THE SOUTH AFRICAN MEDICAL RESEARCH COUNCIL

ETHICS COMMITTEE FOR RESEARCH ON ANIMALS (ECRA)

STANDARD OPERATING PROCEDURES

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1. AUTHORITY

- The South African Medical Research Council (SAMRC) Ethics Committee for Research on Animals (ECRA) was established as set out in its Research Ethics Policy and Terms of Reference (ToR).
- Its authority has been conferred upon it by the SAMRC Board.

2. TERMS OF REFERENCE

- These guidelines apply to the use of sentient animals for research, teaching and testing within the SAMRC.
- They are applicable to all SAMRC staff that are occupationally involved with the production, care and use of laboratory animals, and to scientists and educators whose research, teaching and testing on animals is done in collaboration with SAMRC staff or with financial or other support from the SAMRC and its employees.
- Studies that may result in severe or chronic pain or significant alterations in the animals' ability to maintain normal physiology, or adequately respond to stressors, should include descriptions of appropriate humane endpoints or provide science-based justification for not using a particular, commonly accepted humane endpoint. Veterinary consultation must occur when pain or distress is beyond the level anticipated in the protocol description or when interventional control is not possible. The "three R" principles, introduced by Russell and Burch (1959)[1], of Replacement, Reduction and Refinement should be applied. The values of these principles are as follows:

  Replacement refers to methods that avoid using animals. The term includes absolute replacements (i.e. replacing animals with inanimate systems such as computer programs) as well as relative replacements (i.e. replacing animals such as vertebrates with animals that are lower on the phylogenetic scale or by cell culture).
  Reduction involves strategies for obtaining comparable levels of information from the use of fewer animals or for maximizing the information obtained from a given number of animals (without increasing pain or distress) so that in the long run fewer animals are needed to acquire the same scientific information.
  Refinement refers to modifications of husbandry or experimental procedures to enhance animal well-being and minimize or eliminate pain and distress.

- Researchers should guard against any tendency to underrate or ignore the potential discomfort or suffering of animal subjects, and may not attempt to achieve cost savings by compromising the quality of care afforded to animals.

3. ETHICAL REVIEW PROCESS

Every experiment in which sentient animals are used, either for research, for testing or for educational purposes to demonstrate known principles or acquire manual skills, is to be subjected to a formal process of ethical review by the ECRA.

Duties of the ECRA are to:

a) Provide ethical guidance to researchers and educators regarding: standards of animal care and welfare; the manner in which experimental procedures are conducted; and ethical issues arising from proposed or ongoing studies.

[1]Russell W. and Burch R. (1959) *The Principles of Humane Experimental Technique*. London UK: Methuen.

b) Promote the use of ethical analysis to increase awareness of animal welfare issues and the implementation of the principles of *replacement, reduction and refinement* in animal studies, and to give guidance to relevant sources of information that will facilitate these practises.
c) Examine proposed experimental and teaching protocols submitted by institutional staff with consideration of the likely harm that may be caused to the animals and likely benefits that may arise from such work and to determine how these considerations are recorded in relation to each other.
d) Examine a hypothesis that is well considered, plausible and have a reasonably prospect of yielding good results.
e) Approve applications that comply with the ethical principles for humane animal experimentation.
f) Propose amendments and modifications, seek clarifications and request revised submissions in the event of applications not approved.
g) Re-evaluate applications that have not been completed within their proposed experimental period and serve notices for those in which there is no justification for time extensions.
h) Consider the sourcing, care and accommodation standards applied to all animals within the institution, including breeding stocks, and monitor the humane termination of surplus animals.
i) Regularly consult and engage with recognised authorities, concern groups and reputable sources of information to stay abreast of developments in the field of ethical review and analysis.
j) Regularly review managerial systems, procedures and protocols in relation to the proper use of animals.
k) Establish that researchers/educators and all individuals under their supervision have the competence, training and skills to ensure the comfort, health and humane treatment of animal subjects.
l) Sponsor seminars and workshops on laboratory animal science, animal welfare and the ethics of animal experimentation and make resources and material available to heighten ethical sensibility amongst researchers and educators.

4. MEMBERSHIP

The ECRA shall comprise of at least six persons, 50% of which shall be independent of the institution. Appointment of members is based on the guidelines of the South African National Standard (SANS 10386:2021) for Care and Use of Animals for Scientific Purposes.

4.1 Member categories

The committee shall have members in the following four categories that will allow it to fulfil its ToR. The chairperson shall be appointed in addition to categories A to D members. Categories C and D members shall, together, represent at least one-third of the ECRA membership.

Category A: A veterinarian with experience relevant to the studies of the institution or, in special circumstances a person(s) with qualifications and experience to provide comparable expertise.

Category B: A person(s) with substantial recent experience in the use of animals in scientific studies or teaching activities.

Category C: A person(s) with demonstrable commitment to and established experience in furthering the welfare of animals, who is not employed by or otherwise associated with the institution, and who is not involved in the care and use of animals for scientific purposes. The person should, where possible, be selected on the basis of active membership of and nomination by an animal welfare organisation.

Category D: An independent person(s) who does not currently and has not previously conducted scientific studies or teaching activities using animals, and who is not an employee of the institution, except under defined circumstances (for example, tenured academic staff from non-scientific departments). If such an employee is appointed, the individual shall be in a senior position and shall not be supervised by other members of the committee or by anyone involved in animal research at the institution. The institution shall provide clear reasons for the necessity to appoint an employee in this category.

4.2 Conflict of interest

No member of an ECRA may participate in a review or approval of a proposed animal study in which that member has a conflicting interest (e.g. such as being personally involved in such a study), other than to provide information. Members with conflicting interests should declare these and may not count towards a quorum or vote in such circumstances. Conflict of interest includes involvement in potentially competitive research programmes, research, funding or intellectual information which may provide an unfair competitive advantage. A member's bias as such may constitute a conflict of interest and interfere with impartial judgement.

4.3 Confidentiality

All newly appointed ECRA members shall acknowledge acceptance of their nomination in writing and, in addition, the signing of a confidentiality agreement as required by the ECRA ToR and any other institutional policies.

5. ECRA OPERATING PROCEDURES

5.1 Appointment of committee

The SAMRC Board shall formally appoint the ECRA after detailed consultation with the relevant authorities. The SAMRC Board delegates processes leading to appointment of ECRA members to the SAMRC President.

5.2 Duration of membership

The period of membership of individuals may be prescribed, such as from 3 to 5 years, and may be renewed. It is reasonable that new members will require time to absorb the ethos and develop the skills of ethical review.

5.3 Election of chairperson

The SAMRC Board will review recommended names of potential ECRA members in consultation with the SAMRC President and shall make the final appointment of the ECRA members, including the chairperson.

5.4 Administrative support

The ECRA shall be supported by a secretariat based within the SAMRC to perform its

administrative duties, provide secretarial assistance and maintain records of all ECRA documents and correspondence.

5.5 Meetings

The ECRA convene four times a year to review applications for ethical review and to conduct other matters which falls within its ToR. The meetings dates are determined at the first ECRA meeting of each year. Notice of a meeting and working documents are distributed to ECRA members 7 days before assembly of the meeting.

5.6 Quorum

At least 50% + 1 of the members, representing each of the four member categories, are required to compose a quorum. Poor meeting attendance impacts on the quorum and can result in a meeting being cancelled. To ensure timely and efficient review of research proposals, ECRA members are expected to attend meetings punctually and regularly. Members that are unable to attend a meeting should send their comments to the secretariat before the meeting in order for it to be included in the discussion and minutes. If a meeting is not quorate, contentious issues on the agenda will still be discussed among attendees and thereafter a separate meeting will be organised with the members not in attendance to discuss these matters and record their inputs.

5.7 Co-option

The ECRA is empowered to nominate additional non-scientist members and professional advisors onto the committee. Such nominations are to be approved by the SAMRC Board.

5.8 Recording of proceedings

Minutes are kept to document decisions and all other aspects of the ECRA's deliberations and business.

5.9 Equity in ethical review

The ethical review of proposed animal studies shall be conducted fairly and in a comparable manner. Where possible, decisions on whether or not to approve applications shall be made on the basis of consensus rather than the majority. The decision-making process should systematically evaluate the morally relevant factors which should be assessed. These should be formally documented at ethical analysis meetings. These documentations should include a harms-benefit assessment to assist in clearly justifying the choices made by the reviewing committee. The assessment practise to be used is not prescribed. However, the evaluation approach described by Stafleu *et al.* (1999)[2] can be used as a guideline.

5.10 Committee and chairperson's approval

General guidelines for approval of applications and reports are as follows:

- If a study or report was not provisionally approved at the meeting, it needs to be resubmitted by the principal investigator and serve on the next meeting.
- If a study or report was provisionally approved but important information was lacking, it will be sent for round robin approval by ECRA members.

[2]Stafleu R.R., Tramper R., Vorstenbosch J. and Joles J.A. (1999) *The ethical acceptability of animal experiments: a proposal for a system to support decision-making.* Laboratory Animals 33, 295-303.

- If a study or report was provisionally approved but only minor corrections were needed, it will be checked and approved by the chairperson.

The chairperson may deal with minor matters with or without consulting the other members. Progress reports and the outcomes of all completed animal studies will be reported to all members at the next meeting of the ECRA. During other periods, the chairperson will communicate with ECRA members for consensus on urgent matters. Decisions taken should be ratified or noted and formalised in the minutes of the next ECRA meeting.

5.11 Grant application approvals

Special consideration will be granted to provisionally approve applications that are required to meet deadlines for grant applications. These applications can be considered by e-mail consultation and communication between the chairperson and ECRA members in order to expedite the provisional approval with a turn-around time of 7 working days. Such applications, which often propose a series of animal studies, may be subjected to an additional ECRA review for the study to proceed after the grant application was approved.

5.12 Communication with applicants

Researchers and educators will be informed of ECRA decisions in writing within 15 working days after the meeting date. The principal investigator will be given 10 working days to respond to all ECRA queries. Hereafter, ECRA will give a final decision within 7 working days whether the project is approved or not. No animal-based research, testing or teaching activities may commence before written ECRA approval has been received.

5.13 Adverse decision and appeal

Although it is unusual for a proposal to be considered unacceptable, it is accepted that projects requiring modification on the advice of the ECRA are returned to the principal investigator for revision. Any adverse decisions and detailed descriptions or recommendations will be communicated to the applicants. Applicants are permitted to argue such a decision by written submissions and oral presentations to the ECRA. Alternatively, the applicant may request the option of an external expert or an *ad hoc* committee to re-evaluate the application for a final verdict.

5.14 ECRA register

A register of all approved projects, with commencing dates, six-monthly reporting dates and end-of-project reporting dates will be maintained (electronically and hard copy).

5.15 Monitoring

Continuing ECRA oversight of animal activities is required and a variety of mechanisms can be used to facilitate ongoing protocol assessment and regulatory compliance. Post-approval monitoring (PAM) is considered here in the broadest sense, consisting of all types of protocol monitoring after the ECRA's initial protocol approval. PAM helps to ensure the well-being of the animals and may also provide opportunities to refine research procedures. Methods of PAM include: continuing protocol review; laboratory inspections (conducted either during regular facilities inspections or separately during ECRA members' active monitoring); veterinary observation of selected procedures; and

observation of animals by animal-care staff. During facility inspections by the ECRA, a representative of each membership category must participate.

The submission of a six-monthly report is mandatory for all ongoing studies. This report will permit ECRA to determine if the study remains compliant with the original proposed and approved protocol. This report will also provide the opportunity to request or clarify any minor deviations or problems experienced.

5.16 Reports

The ECRA shall report annually to the SAMRC Board on membership status, the meetings conducted, training received and a list of project titles submitted. The identity of the investigators will not be revealed in these reports. A complete record of such research and six-monthly reporting must be kept by the ECRA secretariat.

An annual report shall also be sent to the National Health Research Ethics Council (NHREC), including information as required on their Annual AREC Report Form.

6. RESPONSIBILITY FOR COMPLIANCE WITH STATUTES AND PROVINCIAL ORDINANCES THAT SPECIFICALLY REGULATE ASPECTS OF ANIMAL EXPERIMENTATION

The Director/Manager of the animal research facilities have a primary responsibility to comply with all laws and ordinances that regulate the acquisition, capture, importation, breeding, transportation, treatment, care and/or termination of laboratory animals. Health and welfare concerns override protocol compliance. Additionally, the acquisition, storage and use of hazardous substances, micro-organisms and parasites must be controlled. These regulatory requirements include (see https://www.samrc.ac.za/research/ethics/guideline-documents):

a) Animal Disease Act No. 35 of 1984;
b) Animal Health Act, 2002 (Act No. 7 of 2002);
c) Animals Protection Act No. 71 of 1962;
d) Convention of International Trade in Endangered Species of Wild Fauna and Flora (CITES);
e) Department of Health Guidelines on Ethics in Health Research: Principles, Processes and Structures - 2015
f) Medicines and Related Substances Control Act 101 of 1965;
g) South African National Standard (SANS) for the Care and Use of Animals for Scientific Purposes (SANS 10386:2021);
h) The Provincial Nature Conservation Ordinance; and
i) Veterinary and Para-Veterinary Professions Act No. 19 of 1982 (amended 1993).

7. RESPONSIBILITIES OF RESEARCHERS, EDUCATORS AND ANIMAL-CARE PERSONNEL

- The responsible researcher, educator and animal-care staff are to be appropriately qualified, registered, authorised and experienced to ensure that all procedures conducted on laboratory animals will be undertaken with due discretion and precautions to protect the welfare of the animals.
- Adequate preliminary studies of the literature pertaining to their proposed work should have been undertaken to define as far as possible the risks inherent in their animal studies, and they should be fully conversant with these.
- Ethical issues regarding the role of the principal investigator and co-worker in an animal experiment include possession of the necessary attributes, competence to perform the studies, and the release of publication of the results.

- The users of laboratory animals require two attributes: *sensitivity* to identify an ethical issue and *responsibility* to act appropriately in regard to such an issue. Users will adhere to the Standard Operating Procedures (SOPs) of the animal unit.
- The character of laboratory animal users is critical to the quality of scientific knowledge and for the soundness of ethical decisions in any research or teaching project. The integrity of investigators and educators, their honesty and fairness, knowledge, qualifications and experience are the decisive factors.
- The users of laboratory animals have a responsibility to their professions, to the animals which they use and to the public to ensure that an animal experiment is likely to yield information worth knowing, and that such information is well supported by valid experimental data and analysis of that data.

8. RESPONSIBILITIES OF OTHER INSTITUTIONAL STAFF RECEIVING SAMRC FUNDING AND SUPPORT FOR ANIMAL EXPERIMENTATION

- It is required that all institutions receiving SAMRC support establish and maintain an ethical review process which conforms to these guidelines.
- The exact nature of the process used will depend on that particular establishment and is not prescribed.
- An appropriate structure of an ECRA is mandatory. A standard condition of SAMRC funding, collaboration and support is that a formal ethical review process has been performed in respect of all applications.
- The function of an institutional ECRA will be to scrutinise the ethics of proposed projects, to propose *reductions* in the numbers of animals used, to propose *refinements* in the procedures to reduce fear, deprivation, distress and pain in the animals, *replacements* with non-sentient systems whenever possible, and to advise on the care and welfare of laboratory animals.
- It is required that institutions also actively promote and present appropriate educational programmes to all animal users to create an understanding of the ethics of animal experimentation and a general knowledge of the theoretical and practical aspects of conducting animal studies which at least includes:
    i) the use of animals in biomedical research and alternatives;
    ii) the ethical aspects of animal experimentation and the ethical review process;
    iii) the laws relating to animal experimentation;
    iv) the design of animal experiments;
    v) the supply of laboratory animals;
    vi) quality in laboratory animals;
    vii) principles of laboratory animal husbandry;
    viii) hazards and safety aspects of animal work;
    ix) animal behaviour;
    x) animal handling and manipulations;
    xi) anaesthesia, analgesia and euthanasia;
    xii) non-surgical experimental procedures;
    xiii) standards of surgery for experimental animals; and
    xiv) other investigator responsibilities.
- It is required that course participation and accreditation of all individuals who use animals in research, testing and teaching become mandatory, and that successful completion of institutional courses by individuals be recognised by the issuing of a certificate by the institution.

- These courses will constitute research compliance training and may be a prerequisite for qualification for SAMRC funding for animal studies at both an institutional and personal level.
- The exact nature of presentation of courses by an institution receiving SAMRC funding and requirements for examination and certifications of persons who are to use animals for teaching, testing and education is not prescribed by the SAMRC.
- SAMRC research support staff will have full coverage from research insurance provided by the SAMRC. The policies are managed by the SAMRC Research Integrity Office. External collaborators to the SAMRC need to confirm research insurance from their employer.

9. FORM OF APPLICATION

9.1 Written proposals

A proposal should provide the ECRA with sufficient information to enable the committee to perform an ethical assessment and to conclude that the proposed use of animals in unavoidable, and that:

a) the use of animals is justified by a harm/benefit assessment;
b) the application of the "3 R" principles of *replacement*, *reduction* and *refinement* will be evident in the proposed design and conduct of the study;
c) the applicants are competent to perform the proposed studies;
d) the resources supporting the project (competent qualified/registered staff, and facilities) are adequate and that procedures reserved for veterinarians and members of the para-veterinary profession will be conducted only by persons registered with the SA Veterinary Council; and
e) the project will be conducted in a responsible manner and its conclusion will be formally reported on to the ECRA by the principle investigator.

❖ If a study will include **research on invertebrates**, a notification (see Templates) instead of a full written proposal should be submitted to ECRA in order to get an ethics clearance number. The notification should contain information on the species to be used, where the animals will be sourced from, facility where animals will be kept and the facility's SOPs.

9.2 Form of proposal

Written proposals should be presented in a way that allows the ECRA easy access to information which is essential for ethical review and written in a language and format that they can be comprehended by non-scientists who serve on an ECRA. The PREPARE and ARRIVE Guidelines (see Annexures) for animal studies should be consulted before preparation of proposals.

All documentation for a new application (see Templates) should first be submitted to the Scientific Review Committee (SRC) of the ECRA.

9.3 Scientific review process

All applications to the ECRA must have undergone scientific review first (see 9.4.5). To assist with this process, applicants need to provide a clear and comprehensive proposal for assessment. A new proposal must be examined by at least two of the co-workers mentioned in the proposal and preparatory contact with the animal facility is recommended to discuss issues of animal sourcing, ordering, housing and husbandry.

Enough time should be allowed prior to the ECRA meeting submission dates for this review process. All documentation must be submitted to the SRC by due dates specified on the ECRA's calendar (± 1.5 months before the ECRA meeting).

9.4 Checklist of information required for ethical analysis

Written proposals should contain the following information.

9.4.1 Applicant's profile

The name, institutional and departmental affiliations, contact details and qualifications of the person applying for clearance to conduct the animal experiments must be specified. Additional background information on past experience in animal experimentation will provide assurance of competence.

9.4.2 Co-workers

The names, departmental affiliations, contact details, qualifications, appropriate experience in animal research and nature of involvement of all other co-workers involved with the proposed study are to be stated.

9.4.3 Accreditation compliance

The names and accreditation numbers of all listed co-workers who have successfully completed the institutional course of accreditation to use the institutionally approved laboratory animal facilities and perform animal experiments should be given.

9.4.4 Declaration of principal investigator/educator

A signature of acceptance by the principal investigator is required as declaration of adherence to the *pro forma* SAMRC policy statement on:

a) the moral philosophy that supports animal experimentation;
b) the recognition and acceptance of animal interests;
c) the principles (the 'three Rs') of humane experimental technique;
d) the protection of animals against harmful studies unless imperative to address health, welfare and environmental problems;
e) a requirement for relevance of the proposed research in the context of the SAMRC's objectives of advancing education, science, and human and animal welfare;
f) the assumption of responsibility on a personal basis for ensuring that the highest levels of welfare shall be maintained and that animals shall be protected from abuse and any unnecessary violation of their interests; and
g) a personal declaration of understanding and acceptance of the principles detailed above (a-f), an undertaking not to deviate from experimental protocol after it was approved by ECRA, an undertaking to immediately report any adverse effects of the methods or drugs used and an undertaking to report on the progress of the study at six-month intervals once it has been started, as well as on its outcome when it has been completed.

9.4.5 Peer review statement

The application is to be supported by a peer review statement from the SRC, indicating that in the opinion of the reviewers the proposal has been judged in accordance with accepted scientific practice and norms, and is likely to be successful in achieving its objectives.

- The chairperson of the SRC conducts an initial screening/assessment to ascertain all sections of the application have been adequately completed. The application must be in MS Word document format.
- The chairperson will forward the screened application to three SRC reviewers for assessment by track change comments.
- The chairperson collates all the comments and suggested corrections from the reviewers into one document and forwards the reviewed application with track changes to the applicant in order to address the comments and make the corrections. In a case that an applicant does not agree with the SRC comments or suggestions, a letter stating the details must be communicated on a separate form.
- The chairperson re-evaluates the corrected application to verify if all the reviewers' remarks were adequately addressed. The accepted application will be signed off by the chairperson and committee members. Thereafter the application and a separate approval statement are forwarded to the ECRA secretariat for an ECRA review.
- A typical signed statement of approval by the SRC is as follows: *"The Scientific Review Committee has approved the scientific merit of the proposed study protocol submitted by Dr K N Unknown, Effect of animal fat consumption on body weight in mice. This study may proceed, provided that approval has been obtained from the ECRA"*.

❖ Research that is conducted for doctoral and master's degree purposes using SAMRC facilities should first obtain approval from the SRC and ECRA before it is submitted to a registered NHREC research ethics committee of the institution where the degree will be obtained.

❖ If a study is conducted outside SAMRC facilities by SAMRC staff, the onus is on the staff member to obtain ethical clearance from that particular institution's REC. Only if part of the study is to be conducted at SAMRC facilities should they submit their obtained ethics approval letter to ECRA.

9.4.6 Project title

Provide a short project title using keywords that best describe the study.

9.4.7 Categorisation of project

The proposed project is to be categorised in terms of its purposes, either to educate or train students/staff or to perform research. If animals are to be used for training purposes, the nature of the course and number of students to be trained must be provided. The proposed dates for commencing and completing the study will indicate the duration of the proposed study.

9.4.8 Background information

A brief introductory statement (non-scientific summary) must be provided that explains the problems, questions, needs or novel ideas that initiated the planning of the experiment. A few key journal references must be included to substantiate viewpoints or premises.

9.4.9 Aim(s) of the proposed study

The main aim(s) and objectives of the study should be concisely stated.

9.4.10 Potential benefits of research findings or teaching exercise

A harm-benefit analysis is an ethical analysis weighing the harms to the animals against the benefits to be derived from the study. It is generally considered to be a function of professional judgement rather than a quantifiable assessment. The benefits arising from the potential results or the expected outcome of animal studies should be stated in terms of how they may contribute to either new knowledge or knowledge that will be useful for the treatment or protection of either humans or animals or the environment. This enables the ECRA to weigh the harms to the animals against the potential benefits which arise from the results of the experiment.

9.4.11 Statement of hypothesis

If the proposed research project is of an explanatory nature rather than for gathering descriptive data, it is likely that a hypothesis is being tested. If this is the case, the postulate should be briefly stated (in non-scientific terminology) to assist the reviewers in following the rationale of the experimental design. If no hypothesis is being tested, this should be stated.

9.4.12 Animal requirements

The species, strain, gender, body mass, age and health (microbial) status of the proposed experimental animals to be used must be specified. In addition, the total minimum number of animals required for all experiments as well as the source of the animals should be detailed. This information is important for defining the 'quality' of the proposed experimental system.

9.4.13 Justification for need to use sentient animals and species selected

Applicants should state why a non-sentient experimental system cannot be used for their study, what non-sentient model(s) were considered, and on what grounds they were rejected. The use of the selected animals should then be justified in terms of their biological appropriateness for use as a test system in the proposed study, i.e. in what way will they approximate humans or other animal species in terms of the question being asked or problem being addressed in the study. A brief explanatory statement should be given.

9.4.14 Reduction of number of animals to be used to a minimum

An explanation of how the minimum number of animals required was calculated to achieve the scientific objective of the study. This could be by either calculation (statistical design) or specification (i.e. use of a validated test protocol) or a reference.

9.4.15 Animal caging and care

A statement explaining where the experimental animals are to be housed, what provisions will be made for their physical and psychological (behavioural) well-being, and who will care for them on a daily basis.

9.4.16 Animal care competence, expertise and experience

A statement on the scientific knowledge competence and experience of the person(s) appointed to ensure the comfort, health and humane treatment of the animal subjects in the study. If procedures specific to the practicing of a veterinary or para-veterinary profession is to be performed in this study, authorization by the South African Veterinary Council may need to be obtained as a pre-requisite for the application.

9.4.17 Experimental design

A description of how the animals will be allocated to the experimental and control groups, what experimental treatments will be assigned to each group, and frequencies of these treatments.

9.4.18 Experimental procedure

A brief description on all steps to be performed in conducting the experiment(s), including operative procedures, collection of samples (e.g. give frequencies, blood volumes to be drawn, routes of collection) and any other measurements to be performed during the study. Describe also what will be measured in the samples and why this is being done. A non-scientific summary is required.

9.4.19 Physical restraint of the animals

If the animals are to be physically handled, describe what situations are likely to involve physical and chemical methods, describe the restraint methods to be used, state who will be restraining the animals and what steps will be taken to minimise stress in the animals.

9.4.20 Severity of the experimental procedures and category of invasiveness

Experimental procedures can cause fear, deprivation, illness, distress and pain in varying degrees. All of these conditions can be caused singly or in various combinations or, by the nature of the experiment, be absent altogether.

Applicants are required to state briefly what the physical and psychological effects of their experimental treatments are likely to be on a single animal in each of their experimental groups and the associated procedures in terms of *sensation anticipated, severity, frequency/duration, alleviation and anticipated effectiveness of interventions* (see examples in tables below on page 16-17).

Applicants are also required to select the appropriate category (A-E) from the ECRA Invasiveness Categories (see Annexures) which they deem to fit the entire study.

The severity of the proposed procedure should be rated as *minimal, intermediate or high* on the basis of the criteria detailed below. The administration of highly irritating substances may increase the severity scores, and this should be considered when rating the severity of the procedure.

Procedure	***Anticipated sensation***	***Severity score***	***Frequency & Duration***	***Steps to alleviate***	***Anticipated effectiveness***
Mouse physically restrained	Transient fear	12	Every day or once a week for 10 weeks	Habituation Providing hiding areas	Moderate
Mouse gavaged	Transient fear, discomfort, distress (5-8 sec)	7	12 times	Trial use of oral bait cubes Using non-traumatic technique with trained personnel Use of flexible soft tubing Minimum volume possible gavaged	High if possible Moderate Moderate Moderate
Mouse anaesthetised and laparotomy performed	Transient fear and minor pain of injection Transient distress on recovery from anaesthetic Moderate postoperative discomfort and pain for 2-3 days.	4 4 9	Once	Use smallest gage needle possible for injections Meloxicam and opioid during induction (s/c) then meloxicam orally for 3 days postop (pain relief) with additional use of opioids if needed	Moderate High
Mouse inoculated with pathogen	Transient fear, mild pain on inoculation, followed by mild/moderate/ severe illness for 3 weeks with weight loss	4 20	Inoculation once Illness 3 weeks	Use smallest needle practicable Symptomatic treatment of illness	Moderate Would depend on the illness and symptomatic treatment available, likely to be low/moderate
Category of invasiveness for entire study		D			

Severity scale: 0 – 8 = Minimal; 9 – 20 = Intermediate; > 20 = High

ADMINISTRATION OF SUBSTANCES		COLLECTION OF TISSUES AND BODY FLUIDS		SURGICAL PROCEDURES		RESTRAINT	
Conscious		**Conscious**		**All anaesthetised**		**Conscious**	
Topical		***Blood***		Skin incision	3	***Whole body***	
Mucous membranes	4	Venepuncture	5	Skin graft	10	Continuous	18
Skin	3	Venesection	8	Skin biopsy	3	Discontinuous	12
Eye	6	Orbital sinus	11	Laparotomy	9	Crush cage	9
Scarifying skin	11	Tail prick	9	Thoracotomy	11		
				Adrenalectomy	9		
Injection		***Peritoneal lavage***		Caesarean section	11	Metabolic cage	
Intradermal	7	Peritoneal lavage		Castration	7	confinement	6
Subcutaneous	3	7		Gastric fistula	13		
Intramuscular	4			Partial hepatectomy	14		
Intravenous	4			Hypophosectomy	12		
Orbital sinus	11			Nephrectomy	10		
Intra-lymphatic	7			Ovariectomy	6		
Intra-peritoneal	5						
Installation		***Urine***		Lymphadenectomy			
Intra-nasal	9	Percutaneous centesis	3	Superficial	4		
Intra-auricular	6			Visceral	10		
Intra-rectal	5			Splenectomy	5		
Intra-vaginal	3			Thymectomy	10		
Intra-tracheal	8			Thyroidectomy	8		
Oral		***Saliva***	5	Permanent cannulation			
Oral gavage	7	***Milk***	7	of major vascular			
Per os	5			component	11		
Anaesthetised		**Anaesthetised**					
				Permanent cannulation of superficial blood vessel	7		
				Bile duct	12		
				Thoracic duct	12		
Injection		***Blood***		Parabiosis (the surgical			
Orbital sinus	4	Venepuncture	2	joining together of two			
Intra-cardiac	7	Venesection	3	animals)	24		
Intra-cerebral	6	Cardiac puncture	6				
Intra-lymphatic	2	Orbital sinus	4				
Perfusion	2	Section of tail tissue	4				
		Peritoneal lavage					
		Peritoneal lavage	4				
		Urine					
		Catheter	5				
		Saliva	2				
		Semen	5				

NOTE:

- Any procedures which are likely to cause severe deprivation, fear, illness, distress and pain that will endure or are likely to endure will generally not be approved by ECRA.
- Components of severity considered in this scale: Conscious – anaesthesia – preparation – restraint – duration – tissue sensitivity – organ risk – mortality – pain – distress – deprivation.
- Numerical values are for single applications; multiple and more frequent applications over short periods of time may increase severity.

9.4.21 Fate of animals and their disposal at end of study

If this information was not previously provided in the application, briefly state what the fate of the group of experimental animals is to be at the end of the study (rehabilitation, release or euthanasia). Also indicate what method of euthanasia will be applied, the humane rationale to support this choice, and the method of animal carcass disposal.

9.4.22 Administration of scheduled medicinal (Medicines Control Act) and other experimental substances

Describe the route of substance administration and dosage (mass or volume per body mass). The volumes of doses to be administered must also be specified for all medicinal and experimental substances to be used in the study.

If scheduled substances (Schedules 3-6) are to be administered by any person other than a registered medical, dental or veterinary practitioner, then the registered person who is legally responsible for supervising and directing such use must be named. This person will accept responsibility by signing the application form.

9.4.23 Statistical design and analysis

Briefly describe the basis of the statistical design of the study (in terminology comprehensible to non-scientists) and state how the statistical analysis of data obtained from the study will be processed for descriptive analysis (e.g. calculation of mean, standard deviation, standard error) and statistical evaluation (e.g. calculations of probabilities, tests of significance, determination of associations and correlations). If this analysis is to be done in collaboration with a statistician, state who that person is and what their institutional affiliations are.

9.4.24 Refinement of methodology to promote humaneness

Briefly and pertinently describe what steps will be taken to refine the experimental procedures in order to reduce the potential severity of harm to a minimum i.e. gentle handling/restraint, use of chemical restraint, use of appropriate anaesthetics, use of aseptic procedure, postoperative care and analgesia, improvisation of methods to bypass stressful treatments.

9.4.25 Assurance of technical support and competence

Identify the staff member(s) responsible for the pre-, intra-, and postoperative/experimental treatment care of animals. Detail their experience, qualifications and competence in monitoring the well-being of the animals. Briefly state what behavioural and other criteria will be used to assess the well-being of the animals during the pre-, intra-, and post-operative phases of the study.

9.4.26 End-points for animal experiments that may cause illness and death of animals

In studies in which illness or death of an animal may be an end-point (e.g. regulatory toxicology, diagnostic toxicology, acute toxicity studies in research, infections, disease studies, micro-organism virulence studies, vaccine efficiency trials, cancer research and cancer treatment), discomfort should be alleviated by selecting the earliest end-point that is compatible with the scientific objectives of the research.

If end-points are given, the applicant must submit a brief explanatory statement to justify the specific end-point selected. The method can also be referenced. The

specification of end-points may be discussed in consultation with a laboratory animal veterinarian and the animal-care committee.

The specifications of end-points should also be supported by a statement of what detailed observations will be performed on the animals during the experimental period. Collectively, a list of the most significant predicators of deterioration of the animal's condition must be provided as well as how the severity will result in the decision to remove the animal from the study and terminate it. However, animal welfare remains the responsibility of the animal unit. All ill experimental animals will be reported to the principal investigator and thereafter treated in consultation with the veterinarian. Health and welfare concerns override protocol compliance.

9.4.27 Staff activities

The specific activities and duties of each staff member who will be involved in any procedures should be stated.

9.4.28 Biohazard statement

The principal investigator is responsible for (a) the correct collection/storage and disposal of all biological, chemical and other waste classified as hazardous, in terms of the NEMWA (National Environmental Management Waste Act) and HCRW (Health Care Risk Waste Management) regulations and standards, and (b) guarantees of an appropriate waste disposal budget for the project. Waste includes those generated during the course of the study as well as those generated after completion of the study and which are directly related to procedures on fresh/stored material of the study that will be incinerated by the appropriate SAMRC/institutional accredited waste disposal companies.

9.4.29 Repetition

It must be stated if the experiment(s) or any part of it is a repetition of work previously performed by the applicant or other persons. A justification must be provided for repeating previous work.

10. REPORTING OF PROTOCOL DEVIATIONS

- Reporting on on-going experiments should be conducted every six months by submission of an interim or final progress report (see Templates). If the principal investigator is a student, then the supervisor also needs to sign these reports. For an ongoing study, the authorised veterinarian of the facility also needs to sign the interim reports.
- It is the responsibility and duty of all researchers of the SAMRC or other institutions to report any incident (adverse or unanticipated) or deviation of the experiment (See Templates). Failure to report an incident may be construed as irresponsible (non-compliance) and may have consequences for any person involved with such a study and any other future applications.
- In case of any major or emergency event (e.g. adverse effects of the approved methods used or drugs administered to the animals are detected), the principal investigator will immediately report it to the laboratory animal technologist and communicate it to the ECRA secretariat. The ECRA will deliberate on the actions required and will give feedback to the principal investigator within 24 hours.
- In case of a minor deviation which has no impact on the outcome of the study or the welfare of the animals no further action will be taken. However, a narrative report on the welfare and status of the animals must be submitted to ECRA.

- Any planned modifications or extensions of an already approved project must be formally applied for by the principal investigator (see Templates). Applications for amendments must be approved by ECRA before it is carried out (for modification) or before completion of the study (for extension).

11. ANNEXURES AND TEMPLATES

11.1 Annexures

The following documents for submissions can be downloaded from the SAMRC website (https://www.samrc.ac.za/research/ethics/guideline-documents):

- ARRIVE Guidelines
- PREPARE Guidelines
- ECRA Invasiveness Categories

11.2 Templates

The following documents for submissions can be downloaded from the SAMRC website (http://www.mrc.ac.za/research/ethics/submission-documents):

- Application form for new project
- Checklist for animal research proposal
- Invertebrate ethics notification form
- Interim progress report
- Final progress report
- Application for amendment of approved project

Level:	3
Risk:	Strategic
Effective Date:	1 February 2023
Review Date:	January 2026
Standard Operating Procedures Owner:	Chief Research Operations Officer
Policy Manager / Cognisant Person:	Research Integrity Officer
EMC Approval	

Confirmation of Approval

26 January 2023

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Prof Glenda Gray **Date**

President & CEO