back-up lab if needs be.

Before going on to form the colony, progeny will be quality-assured by genotyping and sequencing to confirm that the mutation is as expected with no secondary off-target mutations. We will seek the advice of an acknowledged expert/centre of expertise, for advice on the most appropriate approach to confirming the sequence of the allele/locus being altered.

Performance Outcomes

- Genotyping error rate;
- Genotyping turnaround time (sample collection to results available);
- Genotyping service downtime.

EXAMPLE FOLLOW-UP QUESTIONS What is your quality control process for genotyping?

An efficient breeding establishment...

- Will have a quality control process for their genotyping;
- Will have assessed the relative merits of in-house versus outsourced genotyping;
- Will have minimised the time that elapses between taking the sample and receiving genotype data;
- Will prepare the genotyping process in advance of bringing in/producing new lines;
- Will have access to an archive or bank for samples;
- Will have maintenance, repair and contingency plans in place for critical equipment (e.g. PCR) to minimise downtime.

Background

Oversight, leadership and training can have a vital impact on skills and teamworking, and therefore animal welfare.

It is essential that roles and responsibilities are clearly defined. Different establishments may prefer different structures and arrangements, but the underlying principle - that everyone knows who is responsible for what - remains the same.

EXAMPLES OF LINES OF ENQUIRY

How do you know who is in charge of each colony?

Do you have a GA breeding lead who has oversight of all the GA breeding activities that are taking place at the establishment?

Do you have a GA breeding expert at the establishment?

How do you ensure that your researchers, colony managers and technicians have the required skills when they first start at your unit?

How do you ensure that your researchers, colony managers and technical staff keep up to date with new skills and techniques?

What sources of expert advice do you recommend to your researchers, colony managers and technical staff? How do you make sure that the advice is appropriate to the context of *this* establishment?

EXAMPLES OF SATISFACTORY FINDINGS

Each colony has a named colony manager. This may be the PI, a member of the research group, a technician or the GA breeding lead themselves, depending on the people and animals involved.

Yes, colony managers report to the GA breeding lead, who reports to the AWERB. The GA breeding lead oversees the breeding, and advises colony managers on best practice.

Yes, we have an in-house breeding expert who is also the GA breeding lead.

No, but we have established a relationship with a breeding expert at another establishment who can help us with any issues.

We have formal induction and training for new starters but also a mentor system. We also make sure we have frequent meetings between staff which breaks down barriers and makes everybody more approachable.

Our staff have a CPD allowance and personal development goals set each year with their line manager.

We have a GA breeding lead who is our in-house expert. He/she is available for advice on an informal basis or by appointment.

What proactive measures do you take to ensure that the people involved in breeding GA animals have enough support?

We have a staff survey every year which anonymously asks staff to assess the support to which they have access.

The GA breeding lead works on the floor regularly which provides informal routes for feedback.

How often is the NVS in the unit? Does he/she take an active interest in GA breeding?

The NVS visits regularly and always checks the breeding colonies.

Performance Outcomes

- Proportion of staff inducted/trained on starting;
- Proportion of staff meeting CPD targets;
- Proportion of staff reporting that they feel adequately supported in their role through access to specialist assistance.

EXAMPLE FOLLOW-UP QUESTIONS How are good ideas propagated within the unit? Do staff have enough time and space to innovate, or even just share best practice?

An efficient breeding establishment...

- Will have an individual identified as the primary colony manager for each colony;
- Has an individual who is identified as the GA breeding lead, who has oversight of the activities of the colony managers;
- Will provide training and support to new staff to equip them with the skills they need, keep their skills up to date and assist them with challenging situations;
- Will have opportunities for formal and informal interactions between scientists, colony managers and technicians;
- Will have ongoing training/CPD opportunities for staff, with hours tracked;
- Will monitor staff views of their working conditions and be responsive to any issues raised;
- Will have appropriate in-house or external expertise available to advise on breeding strategy and practices;
- Will have an NVS who is actively involved with the GA breeding programmes.

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Background

Quality assurance of lines requires that they are periodically rederived. In addition, lines may need rederivation in order to move from a low health status to a high health status facility, or to restore a line that has been cryopreserved.

This rederivation process requires the use of a regulated procedure, and often additional animals.

Different methods of rederivation will be appropriate in different circumstances.

EXAMPLES OF LINES OF ENQUIRY

How do you decide whether/when a line requires rederivation?

What policy or oversight do you have to ensure that any rederivation on the grounds of biosecurity is proportionate to the biosecurity risk?

How do you monitor lines to ensure that their genotype does not drift in a manner detrimental to the scientific aims?

How do you quality assure the rederivation process?

Where are new lines created? In house or at a supplying establishment?

EXAMPLES OF SATISFACTORY FINDINGS

We consider the research demands and strain demands (specifically in relation to health status) versus the animal cost of rederivation and come up with the most appropriate answers on a strain by strain basis.

We consider each rederivation request on its merits, balancing a risk of a biosecurity breach and the consequence of such a breach against the welfare impact of the rederivation.

For each strain we monitor the number of inbred generations and the potential magnitude of any effect that genetic drift would have on the science. If the impact would be significant we refresh the line. This is commonly done every ten generations.

We regularly review the skill of the staff performing the rederivation. This includes standards of asepsis and tracking the success rates of each individual. We ensure that staff involved in rederivation undertake regular continuing professional development activities.

We have the facilities to create new lines in house, but it is ultimately up to the researcher to decide on the best approach, considering the complexity of the genetics and the resources available.

We do not have the facilities or skills to create new lines in house, so we import them from a specialist supplying establishment.

- Proportion of colony managers who include considerations around genetic drift in their colony reviews.

EXAMPLE FOLLOW-UP QUESTIONS How do you assess the impact, if any, of genetic drift on your science? What is your strategy for limiting the impact of genetic drift? How do you ensure your staff stay up to date and skilled in the techniques required to create new lines, particularly if they don't do it that often? Do you have any policies or procedures for vetting/approving rederivation requests?

An efficient breeding establishment...

- Will have a flexible, situation-led policy on rederivation that allows case by case consideration, rather than a “one size fits all” approach;
- Will have a risk based approach to biosecurity rather than a blanket requirement for lines to be rederived as they enter the facility;
- Will consider the risk of genetic drift on scientific outcomes and have procedures in place to prevent significant impact, through appropriate colony management;
- Will have considered the pros and cons of generating lines in-house versus importing custom-created lines from a specialist supplier.

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Background

Breeding of GA animals produces unavoidable and avoidable surplus animals. “Non-target” animals are created as a by-product of the creation of “target” animals.

Unavoidable surplus is caused by Mendelian genetics and the fact that technology for genetic manipulation is not 100% efficient. In addition, not all non-target animals produced can necessarily be used for a scientific purpose.

Avoidable surplus occurs if the non-target animals are not used for a scientific purpose (where this is possible), or where more of them are produced than the inevitable minimum. In addition, some researchers only use animals of one sex for their research, with the potential to waste the animals bred of the opposite sex.

Formal and/or informal systems can reduce the number of animals that are “bred but not used”.

CRISPR and other gene editing techniques are relatively new, simple and inexpensive technologies that can be used in the generation of genetically-altered animal strains. Due to the ease, low cost and simplicity of this technique, there is a risk that scientists may create lines for use in their work where there already exists an appropriate strain held at other establishments or in national/international archives.

EXAMPLES OF LINES OF ENQUIRY

Why do you use animals of only one sex in your research?

How do you ensure that bred animals are used, wherever possible, for a beneficial scientific purpose? What happens to unwanted animals (e.g. wrong genotype)?

EXAMPLES OF SATISFACTORY FINDINGS

The model is of a disease only occurring in males.

There is a fundamentally different mechanism in males and females - we only wish to study one mechanism at this stage.

We have a formal arrangement to share strains and/or tissues on our intranet.

We are a small unit and informal communication with collaborators ensures that animals/tissues are shared as much as possible.

All surplus animals are used for tissue harvest or teaching purposes.

Because the [GA breeding lead](#) has a good oversight of all the projects and colonies, he/she can help to ensure that researchers are aware of opportunities to share and collaborate.

External collaborations can reduce the need to create *de novo* lines, however it is important that facility health status (e.g. the need for rederivation) and transport factors are considered within the overall 3Rs analysis. Essential strain information should be effectively communicated (e.g. via a passport).

How do you ensure that all researchers at your establishment are aware of the lines already being bred here?

We have a searchable database that all researchers can access. We also publicise new lines in our newsletter that goes out to users

How do you check whether you can bring in a line from an external collaborator, rather than creating the line *de novo*?

We ensure that researchers have searched the appropriate external databases to check for possible external collaborations before allowing a new line to be created here.

Transporting live animals usually has an associated welfare cost, and it may be preferable to transport frozen tissue instead. However the number of animals and welfare impact of archiving and rederivation must be balanced against the welfare cost of transport (see [archiving](#)). This is likely to vary from case to case.

When considering importing a line, what information do you request and evaluate?

We ask for the strain [passport](#) (to provide essential biological and husbandry information) and information about the facility's health status (that may impact on quarantine/rederivation). If live animals are to be sent (as opposed to frozen tissue) we require specific justification for this, and information about the impact of the journey/travel arrangements on animal welfare.

Performance Outcomes

- Number of animals bred but not used for a scientific purpose;
- Proportion of scientists who report that they have access to information about animals being bred at the establishment and sharing colonies and/or tissues.

EXAMPLE FOLLOW-UP QUESTIONS Why don't you use age *and* sex matched controls? How do you track the number of animals that are "bred but not used"? How do you monitor how surplus animals are used? How do you ensure your database of lines being bred is up-to-date and complete? How do you manage researchers' concerns regarding potential Intellectual Property issues in the context of sharing lines/tissues? Can you identify core colonies that could be centrally managed for all researchers? How do you ensure that researchers have appropriate licence authorities in place before importing or creating a new line? Are you aware of Mouse Locator UK (hosted by The Francis Crick Institute) and the International Mouse Strain Resource (IMSR, www.findmice.org)?

An efficient breeding establishment...

- Will have systems in place to ensure that researchers know what lines are currently being bred at the establishment;
- Will have one or more systems in place, formal or informal, to ensure that researchers share the available animals or their tissues whenever possible;
- Will question the exclusive use of male or female animals in experiments and ensure the approach is scientifically necessary.

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Background

Successful breeding of GA animals relies on partnership between the scientists, unit managers and animal technicians.

EXAMPLES OF LINES OF ENQUIRY

How do you organise which technician works with which colonies?

How do you ensure that the technicians understand the scientific requirements of the programme?

What happens if the technician does not feel the instructions given by the colony manager are appropriate, or if he/she does not understand the instruction or the rationale behind it?

Do the technicians have an alternative to direct communication with the colony manager if needs be?

How do the scientists regard the technicians?

EXAMPLES OF SATISFACTORY FINDINGS

There is a named technician attached to every group, so although every technician can do all the procedures for all groups, there is one person with an in-depth knowledge of the group's colonies.

We have regular meetings between the scientists and the technicians where the scientists explain the background and importance of the work that the technicians are facilitating.

The technicians are empowered to challenge the colony managers directly in this situation.

The technicians are able to use their professional judgement (e.g. if a requested pairing involves animals that don't look in the best clinical condition on the day).

The technicians have a route to challenge the colony managers which does not involve direct conversation with them if needs be (e.g. via a supportive unit manager or the GA breeding lead).

The scientists feel supported by the technicians, and respect their skills. They work effectively together as a team.

Background

Successful strategy here will ensure that planned or unplanned absences of the colony's lead technician does not result in a drop in standards of animal welfare or colony management.

EXAMPLES OF LINES OF ENQUIRY

How do you ensure continuity of the colony manager-technician relationship (i.e. reduced rotation of technicians) while still maintaining strength and depth in the skills of the technical staff (e.g. to cover absence and maintain interest through variety)?

How do you ensure that the phenotype of new or existing strains, and any associated welfare information, is recorded and made immediately available to technicians, scientists and people concerned with animal welfare, for example the NVS?

EXAMPLES OF SATISFACTORY FINDINGS

We balance the need for more than one technician to be knowledgeable about each group's colonies against the need for continuity by slowly rotating technicians between groups. Although the colony managers would prefer that we never rotate, they also recognise the need for all our technicians to be sufficiently familiar with the strains that they can detect any issues at the weekends, for example.

When the strain is imported or created we work out when the phenotype assessments need to take place, according to the known and unknown strain characteristics. We perform these assessments and carefully record our findings and any welfare or husbandry implications. We have a cage-side phenotype card which alerts people to the expected harmful phenotypes and any special welfare or husbandry requirements. It also clearly indicates what is and is not permitted by the project licence. In addition, we create mouse passports that are held on a shared drive.

Performance Outcomes

- Proportion of strains that have cage-side basic phenotype information available.
- Proportion of strains that have phenotype information held in a mouse passport.

EXAMPLE FOLLOW-UP QUESTIONS If you were working at the weekend, would you easily be able to check the expected phenotype of an unfamiliar strain, permitted adverse effects and humane endpoints, and act appropriately? In the bigger picture, how do you ensure that personal and project licence holders, named persons and the AWERB work together with the colony managers and GA breeding lead to promote the 3Rs and best practices across the establishment?

An efficient breeding establishment...

- Will have scientists who regularly take time to explain the science behind the strains and the benefits of the work being done to the technicians;
- Will have technicians who are empowered to challenge colony managers directly or indirectly if unusual requests are made;

An efficient breeding establishment... (continued)

- Will have technicians who are skilled and confident enough to use their professional judgement when carrying out instructions given to them by colony managers if the instructions don't seem to be right for the animals in front of them, or if there may be a better alternative way of achieving the same end result;
- Will have an indirect route to raise concerns and/or resolve disagreements between the technicians and colony managers, for example via the unit manager; Will have constructive working relationships between the technicians and the colony managers, based on mutual respect;
- Will have a strategy for ensuring that the need for technicians to have an in-depth knowledge of a small number of colonies is balanced against the need for sufficient technicians to have enough knowledge of multiple colonies;
- Will have a strategy for assessing the phenotypes of newly created strains;
- Will have a strategy for capturing unexpected phenotypic traits of established strains;
- Will have a system for recording phenotype information, including making critical information available at cage-side.

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An efficient breeding establishment...

1. Archiving

- 1.1. Will have or make use of facilities to archive lines;
- 1.2. Will have minimised as far as possible the barriers faced by scientists to archiving lines;
- 1.3. Will have a policy and process in place to ensure that tick-over colonies are assessed to determine the point at which archiving would represent a reduction;
- 1.4. Will have considered the optimum strategy for managing tick-over colonies to minimise the over-production of animals.

2. AWERB

- 2.1. Will have active oversight of the GA breeding programme by the AWERB.
- 2.2. Will ensure that researchers have access to expert advice when they are first considering the use of a GA model, and to advise on *de novo* model design.

3. Breeding-only establishments

- 3.1. Will have minimised the number of animals kept “on the shelf” and will, as far as possible, breed on demand;
- 3.2. Will have considered incentives and disincentives to customers for appropriate timings of orders, and to minimise cancellations.

4. Colony management

- 4.1. Will have an individual identified as the primary colony manager for each colony;
- 4.2. Will have regular reviews of colony performance and management at individual colony and establishment-wide levels;
- 4.3. Will have colony managers who are skilled in matching supply and demand, so that sufficient animals are available to ensure high quality science, while minimising the avoidable production of surplus animals;
- 4.4. Will provide training and support to colony managers to equip them with the skills they need, keep their skills up to date and assist them with challenging situations;
- 4.5. Will have oversight of the relative strengths of their colony managers, and will understand situations where individuals may require extra support or training;
- 4.6. Will have colony managers who are able to keep up to date with accurate information about their colonies;
- 4.7. Will gather all the information required by colony managers to make sound breeding decisions;
- 4.8. Will have technicians who are empowered to challenge colony managers directly or indirectly if unusual or unclear requests are made;
- 4.9. Will have defined strain-appropriate breeding performance indicators for each colony, and be monitoring against them;
- 4.10. Will have a methodology for assessing strain-specific tendencies, preferences and phenotypes and planning and providing optimum conditions for those strains;
- 4.11. Will have considered the optimum strategy for maintenance of colonies, balancing genetic needs against practical constraints;
- 4.12. Will have considered the optimum controls for conditional knock-outs and will have a system for making these available across research groups;
- 4.13. Will have considered environmental requirements for each strain and will make strain-specific adaptations as necessary.

5. Financial pressures

- 5.1. Will have analysed the barriers to efficient breeding and ensured that any influenceable barriers are minimised or removed, including financial barriers;
- 5.2. Will have considered the design and use of charging structures that encourage desirable practices as well as encouraging and supporting good science.

6. Genotyping

- 6.1. Will have a quality control process for their genotyping;
- 6.2. Will have assessed the relative merits of in-house versus outsourced genotyping;
- 6.3. Will have minimised the time that elapses between taking the sample and receiving genotype data;
- 6.4. Will prepare the genotyping process in advance of bringing in/producing new lines;
- 6.5. Will have access to an archive or bank for samples;
- 6.6. Will have maintenance, repair and contingency plans in place for critical equipment (e.g. PCR) to minimise downtime.

7. Oversight, leadership and training

- 7.1. Has an individual who is identified as the GA breeding lead, who has oversight of the activities of the colony managers.
- 7.2. Will provide training and support to new staff to equip them with the skills they need, keep their skills up to date and assist them with challenging situations;
- 7.3. Will have opportunities for formal and informal interactions between scientists, colony managers and technicians;
- 7.4. Will have ongoing training/CPD opportunities for staff, with hours tracked;
- 7.5. Will monitor staff views of their working conditions and be responsive to any issues raised;
- 7.6. Will have appropriate in-house or external expertise available to advise on breeding strategy and practices;
- 7.7. Will have an NVS who is actively involved with the GA breeding programmes.

8. Rederivation

- 8.1. Will have a flexible, situation-led policy on rederivation that allows case by case consideration, rather than a “one size fits all” approach;
- 8.2. Will have a risk based approach to biosecurity rather than a blanket requirement for lines to be rederived as they enter the facility;
- 8.3. Will consider the risk of genetic drift on scientific outcomes and have procedures in place to prevent significant impact, through appropriate colony management;
- 8.4. Will have considered the pros and cons of generating lines in-house versus importing custom-created lines from a specialist supplier.

9. Sharing animals and minimising avoidable surplus

- 9.1. Will have systems in place to ensure that researchers know what lines are currently being bred at the establishment;
- 9.2. Will have one or more systems in place, formal or informal, to ensure that researchers share the available animals or their tissues whenever possible;
- 9.3. Will question the exclusive use of male or female animals in experiments and ensure the approach is scientifically necessary.

10. Teamworking and cooperation

- 10.1. Will have scientists who regularly take time to explain the science behind the strains and the benefits of the work being done to the technicians;
- 10.2. Will have technicians who are empowered to challenge colony managers directly or indirectly if unusual requests are made;
- 10.3. Will have technicians who are skilled and confident enough to use their professional judgement when carrying out instructions given to them by colony managers if the instructions don't seem to be right for the animals in front of them, or if there may be a better alternative way of achieving the same end result;
- 10.4. Will have an indirect route to raise concerns and/or resolve disagreements between the technicians and colony managers, for example via the unit manager;
- 10.5. Will have constructive working relationships between the technicians and the colony managers, based on mutual respect;
- 10.6. Will have a strategy for ensuring that the need for technicians to have an in-depth knowledge of a small number of colonies is balanced against the need for sufficient technicians to have enough knowledge of multiple colonies;
- 10.7. Will have a strategy for assessing the phenotypes of newly created strains;
- 10.8. Will have a strategy for capturing unexpected phenotypic traits of established strains;
- 10.9. Will have a system for recording phenotype information, including making critical information available at cage-side.

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